THE AMERICAN PEDIATRIC SOCIETY, INC.

and

THE SOCIETY FOR PEDIATRIC RESEARCH

Combined

Program and Abstracts

Sheraton Park Hotel

Washington, D.C.

May 22-26, 1972

THE AMERICAN PEDIATRIC SOCIETY, INC.

82nd ANNUAL MEETING

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THE SOCIETY FOR PEDIATRIC RESEARCH
42nd Annual Meeting

OFFICERS

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PROGRAM AND ABSTRACTS

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AMBULATORY PEDIATRIC ASSOCIATION

AMERICAN PEDIATRIC SOCIETY

SOCIETY FOR PEDIATRIC RESEARCH

COMBINED PLENARY SESSION

Tuesday, May 23, 1972, 1:00 p.m.

Sheraton Hall

1:00 PRESENTATION OF FIRST ANNUAL AWARD FOR AN OUTSTANDING TEACHING PROGRAM

1. 1:45 CLINICAL COMPETENCE OF CHILD HEALTH ASSOCIATES: COMPARISON OF HISTORY TAKING AND INTERPRETIVE SKILLS WITH THAT OF MEDICAL STUDENTS AND PEDIATRIC RESIDENTS. John E. Ott, John B. Moon and Pavel Machotka, Univ. of Colorado Med. Ctr., Colorado Gen. Hosp., Dept. of Ped., Denver. (p. 67)

2. 2:00 THE USE OF PEDIATRIC PSYCHOLOGY PARA-PROFESSIONALS IN DIAGNOSING AND PRESCRIBING FOR CHILDREN WITH LEARNING DISORDERS. James T. Heriot, Intr. by P. R. Nader, Univ. of Rochester, Sch. of Med., Strong Mem. Hosp., Dept. of Ped., Rochester, N.Y. (p. 67)

3. 2:15 AN EVALUATION OF HOME CARE VERSUS HOSPITALIZATION TREATMENT OF BLEEDING EPISODES IN HEMOPHILIC CHILDREN. Hanna Strawczynski, Andrew Stachewitsch, Gert F. Morgenstern and Marjorie E. Shaw, McGill Univ., Montreal Children's Hosp., Montreal, Canada. (p. 67)

4. 2:30 EVALUATION OF A PROGRAM FOR SICKLE CELL SCREENING AND HEALTH EDUCATION. Lawrence D. Robinson, Jr., Samuel B. Hunter, John Greenlee, McClain G. Garrett, and David G. Doane, Patterson Army Hospital, Fort Monmouth, New Jersey. (p. 67).

5. 2:45 CHILDHOOD LEAD POISONING: A THIRTY CITY NEIGHBORHOOD SURVEY. Roger S. Challop and Edward B. McCabe, U.S. Public Health Service, Cincinnati, Ohio and Cincinnati Childrens Hospital, Cincinnati, Ohio. (p. 67)

- 3:00 Intermission -

6. 3:15 PEDIATRIC GROUP PRACTICE (PGP) AN EDUCATIONAL SIMULATION MODEL FOR HOUSE OFFICERS. B. Duncan and S. Barnett, Univ. of Colo. Med. Ctr., Dept. ped., Denver. (p. 67)

7. 3:30 COMMUNITY CONTROL OF COMMUNITY HEALTH -- BEYOND THE RHETORIC. Merle C. Cunningham, Univ. of Roch. Sch. of Med., Intro by Barry Pless, Dept. of Ped., Rochester. (p. 68)

8. 3:45 FAMILY STRESS, ILLNESS AND USE OF HEALTH SERVICES. Klaus J. Roghmann and Robert J. Haggerty, Univ. of Rochester Sch. of Med. & Dent., Depts. of Ped. and Soc., Rochester. (p. 68)

GEORGE ARMSTRONG LECTURE

4:00

Henry K. Silver
University of Colorado
Medical Center
Denver

SYMPOSIUM

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THE SOCIETY FOR PEDIATRIC RESEARCH

and

THE AMBULATORY PEDIATRIC ASSOCIATION

Tuesday, May 23, 1972, 8:00 P.M.

Sheraton Hall

Moderator: William B. Weil, Jr.

A COUPLING AGENT FOR MEDICAL EDUCATION, RESEARCH AND CARE--THE PROBLEM ORIENTED RECORD
Lawrence L. Weed

THE PROBLEM ORIENTED RECORD IN PEDIATRICS
Luther C. Hansbarger

DISCUSSION AND QUESTIONS--PANEL AND AUDIENCE

AMERICAN PEDIATRIC SOCIETY

BUSINESS MEETING

(Members Only)

Sheraton Hall

Part 1: 8:00 A.M., May 24, 1972
Part 2: 5:00 P.M., May 24, 1972

AMERICAN PEDIATRIC SOCIETY

Wednesday, May 24, 1972, 9:00 A.M.

FIRST PLENARY SESSION

Sheraton Hall

Moderator: Warren E. Wheeler

PRESIDENTIAL ADDRESS: Warren E. Wheeler

1. 9:20 CURRENT APPROACHES AND OUTSTANDING DIFFICULTIES IN PROBLEMS OF DEVELOPMENTAL PHARMACOLOGY. Fabio Sereni, (Intr. by Warren E. Wheeler), Milano Univ. Med. Sch., Dept. of Child Health, Milano. (p. 68)

2. 9:40 WHAT HAPPENS TO THE BABIES BORN TO ADOLESCENT MOTHERS? N. Bingol, D. Reininger, H. Rich, S. Iosub and E. Wasserman, Dept. of Ped., New York Med. Col., New York. (p. 68)

3. 10:00 REDUCING THE LITERAL AND HUMAN COST OF CHILD ABUSE: IMPACT OF A NEW HOSPITAL MANAGEMENT SYSTEM. Eli H. Newberger, Dept. of Medicine, Children's Hospital Medical Center, Boston. (p. 68)

4. 10:30 ENZYME CHANGES IN LEUKOCYTES DURING PREGNANCY. J. Metcoff, T. Yoshida & J. W. Coffelt, Depts. Ped. & Biochem., Univ. Okla. Health Sci. Ctr., Children's Mem. Hosp., Okla. City, A. Bernal, A. Rosado, J. Urrusti, P. Yoshida, S. Frenk and L. Velasco, Dept. Invest. Cient., Hosp. de Ped. Hosp. Ginec.-Obst. #2, Centro Medico Nacional, IMMS, Mexico, D.F. (p. 68)

5. 10:50 INSENSIBLE, SIGNIFICANT AMINO ACID LOSS IN INFANTILE DIARRHEA. H. Ghadimi, F. Abaci and D. Jothianandan, Dept. of Ped., Downstate Med. Ctr., State Univ. of New York and Methodist Hospital of Brooklyn. (p. 69)

6. 11:10 NUTRITIONAL IMPLICATIONS OF LACTOSE MALABSORPTION. David M. Paige and George G. Graham, The Johns Hopkins University, Baltimore, and Instituto de Investigacion Nutricional, Lima. (p. 69)

7. 11:30 ACID-BASE PROPERTIES OF "HYPERALIMENTATION" SOLUTIONS. William C. Heird, Ralph B. Dell and Robert W. Winters, Dept. of Ped., Columbia University College of Physicians & Surgeons, New York. (p. 69)

8. 11:50 CEREBROVASCULAR ACCIDENT (CVA) IN INFANTS AND CHILDREN WITH CYANOTIC CONGENITAL HEART DISEASE (CHD). Charlie Phornphutkul, Amnon Rosenthal, William Berenberg and Alexander S. Nadas, The Children's Hospital Medical Center and Harvard Medical School, Boston. (p. 69)

RECIPIENTS OF THE
JOHN HOWLAND AWARD

(Presented by the American Pediatric Society)

1952 Edwards A. Park

1953 Grover F. Powers

1954 Bela Schick

1955 James L. Gamble

1956 Harold K. Faber

1957 Ethel C. Dunham

1958 Irvine McQuarrie

1959 Daniel C. Darrow

1960 Bronson Crothers

1961 Rustin McIntosh

1962 Joseph Stokes, Jr.

1963 Lawson Wilkins

1964 Samuel Z. Levine

1965 John Caffey

1966 L. Emmett Holt, Jr.

1967 Martha M. Eliot

1968 Paul Gyorgy

1969 Allan M. Butler

1970 Josef Warkany

1971 Helen B. Taussig

1972 Waldo E. Nelson

AMERICAN PEDIATRIC SOCIETY

Wednesday, May 24, 1972, 2:00 P.M.

SECOND PLENARY SESSION

Sheraton Hall

Moderator: Robert Ward

PRESENTATION OF HOWLAND AWARD TO

WALDO E. NELSON BY ANGELO M. DI GEORGE

9. 2:45 URBAN MEASLES IN THE VACCINE ERA; A CLINICAL, EIPDENIOLOGIC AND SEROLOGIC STUDY. James D. Cherry, Ralph D. Feigin, Louis A. Lobes, Jr., Daniel R. Hinthorn, Penelope G. Shackelford, Richard H. Shirley, Robert D. Lins and Sung C. Choi, St. Louis Univ. and Wash. Univ. Med. Sch., Dept. Ped., and St. Louis City Div. of Health. (p. 69)

10. 3:05 REYE'S SYNDROME AND FREE-FATTY ACID-INDUCED COMA. Doris A. Trauner, Ronald B. David, Robert E. Brown and Peter Mamunes, Med. Col. of Virginia, Richmond, Virginia (Intr. by W. E. Laupus). (p. 69)

11. 3:35 THE EFFECT OF CYCLOPHOSPHAMIDE IN CHILDHOOD NEPHROTIC SYNDROME. A REPORT FOR THE INTERNATIONAL STUDY OF KIDNEY DISEASE IN CHILDREN. Adrian Spitzer (Intr. by Henry L. Barnett), Albert Einstein Col. of Med., Bronx. (p. 70)

12. 3:55 A COMPARISON OF NORNOCOMPLEMENTEMIC AND HYPOCOMPLEMENTEMIC PATIENTS WITH ACUTE POST-STREPTOCOCCAL NEPHRITIS. C. Frederic Strife, A. James McAdams, Paul T. McEnery and Clark D. West, Dept. of Ped., Univ. of Cincinnati Col. of Med. and Children's Hospital, Cincinnati. (p. 70)

13. 4:15 HOW USEFUL ARE THE NEW CYTOGENETIC TECHNICS? H. A. Lubs, L. Ewing and S. Merrick, Sponsor: Frederick C. Battaglia, Univ. of Colo. Med. Cntr., Denver. (p. 70)

14. 4:35 INCREASED INDICENCE OF DIABETES MELLITUS IN PATIENTS WITH HASHIMOTO'S THYROIDITIS. Orville C. Green and Robert J. Winter (Intr. by Wayne H. Borges), Northwestern Univ. Med. Sch., The Children's Mem. Hosp., Dept. Ped., Chicago. (p. 70)

SOCIETY FOR PEDIATRIC RESEARCH

BUSINESS MEETING

(Members Only)

Cotillion Room North

Part 1: 8:00 A.M., May 25, 1972
Part 2: 5:15 P.M., May 25, 1972

THE SOCIETY FOR PEDIATRIC RESEARCH

and

THE AMERICAL PEDIATRIC SOCIETY

SPECIALTY SESSIONS

Thursday, May 25, 1972

BEHAVORIAL SCIENCE

Alexandria Room

Moderator: H. Peter Chase

1. 9:00 BEHAVORIAL AND DEMOGRAPHIC CHARACTERISTICS OF DRUG DEPENDENCY IN THE ADOLESCENT 16 AND UNDER. Robert A. Kramer, Univ. of Conn. Sch. of Med., Dept. of Ped., Hartford, Connecticut, (Intr. by Milton Markowitz). (p. 70)

2. 9:20 THE EARLY DEVELOPMENT OF INFANTS OF HEROIN-ADDICTED MOTHERS. Geraldine S. Wilson, Murdina M. Desmond and Willie M. Verniaud, Baylor Col. of Med., Harris County Hospital District, Dept. of Ped., Houston. (p. 70)

3. 9:40 THE BLACK PREGNANT TEENAGER, WHAT BECOMES OF HER AND HER OFFSPRING? Rosalind Y. Ting and Monica H. Wang, The Children's Hospital of Phila., Dept. of Ped. Univ. of Pennsylvania. (p. 71)

4. 10:00 THE PSYCHOLOGICAL EFFECT OF SUMMER CAMP ON THE PERSONALITIES OF JUVENILE DIABETICS AND THEIR PARENTS. Ron McCraw, Luther B. Travis, Warren F. Dodge and Harvey Bunce, Depts. of Ped. and Preventive Med., Univ. of Texas Med. Branch, Galveston. (p. 71)

5. 10:20 DOUBLE BLIND CLINICAL EVALUATION OF THE ANOREXIC ACTIVITY OF MAZINDOL AS COMPARED TO A PLACEBO IN CHILDHOOD OBESITY. P. J. Collipp, R. K. Sharma, J. Thomas, I. Rezvani and John Strimas, Nassau Co. Med. Cntr., E. Meadow, N.Y. (p. 71)

- 10:40 Intermission -

6. 10:50 MATERNAL BEHAVIOR ONE YEAR AFTER EXTENDED POST-PARTUM CONTACT. John Kennell, Richard Jerauld, Harriet Wolfe, David Chesler, Willie McAlpine, Nancy C. Kreger, Meredith Steffa and Marshall Klaus, Case Western Reserve Univ. Sch. of Med., Dept. of Ped., Cleveland. (p. 71)

7. 11:10 LONG-TERM FOLLOWUP ON KIDNEY TRANSPLANT PATIENTS AND THEIR FAMILIES. Barbara M. Korsch, James E. Gardner, Richard N. Fine and Vida F. Negrete, Univ. of Southern California Sch. of Med., Dept. of Ped., Childrens Hosp. of Los Angeles. (p. 71)

8. 11:30 ATTITUDES TOWARD HOSPITALS, PERCEIVED SEVERITY OF ILLNESS AND PHYSICIANS' ESTIMATES OF SEVERITY OF ILLNESS IN CYSTIC FIBROSIS (CF). Maarten S. Sibinga, C. Jack Friedman, Nancy H. Huang and Harry Markow, Dept. of Ped., Temple Univ. Sch. of Med. & St. Christopher's Hosp. for Child., Philadelphia. (p. 71)

9. 11:50 STUDENT HEALTH PROGRAM FOR MIGRANT FARM WORKERS AND RURAL POOR. S. E. Barnett and H. P. Chase, Univ. of Colo. Med. Cent., Denver. (p. 72)

10. 12:10 THE USE OF A GRADED PROBLEM ORIENTED RECORD TO EVALUATE PEDIATRIC TEACHING. Carmi Z. Margolis, William T. Stickley and T. Joseph Sheehan, Yale Univ. Sch. of Med., Dept. of Ped., New Haven; Case-Western Reserve Univ. Sch. of Med., Div. of Res. Med. Ed., Cleveland and Univ. of Conn. Sch. of Med., Dept. of Res. Health Ed., Farmington. (p. 72)

DEVELOPMENTAL BIOLOGY

FIRST SESSION

Wilmington Room

Moderator: Donald B. Cheek

1. 9:00 COMPONENTS OF THE "CRITICIAL" WEIGHT AT MENARCHE AND AT INITIATION OF THE ADOLESCENT SPURT: ESTIMATED TOTAL WATER (TW), LEAN BODY MASS (LBM) AND FAT. Rose E. Frisch, Roger Revelle and Sole Cook, Harvard Center for Population Studies, (Intr. by T. E. Cone, Jr.). (p. 75)

2. 9:20 IRON, NUTRITION AND GROWTH. Ray Hepner, Norma Maiden and Prasanna Nair, (Intr. by Marvin Cornblath), Sch. of Med., Univ. of Md. Hosp., Dept. of Pediatrics, Baltimore. (p. 75)

3. 9:40 TRIMETHADIONE INHIBITION OF DRUG METABOLISM: POSSIBLE ROLE IN TERATOGENESIS. A. B. Rifkind, Cornell Univ. Med. Col. and the Rockefeller Univ., N. Y., (Intr. by M. I. New). (p. 75)

4. 10:00 THE EFFECTS OF HEROIN ON LUNG MATURATION AND GROWTH IN FETAL RABBITS. H. William Taeusch, Jr., Stephen Carson, Nai S. Wang and Mary E. Avery, McGill Univ., Montreal Children's Hosp. Res. Inst. and Dept. of Physiol., McGill Univ., Montreal. (p. 75)

5. 10:20 THE ACCELERATION OF NEUROLOGICAL MATURATION IN HIGH STRESS PREGNANCY AND ITS RELATION TO FETAL LUNG MATURITY. Jeffrey B. Gould, Louis Gluck and Marie V. Kulovich, Univ. of Calif., San Diego Sch. of Med., Dept. of Ped., Div. of Perinatal Med., La Jolla. (p. 75)

- 10:40 Intermission -

6. 10:50 TRANSFER OF METHIONINE AND CYST(E)INE ACROSS THE HUMAN PLACENTA AND THE ROLE OF CYST(E)INE IN FETAL GROWTH. Gerald E. Gaull, Niels C. R. Raiha, J. Saarikoski and John A. Sturman, Dept. of Ped. Res., N.Y. St. Inst. Basic Res. in Mntl. Retd., Staten Island; Dept. of Ped., Mt. Sinai Hosp. Sch. of Med. of City Univ., N. Y., and I & II Clinic of Obstet. & Gyn., Helsinki University, Central Hospital, Helsinki. (p. 76)

7. 11:10 ALTERATIONS IN THE GROWTH PATTERN OF FETAL RHESUS MONKEYS FOLLOWING THE IN-UTERO INJECTION OF STREPTOZOTOCIN. Donald E. Hill, Alan B. Holt, Richard Reba and Donald B. Cheek, Johns Hopkins Univ., Sch. of Med., Dept. of Ped., Baltimore. (p. 76)

8. 11:30 INDUCTION OF RENAL DYSPLASIA IN HUMAN EMBRYONIC IN WHOLE ORGAN CULTURE. John F. S. Crocker (Intr. by Richard B. Goldbloom), Dept. of Ped., Dalhousie University, Halifax. (p. 76)

9. 11:50 CYTOCHALASIN B: EFFECTS ON MUCOPOLYSACCHARIDE SYNTHESIS AND MORPHOGENESIS. Merton R. Bernfield, Ronald H. Cohn and Shib D. Banerjee, Stanford Univ. Sch. of Med., Dept. of Ped., Stanford. (p. 76)

10. 12:10 ISOLATION OF SERUM MACROMOLECULE STRINGENTLY REQUIRED FOR THE MITOSIS OF DIPLOID HUMAN FIBROBLASTS. John C. Houck and Richard F. Cheng, Children's Hosp., Washington, and George Wash. Univ., Washington. (p. 76)

DEVELOPMENTAL BIOLOGY

SECOND SESSION

Wilmington Room

Moderator: Jo Anne Brasel

11. 1:45 BIOCHEMICAL STUDIES OF CELLULAR DIVISION: NUCLEIC ACID BIOSYNTHESIS IN ISOPROTERENOL STIMULATED SALIVARY GLANDS. Nicholas J. Hoogenraad, Jean M. Roux and Norman Kretchmer, Dept. of Ped., Stanford Univ. Sch. of Med., Stanford, and Center of Neonatal Research, Hospital Port-Royal, Paris. (p. 76)

12. 2:00 ISOLATION OF SUBCELLULAR PARTICLES ON A MICROSCALE: MITOCHONDRIAL ENZYME ACTIVITY IN SUBCUTANEOUS ADIPOSE TISSUE OF HUMAN NEWBORNS. Milan Novak, Ellen Monkus, Victoriano Pardo and David Alzamora, Univ. of Miami Sch. of Med., Dept. of Ped. and Veterans' Administration Hospital, Miami. (p. 77)

13. 2:25 CHANGES IN MITOCHONDRIAL AND MICROSOMAL FATTY ACID ELONGATION DURING DEVELOPMENT OF THE RAT. Joseph B. Warshaw and Robert E. Kimura, Harvard Med. Sch., Mass. General Hospital, Shriners Burns Inst., Boston. (p. 77)

14. 2:45 ENHANCEMENT OF LECITHIN SYNTHESIS AND PHOSPHORYLCHOLINE GLYCERIDE TRANSFERASE ACTIVITY IN THE FETAL RABBIT LUNG AFTER CORTICOSTEROID ADMINISTRATION. Philip M. Farrell and Richard D. Zachman, (Intr. by Charles C. Lobeck), Univ., of Wis., Dept. of Ped., Madison. (p. 77)

15. 3:05 BIOGENESIS OF MITOCHONDRIA, AND THE EFFECT OF CHLORAMPHENICOL, DURING NEONATAL RENAL COMPENSATORY GROWTH. Charles E. Mize and Howard G. Worthen, Univ. of Texas Southwestern Med. Sch., Dept. of Ped., Dallas. (p. 77)

- 3:25 Intermission -

16. 3:35 COMPARISON OF RNase ACTIVITY AND PLACENTAL RNA CONTENT DURING NORMAL AND RETARDED GROWTH. Elba G. Velasco, Jo Anne Brasel and Myron Winick, Cornell Med. Cntr., Dept. of Ped., N.Y. (p. 77)

17. 3:55 THE EFFECT OF FETAL THYROIDECTOMY ON GROWTH OF THE OVINE FETUS. A. Erenberg, K. Omori, W. Oh and D. A. Fisher, UCLA Sch. of Med., Harbor Gen. Hosp., Dept. of Ped., Torrance, California. (p. 77)

18. 4:15 DEFICIENCY OF THYROID HORMONE AND DEVELOPMENT OF THE FETAL RHESUS MONKEY. George R. Kerr, Ian Tyson, James R. Allen, John H. Wallace and Guenther Scheffler, Univ. of Wisc., Dept. of Ped., Radiology, Pathology and the Regional Primate Res. Center, Madison. (p. 78)

19. 4:35 EFFECT OF HUMAN GROWTH HORMONE (HGH) ON RNA SYNTHESIS IN RAT LIVER MITOCHONDRIA
G. Bren, V. T. Maddaiah, R. K. Sharma, J. Thomas, P. J. Collipp and S. Y. Chen, Nassau County Med. Cntr., East Meadow, N.Y. (p. 78)

20. 4:55 EFFECTS OF ACTH ON THE SYNTHESIS OF RAPIDLY LABELLED ADRENAL CYTOPLASMIC RNA.
Salvador Castells, Nicholas Addo and Kwaku Kwateng, Dept. of Ped., State Univ. of N.Y., Downstate Med. Cntr., N.Y. (p. 78)

CARDIOLOGY

FIRST SESSION

Annapolis Room

Moderator: Michael A. Heymann

1. 9:00 THE EFFECT OF 17,β-ESTRADIOL ON THE MAGNITUDE AND DISTRIBUTION OF UTERINE BLOOD FLOW IN PREGNANT AND NONPREGNANT EWES. Charles R. Rosenfeld, Allen P. Killam, Giacomo Meschia, Edgar L. Makowski and Frederick C. Battaglia, Div. of Perinatal Med., Univ. of Colo. Med. Cntr., Denver. (p. 80)

2. 9:20 PULMONARY CIRCULATION IN FETAL LAMBS. Abraham M. Rudolph and Michael A. Heymann, Univ. of California, San Francisco, Cardiovascular Res. Inst. and Dept. of Ped. (p. 81)

3. 9:40 THE IN VITRO RESPONSE OF THE LAMB DUCTUS ARTERIOSUS TO PROSTAGLANDINS. Peter M. Olley and Flavio Coceani, (Intr. by Andrew Sass-Kortsak), The Hosp. for Sick Children, Dept. of Ped., Toronto. (p. 81)

4. 10:00 INCIDENCE AND TREATMENT OF PATENT DUCTUS ARTERIOSUS IN THE LOW BIRTH WEIGHT NEONATE. Richard D. Zachman, Marion K. Ledbetter, Richard J. Bothan, George P. Steinmetz and Stanley N. Graven, Univ. of Wis., Dept. of Ped., St. Mary's Hosp. Med. Cntr., Madison. (p. 81)

5. 10:20 AN INTRAVASCULAR ELECTRODE FOR CONTINUOUSLY MONITORING ARTERIAL OXYGEN TENSION. Edwin G. Brown, Chung C. Liu, Francis E. McDonnell, Michael R. Neuman and Avron Y. Sweet, Dept. of Ped. and the Perinatal Gen. Clin. Res. Cntr., Case Western Reserve Univ. at Cleveland Metropolitan Gen. Hosp., Cleveland. (p. 81)

- 10:40 Intermission -

6. 10:50 VENTRICULAR PERFORMANCE, CORONARY FLOW, AND MVO_2 IN THE HYPERTROPHIED RAT HEART. Walter J. Gamble, Charlie Phornphutkul and Amy Kumar, (Intr. by Richard Van Praagh), Harvard Med. Sch., The Children's Hosp. Med. Cntr., Boston. (p. 81)

7. 11:10 LEFT VENTRICULAR ISCHEMIA IN SEVERE VALVAR AND SUPRAVALVAR AORTIC STENOSIS: A COMMON MECHANISM. William R. Vincent, Gerald D. Buckberg and Julien I. E. Hoffmar UCLA Sch. of Med., Depts. of Ped. and Surg., and Cardiovascular Res. Inst. and Dept. of Ped., Univ. of California, San Francisco. (p. 81)

8. 11:30 EFFECT OF AUTONOMIC DRUGS ON EXCITATION AND CONTRACTION IN NORMAL AND DEPRESSED MYOCARDIUM. Henry Gelband, Arthur L. Bassett and Brian F. Hoffman, Dept. of Pharmacology, Col. of Physicians and Surgeons, N. Y., and the Dept. of Ped., Univ. of Miami Sch. of Med., Miami, (Intr. by W. W. Cleveland). (p. 82)

9. 11:50 CARDIOVASCULAR EFFECTS OF PROPRANOLOL IN PUPPIES. Nestor J. Truccone and O Robert Levine, Columbia Univ. Coll. of Phys. and Surgeons, Dept. of Ped., New York. (p. 82)

CARDIOLOGY

SECOND SESSION

Annapolis Room

Moderator: Thomas P. Graham

10. 1:45 THE TRICUSPID VALVE IN DOUBLE INLET LEFT VENTRICLE (DILV), NATURALLY OCCURING IN THE HUMAN, EXPERIMENTALLY PRODUCED IN THE CHICK. I. H. Gessner and L. H. S. Van Mierop, Univ. of Fla., Coll. of Med., Dept. of Ped., Gainesville. (p. 82)

11. 2:00 EARLY ARTERIAL CALCIFICATIONS IN INFANCY AND CHILDHOOD AND ITS RELATION TO THE ARTERIAL GROWTH. W. W. Meyer and J. Lind, Karolinska Inst., Dept. of Ped., Stockhol, Sweden, and Univ. of Mainz, Inst. of Pathology, West Germany. (p. 82)

12. 2:25 CARDIOVASCULAR RESPONSES TO HYPOXEMIA AND TO ACIDEMIA IN UNANESTHETIZED FETAL LAMBS. Herbert E. Cohn, Edmond J. Sacks, Michael A. Heymann and Abraham M. Rudolph. (p. 82)

13. 2:45 EFFECT OF OXYGEN-HEMOGLOBIN AFFINITY ON OXYGEN CONSUMPTION AND CARDIAC OUTPUT OF NEWBORN PIGLETS FOLLOWING EXCHANGE TRANSFUSION. Maria Delivoria-Papadopoulos, Ronald Martens, Frank A. Oski and Robert E. Forster, II, Univ. of Pennsylvania, School of Med. (p. 82)

14. 3:05 CHANGES IN BLOOD PRESSURE AND FLOWS DURING SCIATIC NERVE STIMULATION IN NEWBORN PIGS UNDER HYPERCAPNIA AND HEMORRHAGE. G. Dasaradharama Reddy, N. Buckley, N. Gootman and P. Gootman, Long Island Jewish Med. Cntr., Dept. of Ped., New Hyde Park, N. Y., (Intr. by P. Lanzkowsky). (p. 83)

- 3:25 Intermission -

15. 3:35 QUANTITATIVE ECHOCARDIOGRAPHIC MEASUREMENTS IN NORMAL NEONATES. Univ. of Michigan, Wayne County Gen. Hosp., Dept. of Ped., Ann Arbor and Eloise, Michigan, Sundar Rajan, V., Vinay K. Duggal, Bruce D. Doust and Ruth H. Strang, (Intr. by William J. Oliver). (p. 83)

16. 3:55 CARDIAC ULTRASONOGRAPHY: A NEW STOP-MOTION TECHNIQUE: APPLICATION IN THE DENONSTRATION OF TRANSPOSITION OF THE GREAT VESSELS. Carl N. Steeg, Donald L. King and Kent Ellis, (Intr. by Welton M. Gersony), Div. of Ped. Cardiology, Depts. of Ped. and Radiology, Coll. of Phys. and Surg., Columbia Univ. and Babies Hosp., Columbia-Presbyterian Medical Center, New York. (p. 83)

17. 4:15 LIMB BLOOD FLOW IN CHILDREN WITH TETRALOGY OF FALLOT AND NORMAL HEARTS FROM INFANCY TO CHILDHOOD. Marina A. Corpus and Gershon Hait, Dept. of Ped., Albert Einstein College of Medicine, Bronx. (p. 83)

18. 4:35 EFFECT OF CONTRAST MEDIA USED IN ANGIOCARDIOGRAPHY ON OXYHEMOGLOBIN DISSOCIATION. Amnon Rosenthal, S. Bert Litwin and M. B. Laver, The Children's Hosp. Med. Cntr., Massachusetts Gen. Hosp., and Harvard Med. Sch., Boston. (p. 83)

ENDOCRINOLOGY

FIRST SESSION

Biltmore Room

Moderator: Raphael David

1. 9:00 HUMAN PROLACTIN (HPr) RESPONSES TO THYTOTROPIN RELEASING (TRH) IN NORMAL CHILDREN AND HYPOPITUITARY PATIENTS. Thomas P. Foley, Jr., Laurence Jacobs, William Hoffman, William Daughaday and Robert M. Blizzard, Johns hopkins Univ. Dept. of Ped., Baltimore, and Washington Univ. Dept. of Med., St. Louis. (p. 88)

2. 9:20 PROLACTIN AND TSH RESPONSES TO THYROTROPIN RELEASING HORMONE AND CHLORPROMAZINE IN HYPOPITUITARY DWARFS: AN ATTEMPT TO ASSESS HYPOTHALAMIC FUNCTION. Louis E. Underwood, Raymond L. Hintz, David R. Clemmons, Sandra J. Voina, Roger W. Turkingron and Judson J. Van Wyk, Univ. of North Carolina Sch. of Med., Dept. of Ped., Chapel Hill, and Univ. of Wisconsin, Dept. of Med., Madison. (p. 88)

3. 9:40 FAMILIAL CONGENITAL GLUCOCORTICOID INSUFFICIENCY-ACTH UNRESPONSIVENESS? Thomas Moshang, Jr., Robert L. Rosenfield, Alfred M. Bongiovanni, John S. Parks and James A. Amrhein, The Univ. of Pa. Sch. of Med., The Children's Hospital of Philadelphia. (p. 88)

4. 10:00 UNCONJUGATED ESTROGENS IN THE PERINATAL PERIOD. Kitti Angsusingha, Dora Stinson, Alec Allen, Julane Hotchkiss and Frederic Kenny, Univ. of Pittsburgh Sch. of Med., Depts. of Ped. and Physiol., Pittsburgh. (p. 89)

5. 10:20 EVIDENCE FOR THE EPISODIC SECRETION OF LH AND DECREASING SENSITIVITY OF THE HYPOTHALAMIC-PITUITARY "GONADOSTAT" IN ADOLESCENT PATIENTS WITH GONADAL DYSGENESIS. R. P. Kelch, F. A. Conte, S. L. Kaplan and M. M. Grumbach, Dept. of Ped., Univ. of Calif. San Francisco. (p. 89)

- 10:40 Intermission -

6. 10:50 SERUM PROLACTIN (HPr) IN INFANCY AND CHILDHOOD. Harvey J. Guyda and Henry G. Friesen, McGill University, Montreal Children's Hosp., Res. Inst. and Royal Victoria Hosp., Montreal, (Intr. by Eleanor Colle). (p. 89)

7. 11:10 THE LITTLEST GIANT: HYPOTHALAMIC-PITUITARY RELATIONSHIPS IN A 4 YEAR OLD ACROMEGALIC. Harvey Guyda, Jules Hardy and Eleanor Colle, McGill Univ., Montreal Children's Hosp. Res. Inst., and Hôpital Notre Dame, Montreal. (p. 89)

8. 11:30 HIGHLY SPECIFIC TESTICULAR ISOZYME OF CYCLIC NUCLEOTIDE PHOSPHODIESTERASE ASSOCIATED WITH SEXUAL MATURATION. Robert O. Christiansen and Marcia Desautel, Dept. of Ped., Stanford Univ. Med. Sch., and Stanford Med. Cntr., Stanford. (p. 89)

9. 11:50 GROWTH HORMONE AND MITOCHONDRIAL PROTEIN SYNTHESIS EFFECT OF CORTISOL AND ESTRADIOL. R. K. Sharma, V. T. Maddaiah, P. J. Collipp, S. Y. Chen and J. Thomas, Nassau County Medical Center, East Meadow, N. Y. (p. 89)

10. 12:10 A NEW SYNDROME OF PERIPHERAL AND PITUITARY RESISTANCE TO THYROID HORMONE. Hans H. Bode, M. Danon, F. Maloof, J. D. Crawford, B. Weintraub, Harvard Med. Sch., Mass. Gen. Hosp., Shriners Burns Institute, Boston. (p. 90)

ENDOCRINOLOGY

SECOND SESSION

Biltmore Room

Moderator: Allan Drash

11. 1:45 INTERRELATIONSHIP OF MAGNESIUM METABOLISM AND PARATHYROID FUNCTION IN MAN. Constantine S. Anast, James M. Mohs, Sheldon L. Kaplan and Thomas W. Burns, Depts. of Ped. and Med., Univ. of Missouri Sch. of Med. (p. 90)

12. 2:00 PROPANOLOL ENHANCEMENT OF IMMUNOREACTIVE GROWTH HORMONE (IRGH) RESPONSE TO GLUCAGON IN CHILDREN. Utai Ruangwit, Anita Cavallo, Joseph N. Fisher and John F. Crigler, Jr., Harvard Med. Sch., The Children's Hosp. Med. Cntr., Dept. of Ped., Boston. (p. 90)

13. 2:25 L-DOPA STIMULATION OF GROWTH HORMONE (GH) RELEASE IN CHILDREN AND ITS SIGNIGICANCE. B. A. Porter, R. L. Rosenfield and A. M. Lawrence, Univ. of Chicago Sch. of Med., Depts. of Ped. and Med., Chicago. (p. 90)

14. 2:45 TRIIODOTHYRONINE KINETICS IN MATERNAL AND THYROIDECTOMIZED FETAL SHEEP. A. Erenberg, K. Omori, W. Oh, R. W. Lam and D. A. Fisher, Harbor Gen. Hosp. and UCLA Sch. of Med., Dept. of Ped., Torrance. (p. 90)

15. 3:05 THE ROLE OF TRIIODOTHYRONINE IN THYROID DISORDERS OF THE NEONATAL PERIOD, CHILDHOOD AND ADOLESCENCE. Theodore W. AvRuskin, Shi Ching Tang, Louis Shenkman, Terunori Mitshum and Charles S. Hollander, (Intr. by Joseph Dancis), Dept. of Ped., The Brookdale Hosp. Med. Cntr. and Depts. of Ped. and Med., NYU Sch. of Med., New York. (p. 90)

- 3:25 Intermission -

16. 3:35 RETENTION OF BIOLOGIC AND IMMUNOLOGIC ACTIVITY OF HGH AFTER REDUCTION AND ALKYLATION. M. H. Connors, A. Vinik, S. L. Kaplan and M. M. Grumbach, Dept. of Ped., Univ. Calif.-San Francisco; San Francisco. (p. 91)

17. 3:55 CYCLIC AMP PRODUCTION IN THE RAT FETUS AND NEWBORN: EFFECTS OF GLUCAGON AND PARATHORMONE. Solomon A. Kaplan, Kenneth H. Thaver, Barbara M. Lippe and S-L Raymond Wong, Dept. of Ped., UCLA Sch. of Med., Los Angeles. (p. 91)

18. 4:15 DIFFERENTIAL EFFECTS OF STARVATION UPON THE SECRETION OF LUTEINIZING (LH) AND FOLLICLE STIMULATING (FSH) HORMONES IN INTACT AND CASTRATED ADULT MALE RATS. Allen W. Root and R. David Russ, Temple Univ. Sch. of Med., Albert Einstein Med. Cntr., Div. of Ped., Philadelphia. (p. 91)

19. 4:35 PLASMA PROLACTIN LEVELS IN JUVENILE HYPOTHYROIDISM AND PRECOCIOUS PUBERTY. Gertrude Costin, Maurice D. Kogut, Ann K. Kershnar and Roger W. Turkington, Dept. of Ped., Childrens Hosp., USC Sch. of Med., Los Angeles, California and Dept. of Med., Univ. Wisconsin, Madison. (p. 91)

20. 4:55 ENHANCED GROWTH RESPONSES IN HYPOPITUITARY DWARFS TREATED WITH GROWTH HORMONE-ANDROGEN COMBINATION VERSUS GROWTH HORMONE ALONE. Margaret H. MacGillivray, Marvin Kolotkin, Thomas Aceto, Jr. and Richard W. Munschauer, Sch. of Med., SUNY at Buffalo, Children's Hosp., Dept. of Ped. and Radiology. (p. 91)

GENETICS

FIRST SESSION

Dover Room

Moderator: Arthur D. Bloom

1. 9:00 LESSONS FROM ONE HUNDRED AMNIOCENTESES FOR PRENATAL GENETIC STUDIES. Aubrey Milunsky, Leonard Atkins and John W. Littlefield, Harvard Med. Sch., Children's Serivce, Mass. Gen. Hosp., W. E. Fernald State Sch., Boston and Waltham, Massachusetts. (p. 96)

2. 9:20 GM_1 GANGLIOSIDOSIS, TYPE I: IN UTERO DETECTION AND FETAL MANIFESTSTIONS. M. M. Kaback, H. R. Sloan and A. K. Percy, Depts. of Ped. and Neuro., Johns Hopkins Hosp., Baltimore, and Molecular Disease Branch, NIHL, NIH, Bethesda. (p. 97)

3. 9:40 ABH AND LEWIS SUBSTANCES IN ANMIOTIC FLIUD BY AMNIOCENTESIS. Minerva B. Arcilla and Phillip Sturgeon, UCLA Sch. of Med., Dept. of Ped., Los Angeles. (p. 97)

4. 10:00 THE SCREENING OF NEWBORN INFANTS FOR Y CHROMOSOMAL ABNORMALITIES--FLUORESCENT STAINING OF UMBILICAL CORN CELLS. Arnold Greensher, David Peakman and Arthur Robinson, (Intr. by Henry Silver), Univ. of Colorado Med. Sch., Colorado Gen. Hosp., Dept. of Biophysics and Genetics, Dept. of Ped., Denver. (p. 97)

5. 10:20 FETAL SEX DETERMINATIONS. Cheryl Adams, Byron Kilpatrick, George Kabacy, Gayle E. Fialko and Kenneth W. Dumars, Univ. of Calif., Irvine, Calif., Coll. of Med., Dept. of Ped., Irvine, (Intr. by Thomas L. Nelson). (p. 97)

- 10:40 Intermission -

6. 10:50 DELETION OF SHORT ARM OF CHROMOSOME #9 (46,9p-): A NEW CLINICAL ENTITY. Omar S. Alfi, George N. Donnell, Barbara F. Crandall and Robert L. Podosin, Univ. of Southern Calif. Sch. of Med., UCLA Sch. of Med., and The Childrens Hosp. of Los Angeles, Los Angeles. (p. 97)

7. 11:10 GIEMSA BANDING PATTERN OF HERITABLE 1q+ VARIANT CHROMOSOME CONSISTENT WITH PARTIAL CHROMOSOMAL DUPLICATION. John R. Lobitz, Barbara K. McCaw, Frederick Hecht and Blaine E. Tolby, Univ. of Oregon Med. Sch., Portland. (p. 97)

8. 11:30 RING CHROMOSOME 7 WITH VARIABLE PHENOTYPIC EXPRESSION. Elaine H. Zackai and W. Roy Breg, Yale Univ. Sch. of Med., Depts. of Ped. and Med., Div. of Med. Genetics, New Haven, and Southbury Training School, Southbury, Conn. (p. 98)

9. 11:50 MULTIPLE ANOMALIES INCLUDING THYMIC APLASIA ASSOCIATED WITH MONOSOMY 22. Ira M. Rosenthal, Maureen Bocian and Eva Krmpotic, Abraham Lincoln Sch. of Med. of the Univ. of Ill. Coll. of Med., Chicago Med. Sch., Depts. of Ped. and Path., Cook County Hosp. and Mount Sinai Hosp., Chicago. (p. 98)

10. 12:10 X-LINKED HEART DISEASE? Annemarie Sommer and Jo M. Craenen, (Intr. by Stella B. Kontras), Ohio State Univ. Coll. of Med., Children's Hosp., Dept. of Ped., Columbus. (p. 98)

GENETICS

SECOND SESSION

Dover Room

Moderator: William J. Mellman

11. 1:45 A PILOT PROGRAM IN THE CONTROL OF GENETIC DISEASE. M. M. Kaback, R. S. Zeiger and H. Gershowitz, The John F. Kennedy Inst., Baltimore, (Intr. by Barton Childs). (p. 98)

12. 2:00 EFFECTIVENESS OF NEONATAL PKU SCREENING. Neil A. Holtzman, Allen G. Meek and E. David Mellits, Johns Hopkins Univ., Sch. of Med., Dept. of Med., Baltimore. (p. 98)

13. 2:25 SICKLE CELL HEMOGLOBIN PRODUCTION IN AN ABORTED MINTRIMESTER FETUS. Haig H. Kazazian, Jr., Michael M. Kaback and William S. Nersesian, Johns Hopkins Univ. Sch. of Med., Dept. of Ped., Baltimore. (p. 98)

14. 2:45 FAMILY STUDIES OF LACTASE INTOLERANCE IN NIGERIAN ETHNIC GROUPS. O. Ranson-Kuti, Norman Kretchmer, John Johnson and John T. Gribble, Dept. of Ped., Lagos Univ. Teaching Hosp., Lagos, Nigeria and Stanford Univ., Sch. of Med., Stanford. (p. 99)

15. 3:05 RACIAL DIFFERENCE IN RBC GALACTOKINASE ACTIVITY (EVIDENCE FOR A HIGHER FREQUENCY OF THE GALACTOKINASE DEFICIENCY GENE IN BLACKS). Robert Bonow, Thomas A. Tedesco, Karen Miller, William J. Mellman and Johannes Ipsen, Univ. of Pa. Sch. of Med., Dept. of Ped., Med. Genetics, Community Med., Phila. (p. 99)

- 3:25 Intermission -

16. 3:35 MUTATION AT THE HL-A LOCUS IN CULTURED HUMAN LYMPHOID CELLS. Donald Pious, Pam Hawley and Gary Forrest, Univ., of Wash. Sch. of Med. Dept. of Ped., Seattle. (p. 99)

17. 3:55 HYBRIDIZATION: THE RELATIONSHIP OF G_1 AND G_2 STAGES OF THE PARENTAL CELL CYCLE TO CHROMOSOME LOSS. Betty Paul, Karen Gaudio and I. H. Porter, (Intr. by Herbert S. Strauss), N.Y. St. Dept. of Health Birth Defects Inst., Albany. (p. 99)

18. 4:15 SEX DIFFERENCES IN ACTIVITY OF G6PD IN CULTURED FETAL LUNG CELLS DESPITE X-INACTIVATION. Mark W. Steele and Barbara R. Migeon, Dept. of Ped. Univ. of Pitts. and Johns Hopkins Univ., Children's Hosp. of Pitts. and Johns Hopkins Hosp., Pitts., Pa. and Baltimore. (p. 99)

19. 4:35 HUMAN FIBROBLASTS IN CULTURE. FURTHER STUDIES OF GLYCOGEN METABOLISM. Salvatore A. DiMauro, W. J. Mellman and Lewis P. Rowland, Univ. of Pa. Sch. of Med., Dept. of Neurology, Ped. and Med. Genetics, Philadelphia. (p. 99)

20. 4:55 INDUCTION OF UDP-GLUCURONYL TRANSFERASE ACTIVITY IN GUNN RATS FOLLOWING GRAFTING OF NORMAL LIVER. Anil B. Mukherjee and Joseph Krasner, (Intr. by Sumner J. Yaffe), Dept. of Ped., State Univ. of N. Y. at Buffalo, Children's Hosp. of Buffalo. (p. 100)

HEMATOLOGY

FIRST SESSION

Park Ballroom

Moderator: Peter R. Dallman

1. 9:00 A SIMPLE MICRO-METHOD FOR THE SIMULTANEOUS DETERMINATION OF HEMOGLOBINOPATHY AND GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY. Lance Sieger and Myron Karon, Div. of Hematology, Children's Hosp. of Los Angeles and Dept. of Ped., Univ. of Southern Calif. Sch. of Med. (p. 105)

2. 9:20 INFECTION AND SPLENIC FUNCTION IN SICKLE CELL ANEMIA. Maria L. Falter, Margaret G. Robinson, Ok S. Kim and Suat Ch. Go, SUNY, Downstate Med. Cntr., Brooklyn, Dept. of Ped. and Nuclear Med. (p. 105)

3. 9:40 THE EFFECT OF CYANATE ON THE SURVIVAL OF SICKLE RETICULOCYTES. Blanche P. Alter, Yuet W. Kan and David G. Nathan, Children's Hosp. Med. Cntr. and Harvard Med. Sch., Boston. (p. 105)

4. 10:00 POTASSIUM THIOCYANATE (KCNS) AS AN INHIBITOR OF SICKLING OF ERYTHROCYTES. Robert L. Kaufman and Harold S. Zarkowsky, (Intr. by William S. Sly), Wash. Univ. Sch. Med., St. Louis Children's Hosp., Dept. of Ped., St. Louis. (p. 105)

5. 10:20 GLUTATHIONE INSTABILITY OF CYANARE TREATED RED BLOOD CELLS IN VITRO. Bertil E. Glader, Linda Winn and Marcel E. Conrad, (Intr. by David G. Nathan), Walter Reed Army Inst. of Res., Washington. (p. 105)

- 10:40 Intermission -

6. 10:50 RED CELL OXYGEN (O_2) CONSUMPTION AND HYDROGEN PEROXIDE (H_2O_2) FORMATION. Fred Lipschutz, Bertram Lubin and Frank A. Oski, Univ. of Pa. Sch. of Med., Children's Hosp., Philadelphia. (p. 105)

7. 11:10 HEMOGLOBIN BARTS AND ALPHA THALASSEMIA IN THE NEGRO NEWBORN. Shlomo Friedman, Jean Atwater and Elias Schwartz, (Intr. by Robert L. Brent), Jefferson Med. Coll., Cardeza Fndn. and Dept. of Ped., Philadelphia. (p. 106)

8. 11:30 EFFECT OF pH ON GLYCOLYSIS IN THE ERYTHROCYTES OF THE NEWBORN INFANT. Frank A. Oski and Susan F. Travis, Univ. of Pa. Sch. of Med., Children's Hosp. of Phil., Philadelphia. (p. 106)

9. 11:50 FREE ERYTHROCYTE PROTOPORPHYRIN CONCENTRATION: A PROMISING SCREENING TEST FOR LEAD POISONING. Sergio Piomelli and Bernard Davidow, Dept. of Ped., N. Y. Univ. Sch. of Med. and N. Y. City Food and Drug Lab., New York. (p. 106)

10. 12:10 RED CELL δ-AMINOLEVULINIC ACID DEHYDRASE (ALAD) ACTIVITY AS AN INDEX OF BODY LEAD BURDEN. Phillip I. Nieburg, Barbara F. Oski, David Cornfeld and Frank A. Oski, Children's Hosp., Philadelphia. (p. 106)

HEMATOLOGY

SECOND SESSION

Park Ballroom

Moderator: James J. Corrigan

11. 1:45 A DEFICIENCY IN THE PHAGOCYTOSIS STIMULATING TETRAPEPTIDE TUFTSIN FOLLOWING SPLENECTOMY. Andreas Constantopoulos, Victor A. Najjar and Thomas F. Necheles, Tufts Univ. Sch. of Med., Div. of Protein Chem., and the Dept. of Ped., Boston Fl ating Hosp. for Infants and Children, Boston. (p. 106)

12. 2:00 SURFACE-ASSOCIATED DISORDERS OF HUMAN NEUTROPHIL FUNCTION. P. J. Edelson, D. P. Stites and H. H. Fudenberg, Dept. of Med., UCSF, San Francisco, (Intr. by M. M. Thaler). (p. 106)

13. 2:25 QUANTITATION OF BACTERICIDAL CAPACITY IN NORMAL AND ABNORMAL HUMAN NEUTROPHILS C. C. Clawson, John E. Repine and James G. White, Univ. of Minn., Dept. of Ped., Minneapolis. (p. 107)

14. 2:45 THE PROSPECTS FOR CURABILITY OF CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA (ALL). Joseph V. Simone, Rhomes J. A. Aur, H. Omar Hustu and Donald Pinkel, St. Jude Children's Res. Hosp., Memphis. (p. 107)

15. 3:05 ANTIGENIC DISPARITY BETWEEN LEUKEMIC LYMPHOBLASTS AND NORMAL LYMPHOCYTES IN IDENTICAL TWINS. Jaw J. Wang, Tin Han and Lucius F. Sinks, Roswell Park Mem. Inst., Dept. of Ped., Buffalo. (p. 107)

- 3:25 Intermission -

16. 3:35 DEFICIENCY OF NATURALLY OCCURRING ANTICOAGULANTS IN NORMAL AND SICK INFANTS. Chularatant Mahasandana and William E. Hathaway, Univ. of Colo. Med. Cntr., Dept. of Ped., Denver. (p. 107)

17. 3:55 EFFECTS OF CATIONIC POLYPEPTIDES ON AFIBRINOGENEMIC AND THROMBASTHENIC PLATELETS. James G. White, Univ. of Minn. Sch. of Med., Dept. of Ped., Minn. (p. 107)

18. 4:15 ABNORMAL PLATELET AGGREGATION AND THROMBOSIS - A FAMILIAL DISORDER. Harold S. Margolis and James J. Corrigan, Jr., Dept. of Ped., Univ. of Arizona Med. Cntr., Tucson. (p. 107)

19. 4:35 HEMOSTATIC EFFICACY OF PLATELET TRANSFUSIONS - EFFECT OF STORAGE AND ASPIRIN. Marie J. Stuart, Scott Murphy, Milton H. Donaldson, Audrey E. Evans, Frank H. Gardner and Frank A. Oski, Univ. of Pa. Sch. of Med., Philadelphia, (Intr. by D. Cornfeld). (p. 108)

20. 4:55 TRANSFUSIONS OF ANTIGENICALLY COMPATIBLE PLATELETS FOR THERAPY AND DIAGNOSIS OF ISOIMMUNE NEONATAL THROMBOCYTOPENIA. L. Sue McIntosh, Richard T. O'Brien and Howard A. Pearson, Dept. of Ped., Yale-New Haven Hosp., New Haven. (p. 108)

GASTROENTEROLOGY AND ENZYMOLOGY

FIRST SESSION

Frederick Room

Moderator: Herbert A. Hessler

1. 9:00 JEJUNAL IMMUNOGLOBULIN A(IgA) SYNTHESIS IN CYSTIC FIBROSIS (CF). Z. Myron Falchuk and Lynn M. Taussig, (Intr. by Paul A. de Sant'Agnese), NIH, Beth. (p. 114)

2. 9:20 MECHANISM OF ANTIGEN UPTAKE FROM THE SMALL INTESTINE: EFFECT OF ORAL AND PARENTERAL IMMUNIZATION. W. Allan Walker, Kurt J. Bloch, Laura M. Davenport and Kurt J. Isselbacher, Harvard Med. Sch., Mass. Gen. Hosp., GI Unit and Arthritis Unit, Boston, (Intr. by J. Warshaw). (p. 114)

3. 9:40 DEVELOPMENT OF INTESTINAL ADENYL CYCLASE AND ITS RESPONSE TO CHOLERA TOXIN. Frank M. Torti, Stephanie Jaksina and Richard J. Grand, Children's Hosp. Med. Cntr., Boston. (p. 114)

4. 10:00 INTESTINAL LACTASE ACTIVITY IN PRETERM, NORMAL AND IUGR RAT PUPS AT BIRTH. M. K. Younoszai, Univ. of Iowa Coll. of Med., Univ. Hosp., Dept. of Ped., Iowa City. (p. 114)

5. 10:20 DISACCHARIDASE ACTIVITIES IN BRUSH BORDER MATERIAL OBTAINED BY INTESTINAL PERFUSION IN THE NORMAL INFANT. R. Torres-Pinedo and Carmen Lugo-de-Rivera, Gen. Clin. Res. Cntr., and the Dept. of Pe., Sch. of Med. of the Univ. of Puerto Rico, San Juan. (p. 114)

- 10:40 Intermission -

6. 10:50 SULFATED PRIMARY BILE SALTS: A NEW METABOLIC PATHWAY IN CHOLESTASIS. M. M. Thaler, Adolf Stiehl and William H. Admirand, (Intr. by M. M. Grumbach), Depts. of Ped. and Med., Univ. of Calif., San Francisco. (p. 115)

7. 11:10 FETAL BILE SALT FORMATION. R. Lester, J. M. Little, R. Greco, G. J. Piosecki and B. T. Jackson, (Intr. by R. Klein), Depts. of Med. and Surgery, Boston Univ. Sch. of Med., Boston. (p. 115)

8. 11:30 INTERRUPTION OF THE ENTEROHEPATIC CYCLE OF BILE ACIDS BY UNABSORBED FAT. Andree Weber, Liette Chartrand, Micheline Ste-Marie and Claude C. Roy, Univ. of Montreal, Hopital Ste-Justine, Dept. of Ped. (p. 115)

9. 11:50 IMPAIRED ABSORPTION OF 3-O-METHYL GLUCOSE IN BILE LIGATED RATS. Claude C. Roy, Reuben S. Dubois, Guy Laurendeau, Victor Ling and Claude L. Morin, Univ. of Montreal, Hopital Ste-Justine, Dept. of Ped. (p. 115)

10. 12:10 HUMAN AMNIOTIC FLUID (AF) ISOANYLASE. Robert O. Wolf and Lynn M. Taussig, (Intr. by Paul di Sant'Agnese), NIH, Bethesda. (p. 115)

GASTROENTEROLOGY AND ENZYMOLOGY

SECOND SESSION

Frederick Room

Moderator: Richard J. Grand

11. 1:45 CHARACTERIZATION OF NEWBORN FECAL LIPID. J. B. Watkins, R. Lester, C. M. Bliss and R. M. Donaldson, (Intr. by R. Klein), Dept. of Med., Boston Univ. Sch. of Med., Boston. (p. 115)

12. 2:00 BLOOD AND FECAL LIPIDS IN LOW BIRTH WEIGHT INFANTS FED A CORN OIL AND A CONVENTIONAL FORMULA. Billy F. Andrews, Vichien Lorchirachoonkul and Roger J. Shott, Univ. of Louisville Sch. of Med., Dept. of Ped., Louisville, Ky. (Intr. by William G. Thurman). (p. 116)

13. 2:25 CHOLESTERYL ESTER STORAGE DISEASES: STUDIES OF THE CHEMICAL AND BIOCHEMICAL ABNORMALITIES. Howard R. Sloan and Donald S. Fredrickson, NIH, Bethesda. (p. 116)

14. 2:45 INTESTINAL AMINO ACID TRANSPORT IN HYPERPHENYLALANINEMIC AND HYPERTYROSINEMIC RATS. Fima Lifshitz and Raul A. Wapnir, Rosewood State Hosp. and Univ. of Md. Sch. of Med., Dept. of Ped., Baltimore. (p. 116)

15. 3:05 INHIBITION OF HEPATIC MICROSOMAL MIXED FUNCTION OXIDASE (HMMFO) BY CHLORAMPHENICOL (CH), Jacob V. Aranda, Stuart M. MacLeod, Kenneth W. Renton and Norman R. Eade, (Intr. by Mary E. Avery), McGill Univ., Dept. of Pharmacology and McGill Univ., Montreal Children's Hosp. Res. Inst., Montreal. (p. 116)

- 3:25 Intermission -

16. 3:35 ANTIBIOTICS AND BILIRUBIN TRANSPORT. B. H. Doray and A. P. Bonin, (Intr. by J. R. Ducharme), Dept. of Ped. and Biochemistry, Univ. of Montreal and Hopital Ste-Justine, Montreal. (p. 116)

17. 3:55 THE EFFECT OF PREGNANCY ON DRUG METABOLISM. Hector Rodriguez, Charlotte S. Catz and Sumner J. Yaffe, Dept. of Ped., State Univ. of N. Y. at Buffalo, Sch. of Med., Children's Hosp. of Buffalo. (p. 116)

18. 4:15 TREATMENT OF CRIGLER-NAJJAR SYNDROME WITH AGAR. Ronald L. Poland, Gordon B. Avery, Elizabeth Goetcherian and Gerard B. Odell, The Johns Hopkins Univ. and Children's Hosp. of the D. C. (p. 117)

19. 4:35 ISOENZYMES OF ALKALINE PHOSPHATASE (AP) AND RELATED SEROLOGIC LIVER FUNCTION STUDIES IN NORMAL ADOLESCENCE AND IN CYSTIC FIBROSIS (CF). John Kattwinkel, Lynn M. Taussig and Bernard E. Statland, (Intr. by Paul A. di Sant'Agnese), NIH, Bethesda. (p. 117)

20. 4:55 USE OF ANGER CAMERA IN EVALUATION OF EXCRETION OF I^{131} ROSE BENGAL FROM THE LIVER. Ruth C. Harris and Philip M. Johnson, Columbia Univ. Coll. of Phys. and Surgeons, Depts. of Ped. and Radiology, New York. (p. 117)

IMMUNOLOGY

FIRST SESSION

Cotillion Room South

Moderator: E. Richard Stiehm

1. 9:00 SERUM AND SECRETORY ANTIBODY RESPONSE TO VIRAL INFECTIONS IN IMMUNOGLOGULIN DEFICIENCY SYNDROMES. Pearay L. Ogra and Margaret H. MacGillivray, Dept. of Ped. Sch. of Med., State Univ. of N. Y. at Buffalo. (p. 119)

2. 9:20 A NON-IMMUNOGLOBULIN VIRUS-BINDING SUBSTANCE IN HUMAN AMNIOTIC FLIUD. Ruth B. Weisinger, Eugene Ainbender, M. Magda Hevizy and Horace L. Hodes, The Mount Sinai Sch. of Med., Dept. of Ped., New York. (p. 119)

3. 9:40 COMBINED IMMUNODEFICIENCY MANIFESTED BY THE LETTERER-SIWE SYNDROME. S. D. Cederbaum, Gen Niwayama, E. Richard Stiehm, Robert C. Neerhout, Arthur J. Ammann and William Berman, Jr., Dept. of Psychiatry, Ped., and Pathology, Univ. of Calif., Sch. of Med., Los Angeles, and Dept. of Ped., Univ. of Calif. Sch. of Med., San Francisco. (p. 119)

4. 10:00 MATERNAL INTRAUTERINE GRAFT OF B LYMPHOCYTES IN COMBINED IMMUNOLOGICAL DEFICIENCY DISEASE (CID). H. J. Meuwissen, R. J. Pickering, S. Litwin and B. Pollara, (Intr. by H. S. Strauss), N. Y. State Birth Defects & Kidney Disease Inst., Albany, N. Y. and Cornell Med. Cntr. (p. 119)

5. 10:20 FAMILIAL THYMIC APLASIA: ATTEMPTED RECONSTITUTION WITH FETAL THYMUS IN A MILLIPORE DIFFUSION CHAMBER. Russell W. Steele, Catherine Limas, Gary B. Thurman, Heinz Bauer and Joseph A. Bellanti, Georgetown Univ. Sch. of Med., Dept. of Ped., Washington, D. C. (p. 120)

- 10:40 Intermission -

6. 10:50 LYMPHOID INTERSTITIAL PNEUMONIA AND A DEFICIENCY IN THYMIC-DEPENDENT LYMPHOCYTES. Elton Dupree, Armond S. Goldman, Randall M. Goldblum and C. Wayne Smith, Shrimers Burns Inst. and The Univ. of Texas Med. Branch, Dept. of Ped. (p. 120)

7. 11:10 CELL-MEDIATED IMMUNE RESPONSES IN TRISOMY 21. Richard J. Bonforte, Photini Papageorgiou and Lawrence R. Shapiro, (Intr. by Philip R. Glade), The Mount Sinai Sch. of Med., Dept. of Ped., New York, N.Y. and The Cytogenetics Lab. Letchworth Village, Thiels, N. Y. (p. 120)

8. 11:30 PROLONGED SURVIVAL OF HEPATIC ALLOGRAFTS AFTER HOST LIVER ISCHEMIA. John R. Lilly, Kathryn D. Anderson, and John C. Houck, Res. Fndn. of Children's Hosp. of the D. C., Section of Surgical Res., George Wash. Univ. Sch. of Med., Washington, D. C. (p. 120)

9. 11:50 THE INCIDENCE AND MANIFESTATIONS OF COW'S MILK ALLERGY (CMA) IN AN UNSELECTED SERIES OF 787 NORMAL NEWBORNS. J. W. Gerrard, J. W. A. McKenzie, N. Goluboff, J. Z. Garson, C. Maningas and M. K. Shokier, Univ. of Saskatchewan Univ. Hosp., Dept. of Paediatrics, Saskatoon, Sask. (p. 120)

10. 12:10 IMMUNOLOGIC STUDIES OF SCLERODERMA IN CHILDREN. Virgil Hanson, (Intr. by Robert Ward), and Helen K. Kornreich, Univ. of So. Calif. Sch. of Med. and Child. Hosp. of Los Angeles, Dept. of Med. (p. 120)

IMMUNOLOGY

SECOND SESSION

Cotillion Room South

Moderator: Rebecca H. Buckley

11. 1:45 SOLUBLE COMPLEXES STIMULATE PHAGOCYTOSIS: IN VITRO AND IN VIVO STUDIES. Lauren M. Pachman, Panida Jayanetra and Richard M. Rothberg, Northwestern Univ., Children's Mem. Hosp., Dept. of Ped., Univ. of Chicago, Wyler Children's Hosp., Dept. of Ped., Chicago. (p. 121)

12. 2:00 DEFICIENT SERUM OPSOMINS IN SICKLE CELL DISEASE. Richard B. Johnston, Jr., Alan Struth and Simon L. Newman, Dept. of Ped., Univ. of Ala. Med. Cntr., Birmingham, (Intr. by Max D. Cooper). (p. 121)

13. 2:25 CHEMOTAXIS AND RANDOM MOBILITY. CHARACTERISATION OF TWO DISTINCT MECHANISMS OF LEUKOCYTE MOVEMENT, THEIR CLINICAL SIGNIGICANCE AND THEIR CORRELATION WITH NEUTROPENIA. Michael E. Miller, Children's Hosp. of Phila., and Charles R. Drew Postgrad. Med. Sch., Los Angeles. (p. 121)

14. 2:45 IN VITRO STUDIES OF CELL-MEDIATED IMMUNITY IN MAN. Samuel P. Gotoff and Somsak Lolekha, Dept. of Ped., The Abraham Lincoln Sch. of Med., Univ. of Ill., Chicago. (p. 121)

15. 3:05 GROWTH INHIBITING AND CYTOTOXIC FACTORS PRODUCED BY HUMAN PERIPHERAL BLOOD LEUKOCYTES IN VITRO. Rudolf F. Eife and Charles S. August, (Intr. by William E. Hathaway), Univ. of Colo. Med. Cntr., Dept. of Ped., Denver. (p. 121)

- 3:25 Intermission -

16. 3:35 ATYPICAL CHRONIC GRANULOMATOUS DISEASE OF CHILDHOOD. George H. McCracken, Jr. and Arthur G. Weinberg, Depts. of Ped. and Pathology, Univ. of Texas Southwestern Med. Sch., Dallas. (p. 121)

17. 3:55 IN VITRO STUDIES ON THE ROLE OF CELL MEDIATED IMMUNITY IN HOST RESISTANCE TO VENEZUELAN EQUINE ENCEPHALOMYELITIS (VEE) VIRAL INFECTION IN MICE. William H. Adler and Stanley Rabinowitz, U. S. Army Med. Res. Inst. of Infect. Dis. (p. 122)

18. 4:15 GENETIC STUDIES OF THE ANTIBODY RESPONSE TO TYPE-III PNEUMOCOCCAL POLY-SACCHARIDE USING A STRAIN OF MICE WITH HYPOGAMMAGLOBULINEMIA-M. David R. Barthold, Diana F. Amsbaugh, Philip W. Stashak, Richard M. Asofsky and Phillip J. Baker, (Intr. by Robert McAllister), Lab. Micro. Immun., NIAID, NIH. (p. 122)

19. 4:35 IgA BEARING B-LYMPHOCYTES IN PATIENTS WITH DEFICIENCY OF CIRCULATING IgA. A. R. Lawton, S. A. Royal, K. S. Self and M. D. Cooper, Depts. of Ped. and Microbiology, Univ. of Alabama in Birmingham, Birmingham. (p. 122)

20. 4:55 ANAPHYLAXIS-LIKE REACTIONS TO CORTICOSTEROID THERAPY. Louis M. Mendelson, Eli O. Meltzer and Robert N. Hamburger, Univ. of Cali., San Diego, Dept. of Ped., La Jolla. (p. 122)

INFECTIOUS DISEASE

FIRST SESSION

Richard-Arlington Room

Moderator: David H. Carver

1. 9:00 ADENINE ARABINOSIDE (ARA-A) TREATMENT OF SEVERE POX AND HER ETIC INFECTIONS OF MAN. Lawrence T. Ch'ien, John W. Benton, Robert A. Buchanan and Charles A. Alford, Univ. of Ala. Sch. of Med., Dept. of Ped., Birmingham, and Parke-Davis and Co., Ann Arbor. (p. 124)

2. 9:20 EXPERIMENTAL ANTIVIRAL CHEMOTHERAPY FOR DISSEMINATED HERPESVIRUS HOMINIS INFECTION IN MARMOSETS. C. T. Cho, K. K. Feng, D. W. Voth and C. Liu, Dept. of Ped. and Med., Univ. of Kansas Med. Cntr., Kansas City, Kansas. (p. 124)

3. 9:40 ELEVATED CSF VACCINIA ANTIBODIES IN MULTIPLE SCLEROSIS. C. Henry Kempe, Univ. of Colo. Sch. of Med., Dept. of Ped., Denver. (p. 124)

4. 10:00 GENTAMICIN: A NEW ENZYMOLOGIC ASSAY A D SOME PHARMACOKINETIC PARAMETERS IN CHILDREN. Paul S. Lietman, Arlene A. Forastiere, Alan E. Zuckerman and Herman M. Risemberg, The Johns Hopkins Univ. Sch. of Med., The Johns Hopkins Hosp. and the Baltimore City Hospitals, Depts. of Ped. and Pharmacology and Experimental Therapeutics, Baltimore. (p. 124)

5. 10:20 THE RATE OF BACTERIOLOGIC RESPONSE TO ANTIMICROBIAL THERAPY IN NEONATAL MENINGITIS. George H. McCracken, Jr., Dept. of Ped., Univ. of Texas Southwestern Med. Sch., Dallas. (p. 124)

- 10:40 Intermission -

6. 10:50 A PROSPECTIVE STUDY OF MATERNAL CYTOMEGALOVIRUS AND ITS EFFECT ON THE FETUS. George A. Nankervis, Frederick E. Cox, Mary L. Kumar and Eli Gold, Dept. of Ped., Case Western Res. Univ. Sch. of Med. at Cleveland Metropolitan Gen. Hosp., Cleveland. (p. 125)

7. 11:10 DISTRIBUTION AND CHARACTERIZATION OF HEPATITIS ASSOCIATED ANTIGEN (HAA), AND ANTI-HAA ANTIBODY IN HUMAN BODY FLIUDS. Pearay L. Ogra, Dept. of Ped., Sch. of Med., State Univ. of N. Y. at Buffalo, (Intr. by David T. Karzon). (p. 125)

8. 11:30 NURSERY EPIDEMIC CAUSED BY A NON-TYPABLE "GREY" COLONY VARIANT OF STAPHYLOCOCCUS AUREUS. Rajam Subramanyam, Sherwood L. Gorbach and Rosita S. Pildes, (Intr. by Ira Rosenthal), Abraham Lincoln Sch. of Med. of Univ. of Ill. Coll. of Med., and Cook County Hosp., Depts. of Ped. and Med., Chicago. (p. 125)

9. 11:50 ANTIBACTERIAL EFFECTIVENESS OF ROUTINE HANDWASHING. Katherine Sprunt, Grace A. Leidy and Winifred Redman, Columbia Coll. of Phys. and Surg., Dept. of Ped., N.Y.C. (p. 125)

10. 12:10 NEONATAL DEFICIENCY IN ENDOTOXIN INACTIVATION. Eugene Ainbender, Helen D. Zepp and Horace L. Hodes, The Mount Sinai Sch. of Med., Dept. of Ped., New York. (p. 125)

INFECTIOUS DISEASE

SECOND SESSION

Richmond-Arlington Room

Moderator: Hugh C. Dillon

11. 1:45 PREVENTION OF VARICELLA IN HIGH RISK CHILDREN WITH ZOSTER IMMUNE GLOBULIN. A. A. Gershon and P. A. Brunell, New York Univ. Sch. of Med., Dept. of Ped.(p. 125)

12. 2:00 SAFETY AND ANTIGENICITY OF TEMPERATURE SENSITIVE (TS) MUTANT RESPIRATORY SYNCYTIAL VIRUS VACCINE IN INFANTS AND CHILDREN. Robert H. Parrott, Hyun Wha Kim, Carl D. Brandt and Robert M. Chanock, Children's Hosp. of D. C., Georgetown Wash. Univ., Sch. of Med., Natl. Inst. of Allergy and Infectious Diseases, Beth. (p. 126)

13. 2:25 ATTACK RATES FOR HOSPITALIZED CROUP IN CHILDREN IN A MILITARY POPULATION. IMPORTANCE OF A2 INFLUENZA INFECTION. Jerry J. Eller, Vincent A. Fulginiti, Caniel C. Plunket, Otto F. Sieber, Jr. and Gordon Meiklejohn, Univ. of Colo. Med. Cntr., Denver. (p. 126)

14. 2:45 VACCINATION OF HEALTHY CHILDREN WITH CVI-78 AND CALF LYMPH SMALLPOX VACCINE. John M. Neff, Wendell C. Speers, Richard B. Wesley, Joel Goldstein, Frederick L. Ruben and Bernard Lourie, (Intr. by David H. Carver), Johns Hopkins, Dept. of Ped., Baltimore. (p. 126)

15. 3:05 PNEUMOCYSTIS CARINII PNEUMONITIS. Walter T. Hughes, Ho K. Kim, Sandor Feldman, Robert A. Price and Thomas P. Coburn, (Intr. by Donald Pinkel), Infectious Disease, Pathology and Radiology Services, St. Jude Children's Res. Hosp. and Univ. Tenn. Med. Units, Memphis. (p. 126)

- 3:25 Intermission -

16. 3:35 COUNTERCURRENT IMMUNOELECTROPHORESIS IN THE DIAGNOSIS OF SYSTEMIC DISEASES CAUSED BY HEMOPHILUS INFLUENZAE TYPE B. David L. Ingram and David H. Smith, Dept. of Ped., Harvard Med. Sch., Children's Hosp. Med. Cntr., Boston. (p. 126)

17. 3:55 CIRCULATING FIBRIN IN MENINGOCOCCEMIA. C. Thomas Kisker and Ruth Rush, (Intr. by Beatrice C. Lampkin), Dept. of Ped., Univ. Cincinnati and Children's Hosp. Res. Fndn., Cincinnati. (p. 126)

18. 4:15 UNEXPECTED HIGH FREQUENCY OF ANTIBODY TO M PNEUMONIAE IN YOUNG CHILDREN. Helmut Brunner, Walter D. James, Robert L. Horswood and Robert M. Chanock, Natl. Inst. of Health, Lab. of Infectious Diseases, Bethesda, Md. 20014; Children's Hosp. of D. C., Washington. (p. 127)

19. 4:35 TRANSIENT BACTEREMIA DURING DENTAL MANIPULATION. Frederic A. Berry, Catherine M. Russell, Sandra Yarbrough, Nelson Yarbrough, Martha A. Carpenter and J. Owen Hendley, Univ. of Va. Sch. of Med., Dept. of Ped., Charlottesville. (p. 127)

20. 4:55 TOTAL SERUM LIPIDS IN INFECTIOUS DISEASE. J. Dennis Pollack, Albert S. Klainer and Henry G. Cramblett, The Ohio State Univ., Coll. of Med., The Columbus Children's Hosp. and Univ. Hosps., Dept. of Med. Microbiology, Ped., and Med., Columbus. (p. 127)

METABOLISM

FIRST SESSION

Cotillion Room North

Moderator: Owen M. Rennert

1. 9:00 PYRUVATE CARBOXYLASE: TWO FORMS IN HUMAN LIVER. E. Delvin, J. L. Neal and C. R. Scriver, McGill Univ., Montreal Children's Hosp. Res. Institute, Montreal. (p. 132)

2. 9:20 THE ULTRASTRUCTURE AND LIPID COMPOSITION OF CULTURED SKIN FIBROBLASTS IN CHOLESTEROL ESTER STORAGE DISEASE. John C. Partin and William K. Schubert, The Children's Hosp. Res. Fndn., Cincinnati. (p. 133)

3. 9:40 THE MOLECULAR BASIS FOR ACHONDROPLASIA IN THE RABBIT. Gerald J. Bargman, Brude Mackler and Thomas H. Shepard, Univ. of Wash. Sch. of Med., Dept. of Ped., Seattle. (p. 133)

4. 10:00 CORRECTION OF IMPAIRED CHEMOTAXIS OF POLYMORPHONUCLEAR LEUKOCYTES (PMNs) FROM PATIENTS WITH DIABETES MELLITUS BY INCUBATION WITH TRIVALENT CHROMIUM IN VITRO. K. Michael Hambidge, Benjamin Martinez, Julia A. Jones, Constance E. Boyle, William E. Hathaway and Donough O'Brien, Dept. of Ped., Univ. of Colo. Med. Cntr., Denver. (p. 133)

5. 10:20 METHYLMALONYL-COA RACEMASE DEFECT: ANOTHER CAUSE OF METHYLMALONIC ACIDURIA. Ellen S. Kang, Philip H. Snodgrass and Park S. Gerald, Harvard Med. Sch., Child. Hosp. Med. Center, Dept. of Ped., and Peter Bent Brigham Hosp., Dept. of Med., Boston. (p. 133)

- 10:40 Intermission -

6. 10:50 HYPOPHOSPHATEMIC RICKETS SECONDARY TO A BENIGN REPARATIVE GRANULOMA OF THE RADIUS. James A. Pollack and John D. Crawford, Harvard Med. Sch., Mass. Gen. Hosp. Children's Service, Boston. (p. 133)

7. 11:10 HORMONAL MODIFICATION OF AMINO ACID TRANSPORT IN CULTURED HEPATOMA CELLS. William L. Risser and Thomas D. Gelehrter, (Intr. by Charles D. Cook), Yale Univ. Sch. of Med., Depts. of Ped. and Med., Div. of Med. Genetics, 333 Cedar Street, New Haven. (p. 133)

8. 11:30 CORRECTION OF THE α-GALACTOSIDASE DEFICIENCY IN FIBROBLASTS FROM PATIENTS WITH FABRY'S DISEASE. R. Matalon, G. Dawson and Y-T. Li, (Intr. by Albert Dorfman) Univ. of Chicago, Chicago, Ill. 60637 and Tulane Univ., Covington, La. (p. 134)

9. 11:50 PROPIONYL-CoA CARBOXYLASE DEFICIENCY (PROPIONICACIDEMIA): ANOTHER CAUSE OF HYPERAMMONEMIA. Richard D. Landes, Gordon B. Avery, Frank A. Walker and Y. Edward Hsia, Children's Hosp. of D. C., Dept. of Ped., George Wash. Univ., Wash., The Milwaukee Children's Hosp., Dept. of Ped., Milwaukee, and Yale Univ. Sch. of Med., Dept. of Med. and Ped., New Haven. (p. 134)

10. 12:10 DEFECTIVE ISOLEUCINE METABOLISM AS A CAUSE OF THE"KETOTIC HYPERGLYCINEMIA" SYNDROME. Richard E. Hillman, Ralph D. Feigin, Stanley M. Tennebaum and James P. Keating, Wash. Univ. Sch. of Med., St. Louis Children's Hosp., Dept. of Ped., St. Louis. (p. 134)

METABOLISM

SECOND SESSION

Cotillion Room North

Moderator: Y. E. Hsia

11. 1:45 CYSTATHIONINURIA ASSOCIATED WITH NEUROPLASTOMA. Paul Wong, Ira M. Rosenthal and Ralph Kathan, Chicago Med. Sch., Abraham Lincoln Sch. of Med. of the Univ. of Ill. Coll. of Med., Mount Sinai Hosp., Univ. of Ill. Hosp., Dept. of Ped., Chicago. (p. 134)

12. 2:00 COLLAGEN METABOLISM IN FIBROBLASTS FROM PATIENTS WITH OSTEOGENESIS IMPERFECTA. David M. Brown, Univ. of Minn. Coll. of Med., Depts. of Ped. and Lab. Med., Minneapolis. (p. 134)

13. 2:25 A HYPERKALEMIC, SALT-WASTING SYNDROME IN INFANCY. Amin Y. Barakat, Zoe L. Papadopoulou and Gilbert P. August, (Intr. by Wellington Hung), Children's Hosp., Washington, D.C. (p. 134)

14. 2:45 FAMILIAL IDIOPATHIC LACTIC ACIDOSIS. PETITE MUTANT DISEASE IN MAN? Anna Binkiewicz, Robert L. Jungas, Hilel Hochman and Boris Senior, Ped. Endocrine-Metabolic Service, Tufts-New England Med. Cntr. and Dept. of Biological Chem., Harvard Med. Sch., Boston. (p. 135)

15. 3:05 VITAMIN D DEPENDENCY WITH DIBASIC AMINOACIDURIA ASSOCIATED WITH ANTICONVULSANT THERAPY. Myron Genel, Peter H. Berman, Grant Morrow and Alfred M. Bongiovanni, Dept. of Ped., Yale Univ. Sch. of Med., Phila.; Children's Hosp. of Philadelphia, Pa. (p. 135)

- 3:25 Intermission -

16. 3:35 A NEW FORM OF HOMOCYSTINURIA DUE TO $N^{5,10}$ -METHYLENETETRAHYDROFOLATE REDUCTASE DEFICIENCY. Vivian E. Shih, Maria Z. Salam, S. Harvey Mudd, B. William Uhlendorf and Raymond D. Adams, Harvard Med. Sch., Dept. of Neuro.; Mass. Gen. Hosp., Joseph P. Kennedy, Jr. Mem. Lab., Neuro. Serv., Boston, NIMH, and NIH, Beth. (p. 135)

17. 3:55 HYPERGLYCINEMIA: IN VIVO COMPARISON OF NON-KETOTIC AND KETOTID (PROPIONIC ACIDEMIC) FORMS. II. VALINE RESPONSES IN NON-KETOTIC HYPERGLYCINEMIA. Harvey L. Levy, Robert N. Nishimura, Arlene M. Erickson and Stanislawa E. Janowska, Harvard Med. Sch., Dept. of Neuro., Mass. Gen. Hosp. Boston: E.K.S. Center for Men. Ret., Waltham. (p. 135)

18. 4:15 DETOTIC HYPOGLYCEMIA: A SYNDROME OF GLUCONEOGENIC SUBSTRATE DEFICIENCY. Mary A. Micke, Glenn T. Peake, R. Phillip Eaton and S. Scott Obenshain, (Intr. by Edward A. Mortimer, Jr.), Univ. of New Mexico Sch. of Med., Bernalillo County Med. Cntr., Depts. of Ped. and Med., Albuquerque. (p. 135)

4:35 STARVATION IN THE OFFSPTING OF HIGH-FAT DIET RATS: A MODEL FOR HYPOGLYCEMIA IN INFANTS OF DIABETIC MOTHERS. Raul A. Wapnir, J. Tyson Tildon and Marvin Cornblath, Univ. of Md. Sch. of Med., Dept. of Ped., Baltimore, Md. 21201 and Rosewood State Hosp., Owings Mills, Maryland. (p. 135)

4:55 AUTOREGULATION OF GLUCOSE PRODUCTION BY THE ISOLATED PERFUSED HUMAN FETAL LIVER. P. A. J. Adam, M. Kekomaki, E-L. Rahiala and A. L. Schwartz, Case Western Res. Univ. Sch. of Med. at Cleveland Metropolitan Gen. Hosp. and Univ. of Helsinki, Dept. of Ped. (p. 136)

NEONATOLOGY

FIRST SESSION

Sheraton Hall

Moderator: Frederick C. Battaglia

1. 9:00 TOTAL INTRAVENOUS NUTRITION IN LOW BIRTH WEIGHT INFANTS. John M. Driscoll, Jr., William C. Heird, John N. Schullinger, Robert D. Gongaware and Robert W. Winters, Depts. of Ped. and Surgery, Columbia Univ. Coll. of Phys. and Surgeons, New York. (p. 143)

2. 9:20 INTRAVENOUS SUPPLEMENTATION OF PURE L-AMINO ACIDS AND DEXTROSE IN LOW BIRTH WEIGHT INFANTS. Rajam Subramanyam, Gladys V. Cordero, Paul W. K. Wong and Rosita S. Pildes, Abraham Lincoln Sch. of Med. of Univ. of Ill. Coll. of Med., Chicago Med. Sch., Cook County and Mount Sinai Hospitals, Chicago. (p. 143)

3. 9:40 MECHANISM OF LATE FETAL BRADYCARDIA. L. Stanley James, H. O. Morishima, Edward Bowe, Wendell Niemann and Salha S. Daniel, Div. of Perinatology, Coll. of Phys. and Surgeons, Columbia Univ., New York. (p. 143)

4. 10:00 CONTROLLED TRIAL COMPARING AGAR, INTERMITTENT LIGHT AND CONTINUOUS LIGHT FOR MANAGEMENT OF NEONATAL HYPERBILIRUBINEMIA. H. M. Maurer, C. N. Shumway, D. Draper and A. Hossaimi, Med. Coll. of Va., Richmond, (Intr. by W. E. Laupus). (p. 143)

5. 10:20 THE DISPLACEMENT OF ALBUMIN-BOUND BILIRUBIN BY BENZOATE: A HAZARD OF THE USE OF DIAZEPAM IN NEWBORN INFANTS. Sanford N. Cohen and Lucy M. Fern, N. Y. Univ. Sch. of Med., Depts. of Ped. and Pharmacology and The Guttman Lab. for Human Pharmacology, New York. (p. 144)

- 10:40 Intermission -

6. 10:50 THE HEMODYNAMIC ASSESSMENT OF EXPERIMENTAL RESPIRATORY DISTRESS SYNDROME. Welton M. Gersony, Hisayo O. Morishima, Steve Kohl, Salha S. Daniel and L. Stanley James, Div. of Ped. Cardiology and Perinatology, Dept. of Ped., Coll. of Phys. and Surgeons, Columbia Univ., New York. (p. 144)

7. 11:10 SERUM TRYPSIN INHIBITOR LEVELS AND THE RESPIRATORY DISTRESS SYNDROME. Hugh E. Evans, Steven Keller and Ines Mandl, Columbia Univ. Coll. of Phys. and Surgeons, Dept. of Ped. and Obstetrics and Gynecology, New York. (p. 144)

8. 11:30 PROGNOSIS OF CHILDREN SURVIVING WITH THE AID OF MECHANICAL VENTILATION IN THE NEONATAL PERIOD. John D. Johnson, William J. R. Daily, Natalie C. Malachowski, Rose Grobstein and Philip Sunshine, Stanford Univ. Med. Cntr., Dept. of Ped., Stanford. (p. 144)

9. 11:50 SYSTEMIC HYPERTENSION FOLLOWING OCULAR ADMINISTRATION OF PHENYLEPHRINE TO THE NEONATE. Virginia Borromeo-McGrail, Joseph M. Bordiuk and Hans Keitel, (Intr. by Welton Gersony), St. Vincent's Hosp. and Med. Cntr., Dept. of Pediatrics, New York. (p. 144)

10. 12:10 EFFECTS OF PHOTOTHERAPY ON TOTAL BLOOD FLOW AND BLOOD FLOW IN THE SKIN AND MUSCLE. Paul Y. K. Wu, Woon H. Wong, Joan E. Hodgman and Norman E. Levan. (Intr. by Paul F. Wehrle), Depts. of Ped. and Dermatology, Los Angeles County-USC Med. Cntr., Los Angeles. (p. 144)

NEONATOLOGY

SECOND SESSION

Sheraton Hall

Moderator: Leo Stern

. 1:45 PERINATAL BILIRUBIN METABOLISM: EFFECTS OF HEMOLYSIS. John A. Kerner, David L. Gemes, Nancy H. Dawber and M. Michael Thaler, Dept. of Ped., Univ. of Calif., San Francisco. (p. 145)

. 2:00 BILIRUBIN BINDING CAPACITY IN HUMAN NEWBORN PLASMA. Joseph Krasner, Lewis J. Stern and Sumner J. Yaffe, Dept. of Ped., State Univ. of N. Y. at Buffalo, Sch. of Med., Children's Hosp. of Buffalo. (p. 145)

. 2:25 FACTORS AFFECTING PARATHORMONE RESPONSIVENESS AND THE ROLE OF HYPOMAGNESEMIA, URINARY CA LOSS AND HYPERPHOSPHATEMIA IN NEONATAL HYPOCALCEMIA (NHC) OF PREMATURITY. Reginald C. Tsang, Leonard I. Kleinman, Irwin J. Light and James M. Sutherland, Univ. of Cincinnati, Dept. of Ped., Cincinnati. (p. 145)

. 2:45 PLASMA PRESSOR ACTIVITY (PPA) DURING NEONATAL STRESS. Reuben B. Young, Dept. of Ped., Med. Coll. of Va., Richmond, Va. (Intr, by W. E. Laupus). (p. 145)

. 3:05 IMPAIRED OPSONIC ACTIVITY OF NEWBORN SERUM AS ASSESSED BY A QUANTITATIVE IODINATION PROCEDURE. Michael S. Kaplan and E. Richard Stiehm, Dept. of Ped., Univ. of Calif., Sch. of Med., Los Angeles. (p. 145)

- 3:25 Intermission -

. 3:35 CARDIOVASCULAR EFFECTS OF APNEA IN PREMATURE INFANTS. Bijan Siassi, John S. McDonald, E. Hon and Joan E. Hodgman, (Intr. by Paul F. Wehle), Depts. of Obstetrics and Gynecology and Ped., Los Angeles County-USC Med. Cntr. of Los Angeles. (p. 145)

. 3:55 LOWER DISCHARGE WEIGHT AND SHORTENED NURSERY STAY FOR LBW INFANTS. Robert G. Dillard and Sheldon B. Korones, (Intr. by J. N. Etteldorf), Dept. of Ped., Univ. of Tenn., Memphis. (p. 146)

. 4:15 THERAPEUTIC CONSEQUENCES OF PARTIAL TRANSFUSION IN SYMPTOMATIC POLYCYTHEMIC NEONATES. D. Gary Benfield, Ronald J. Lubbe and James M. Sutherland, Univ. of Cin. Coll. of Med., Dept. of Ped., Cincinnati. (p. 146)

. 4:35 SURFACTANT APPEARANCE AND SECRETION IN FETAL LAMB LUNG IN RESPONSE TO DEXAMETHASONE. Arnold C. G. Platzker, Joseph A. Kitterman, John A. Clements and William H. Tooley, Cardiovascular Res. Inst., Specialized Center of Research-Pulmonary, and Dept. of Ped., Univ. of Calif., San Francisco. (p. 146)

20. 4:55 ASSISTED VENTILATION IN THE TREATMENT OF HYALINE MEMBRANE DISEASE: THE USE OF CPAP WITH OR WITHOUT ASSISTED VENTILATION UTILIZING A SINGLE VENTILATOR SYSTEM. R. A. deLemos, G. W. McLauglin, H. W. Diserens and R. R. Kirby, (Intr. by M. J. Sweeney), Depts. of Ped. and Anesthesiology, Wilford HallnUSAF Med. Cntr., San Antonio Texas and the Dept. of Ped., Univ. of Texas Med. Sch. at San Antonio. (p. 146)

NEPHROLOGY

FIRST SESSION

Continental Room

Moderator: Alan M. Robson

1. 9:00 SERUM IgE LEVELS IN MINIMAL CHANGE NEPHROTIC SYNDROME. Louis M. Mendelson, Ted D. Groshong, Michael G. Bazaral, Bruce M. Tune, Stanley A. Mendoza and Robert N. Hamburger, Univ. of Calif., San Diego, Sch. of Med., Dept. of Ped., La Jolla, Calif. 92037, Stanford Univ., Sch. of Med., Dept. of Ped., Palo Alto, Calif. 94305, and Ped. Dept., Naval Hosp., San Diego. (p. 154)

2. 9:20 SERUM PROPERDIN AND 1A LEVELS IN GLOMERULONEPHRITIS. R. H. McLean, N. G. Westberg and A. F. Michael, Univ. of Minn., Dept. of Ped., Minneapolis.(p. 155)

3. 9:40 DEMONSTRATION OF SPONTANEOUS CHEMOTACTIC ACTIVITY IN HUMAN GLOMERULONEPHRITIS AND ITS RELATIONSHIP TO THE COMPLEMENT SYSTEM. Michael E. Norman and Michael E. Miller, Univ. of Pa., Sch. of Med., Dept of Ped., Philadelphia. (p. 155)

4. 10:00 THE ENHANCEMENT OF COMPENSATORY RENAL GROWTH BY ANTILYMPHOCYTE GLOBULIN. Baiba Ausinsch and George A. Richard, Dept. of Ped., Univ., Fla. Coll. of Med., Gainesville, (Intr. by W. A. Altemeier). (p. 155)

5. 10:20 INTEFRITY OF RENAL ACIDIFICATION MECHANISM IN POST-RENAL TRANSPLANT PATIENTS. James C. M. Chan, Carl M. Grushkin, Mohammad Malekzadeh, Ori Better and Richard N. Fine, (Intr. by George N. Donnell), Univ. of So. Calif. Sch. of Med., Child. Hosp. of Los Angeles, and Rambam Hosp., Haifa, Israel. (p. 155)

- 10:40 Intermission -

6. 10:50 GROWTH FOLLOWING RENAL TRANSPLANTATION: DAILY VS. ALTERNATE DAY STEROID THERAPY. Carol J. Wilson, Joel Kaye, Foljert O. Belzer, Samuel L. Kou tz and Donald E. Potter, (Intr. by Malcolm A. Holliday), Univ. of Calif., San Francisco and San Francisco Gen. Hosp., Dept. of Ped., San Francisco. (p. 155)

7. 11:10 ACCURATE MEASUREMENT OF GLOMERULAR FILTRATION RATE (GFR) USING A COMPUTERIZED CUMULATIVE INTEGRAL METHOD (CIM). R. Morrison Hurley, John D. Harries and Keith N. Drummond, McGill Univ. Montreal Children's Hosp. Res. Inst., Dept. of Nephrology, Montreal. (p. 155)

8. 11:30 MEASUREMENT OF RENAL FUNCTION WITHOUT URINE COLLECTION: EVALUATION OF THE CONSTANT INFUSION TECHNIQUE FOR DETERMINATION OF INULIN AND PAH CLEARANCES. Barbara R. Cole, Joseph Giangiacomo, Julie R. Ingelfinger and Alan M. Robson, Wash. Univ. Sch. of Med., St. Louis. (p. 156)

9. 11:50 RELATIONSHIPS BETWEEN PTH, cAMP AND RENAL TUBULAR REABSORPTION OF SOLUTES. F. Glorieux, R. McInnes and C. Scriver, McGill Univ., Montreal Children's Hosp. Res. Inst., Montreal. (p. 156)

10. 12:10 METABOLIC BASIS OF FUROSEMIDE INHIBITION OF RENAL SODIUM REABSORPTION. Takashi Yoshida and Jack Metcoff, Dept. of Ped., CMH, Univ. Oklahoma, Oklahoma City. (p. 156)

NEPHROLOGY

SECOND SESSION

Continental Room

Moderator: John E. Lewy

11. 1:45 RENAL RESPONSE TO ACID LOADING IN THE DEVELOPING LAMB FETUS, INTACT IN UTERO. Salha S. Daniel, Robert Baratz, Edward Bowe, Ming Yeh, Roger Lallemand, Allen I. Hyman and L. Stanley James, Div. of Perinatology, Coll. of Physicians and Surgeons, Columbia Univ., New York. (p. 156)

12. 2:00 RENIN-ANGIOTENSIN SYSTEN IN THE FETAL SHEEP. Fred G. Smith, Jr., Richard A. Bashore, Luciano Barajas and Andrei N. Lupu, Depts. of Ped. Ob-Gyn., Zoology and Physiology, UCLA Sch. of Med., Los Angeles. (p. 156)

13. 2:25 SUPERFICIAL NEPHRON AND TOTAL KIDNEY GLOMERULAR FILTRATION RATE DURING DEVELOPMENT. Adrian Spitzer and Matthias Brandis, (Intr. by Chester M. Edelmann, Jr.), Albert Einstein Coll. of Med., Dept. of Ped. and the Rose F. Kennedy Center, Bronx. (p. 156)

14. 2:45 RENAL HANDLING OF GLUCOSE IN THE DEVELOPING CANINE KIDNEY. Billy S. Arant, Jr., Martin A. Nash and Chester M. Edelmann, Jr., Albert Einstein Coll. of Med., Dept. of Ped., Bronx. (p. 157)

15. 3:05 THE EFFECTS OF STRESS ON INTRARENAL DISTRIBUTION OF BLOOD FLOW IN INFANT PRIMATES. Eddie S. Moore, Maurina B. Galvez, John B. Paton, David E. Fisher and Richard E. Behrman, Univ. of Ill. Coll. of Med., Dept. of Ped., Chicago.(p. 157)

- 3:25 Intermission -

16. 3:35 THE NATURAL HISTORY OF MEMBRANOUS NEPHROPATHY IN CHILDREN. Hermann Olbing, Boyce Bennett, Jay Bernstein, Adrian Spitzer and Ira Greifer, (Intr. by Chester M. Edelmann, Jr.), Albert Einstein Coll. of Med., Dept. of Ped, and Pathology, Bronx. (p. 157)

17. 3:55 FAMILIAL NEPHRITIS: GENETIC HETEROGENEITY AND PATHOLOGY. Donald Gribetz, Peter Hathaway, Jacob Churg, Leonard Kasen, Seymour Cohen and Lotte Strauss, Mount Sinai Sch. of Med., Depts. of Ped. and Path., New York. (p. 157)

18. 4:15 HEMOLYTIC-UREMIC SYNDROME: TEN YEARS EXPERIENCE WITH NON-HEPARINIZED PATIENTS. Bruce M. Tune, (Intr. by Robert O. Christiansen), Dept. of Ped., Stanford Univ. Sch. of Med., Stanford. (p. 157)

19. 4:35 RENAL TUBULAR TRANSPORT OF IMINOACIDS AND GLYCINE. Ingeborg Krieger, Child. Hosp. of Michigan, Detroit. (p. 157)

20. 4:55 CONGENITALLY SHORT URETEROVESICAL JUNCTION CAUSING PRIMARY REFLUX. A COMMON FAMILIAL AND HEREDITARY TRAIT. Robert H. Burger, F. F. Thompson Hosp., Dept of Surgery (Urology), Canandaigua, New York, (Intr. by Gilbert B. Forbes).(p. 158)

NEUROLOGY

Alexandria Room

Moderator: John F. Griffith

1. 1:45 NEUROTOXIC EFFECTS OF LEAD IN THE CHICK EMBRYO. Joseph Kochen and Asao Hirano, Albert Einstein Coll. of Med., Montefiore Hosp. and Med. Cntr., Depts. of Ped. and Path., New York, (Intr. by Laurence Finberg). (p. 161)

2. 2:00 INDEPENDENCE OF BLOOD AND BRAIN GLUCOSE LEVELS: DECREASED BRAIN GLUCOSE WITH ELEVATED PLASMA GLUCOSE. Jean Holowach Thurston, Maria Ikossi and Wendel R. Pierce, (Intr. by Philip R. Dodge), Wash. Univ. Sch. of Med., Dept. of Ped., St. Louis. (p. 161)

3. 2:25 THE ROLE OF HYPOXIA IN THE DEVELOPMENT OF NUCLEAR JAUNDICE IN BILIRUBIN ENCEPHALOPATHY. Arthur L. Rose, (Intr. by Henry Barnett), Albert Einstein Coll. of Med., Dept. of Neurol. and Ped., New York. (p. 162)

4. 2:45 RETARDATION OF BRAIN GROWTH BY NEONATAL SEIZURES. Claude G. Wasterlain, and Fred Plum, (Intr. by W. W. McCrory), Cornell Univ. Med. Coll., Dept. of Neurol., New York. (p. 162)

5. 3:05 THYMIDINE KINASE ACTIVITY IN CEREBROSPINAL FLIUD OF HERPESVIRUS HOMINIS INFECTED RABBITS. Milo D. Hilty, Donald C. Thomas, Ralph E. Haynes and Henry G. Cramblett, Ohio State Univ., Coll. of Med., Children's Hosp., Dept. of Ped., Columbus. (p. 162)

- 3:25 Intermission -

6. 3:35 DIFFUSE BRAIN DAMAGE, MICROCEPHALY, INTRACRANIAL CALCIFICATIONS AND "OWL EYE" INCLUSION BODIES ASSOCIATED WITH INTRAUTERINE INFECTION WITH HERPES SIMPLEX VIRUS, TYPE 1. Alfred L. Florman, Anne A. Gershon, Piers R. Blackett and Andre J. Nahmias, New York Univ. Sch. of Med. and Roosevelt Hosp., New York City and Emory Univ. Sch. of Med., Atlanta. (p. 162)

7. 3:55 ELECTROPHORETIC DEMONSTRATION OF THE ENZYME EFFECT IN METACHROMATIC LEUKO-DYSTROPHY. Mario C. Ratazzi, James S. Marks and Ronald G. Davidson, Dept. of Ped., Div. Hum. Genet., SUNYAB, Buffalo. (p. 162)

8. 4:15 MUCOSULFATIDOSIS: BIOCHEMICAL AND ULTRASTRUCTURAL OBSERVATIONS. George Hug, Shirley W. Soukup, William K. Schubert, Kevin Bove and Linda Walling, The Child. Hosp. Res. Fndn., Cincinnati. (p. 162)

9. 4:35 HOMOCYSTINURIA PRESENTING AS REVERSIBLE "SCHIZOPHRENIA." A NEW DEFECT IN METHIONINE METABOLISM WITH REDUCED METHYLENE-TETRAHYDROFOLATE-REDUCTASE ACTIVITY. J. M. Freeman, J. D. Finkelstein, S. H. Mudd and B. W. Uhlendorf, Johns Jopkins Univ. Sch. of Med. Depts. of Neurology and Ped., V.A. Hosp., Wash., D.C. and Natl. Inst. of Mental Health, and Div. of Biologic Standards, NIH. (p. 163)

10. 4:55 CEREBRAL VENTRICULAR FLUID PRESSURE RECORDINGS DURING DRUG THERAPY. Patricia W. Hayden, Univ. of Wash. Med. Sch., Seattle, (Intr. by David B. Shurtletf). (p. 163)

PULMONARY

Franklin Room

Moderator: Emile M. Scarpelli

1. 1:45 SCANNING ELECTRON MICROSCOPY OF THE MAMMALIAN RESPIRATORY TRACT. Martha F. Greenwood and Phillip Holland, Univ. of Ky. Med. Sch., Dept. of Pediatrics, Lexington. (p. 167)

2. 2:00 AN EVALUATION OF NIGHTLY MIST TENT THERAPY IN PATIENTS WITH CYSTIC FIBROSIS. Nora Chang, Henry Levison, Douglas Crozier, Bernard Reilly and Oswald Grosett, (Intr. by Andrew Sass-Kortsak), Dept. of Ped., Univ. of Toronto, Res. Inst., Hosp. for Sick Children, Toronto. (p. 167)

3. 2:25 CERUMEN AND CERUMINOUS GLANDS IN CYSTIC FIBROSIS. Louis Kopito, Aaron Brand-Auraban, Gordon F. Vawter and Harry Shwachman, Depts. of Ped. and Path., Harvard Med. Sch., The Children's Hosp. Med. Cntr., Boston. (p. 167)

4. 2:45 DEVELOPMENT OF PULMONARY FUNCTION IN LATE GESTATION, MEASUREMENTS IN PREMATURE INFANTS. Gerald Lacourt and George Polgar, Universite de Geneve, Dept. of Ped. (Switzerland) and Univ. of Pa., Sch. of Med., Depts. of Ped. and Physiology, Philadelphia. (p. 167)

5. 3:05 PHOSPHORYLCHOLINE-GLYCERIDE TRANSFERASE AND PHOSPHATIDYL METHYLTRANSFERASE OF HUMAN NEWBORN LUNG. Richard D. Zachman, (Intr. by Stanley N. Graven), Univ. of Wis., Dept. of Ped., Madison. (p. 167)

- 3:25 Intermission -

6. 3:35 BIOCHEMICAL ASPECTS OF PULMONARY OXYGEN TOXICITY. Werner N. Keidel, Louis Gluck and Marie V. Kulovich, Univ. of Calif., San Diego Sch. of Med., Dept. of Ped., Div. of Perinatal Med., La Jolla. (p. 168)

7. 3:55 TOXIC EFFECTS OF OXYGEN ON CULTURED HUMAN RESPIRATORY EPITHELIUM. Thomas F Boat, Jerome I. Kleinerman, Avroy A. Fanaroff and LeRoy W. Matthews, Case Western Reserve Univ. Sch. of Med., Depts. of Ped and Path., Cleveland. (p. 168)

8. 4:15 VITAL CAPACITY IN RESPIRATORY DISTRESS. A. N. Krauss, D. B. Klain, J. Soodalter and P. A. M. Auld, Dept. of Ped., Cornell Univ. Medical College, New York City. (p. 168)

9. 4:35 EFFECT OF CONSTANT NEGATIVE PRESSURE ON LUNG MECHANICS IN IDIOPATHID RESPIRATORY DISTRESS SYNDROME. Eduardo Bancalari, Otto Garcia and Mary J. Jesse, Univ. of Miami Sch. of Med., Dept. of Ped., Miami, (Intr. by W. W. Cleveland). (p. 168)

10. 4:55 PULMONARY FUNCTION DURING THE FIRST YEAR OF LIFE IN RECOVERING R.D.S. M. Heather Bryan, Michael J. Hardie and Paul R. Swyer, Dept. of Ped., Univ. of Toronto and The Res. Inst., The Hosp. for Sick Children, Toronto. (p. 168)

SOCIETY FOR PEDIATRIC RESEARCH SYMPOSIA

Friday, May 26, 1972

Cotillion Room

DEVELOPMENTAL PHARMACOLOGY: Current Research and Therapeutic Implications

CHAIRMAN: Bernard L. Mirkin

9:00	Introduction	Bernard Mirkin
9:05	Placental Transfer and Fetal Localization of Drugs	Bernard Mirkin
9:50	Metabolism of Drugs in the Placenta and Fetus	Mont Juchau
10:35	Pharmacokinetic Analysis of Drug Absorption and Elimination in Infants and Children	Gerhard Levy
11:30	Pharmacologically Induced Behavior Modification in Developing Organisms	Kenneth Moore

Bernard L. Mirkin, University of Minnesota, Minneapolis, Minnesota.

Mont R. Juchau, University of Washington, Seattle.

Gerhard Levy, State University of New York at Buffalo.

Kenneth Moore, Michigan State University, East Lansing.

Sheraton Hall

HUMAN GENETICS

CHAIRMAN: Charles R. Scriver

9:00	Introduction	Charles R. Scriver
9:05	Human Chromosome Abnormalities Revisited	Margery W. Shaw
9:35	Interpretation of Enzyme Defects in Man	Henry N. Kirkman
10:05	Experimental Mutagenesis in Cell Culture	John W. Littlefield
10:35	The Biochemical Approach to the Mucopolysaccharidoses. Prospects for Therapy.	Elizabeth F. Neufeld
11:05	The Segregation for Quantitative Traits in Man	C. C. Li
11:35	Application of Knowledge to the Control of Genetic Disease	Michael M. Kaback

Charles R. Scriver, Montreal Children's Hospital, Montreal.

Margery W. Shaw, M. D. Anderson Hospital, University of Texas, Houston.

Henry N. Kirkman, University of North Carolina Medical Center, Chapel Hill.

John W. Littlefield, Massachusetts General Hospital, Boston.

Elizabeth F. Neufeld, National Institutes of Health, Bethesda.

C. C. Li, University of Pittsburgh, Pittsburgh.

Michael M. Kaback, Johns Hopkins University, Baltimore.

Park Ballroom

RESEARCH APPROACHES TO THE DEVELOPING NERVOUS SYSTEM

CHAIRMAN: Guy M. McKhann

9:00	Introduction	Guy M. McKhann
9:05	Viruses and CNS Abnormalities	Richard T. Johnson
9:45	Brain Development and its Modification	Marcus Jacobson
10:25	Development of Lateralization of Function between Cerebral Hemispheres	Marcel Kinsbourne
11:05	INTERMISSION	
11:15	Mechanisms of Seizure Susceptibility in Immature Brain	Peter Huttenlocher
11:55	Effects of Nutrition on the Developing Nervous System	Guy M. McKhann

Guy M. McKhann, Johns Hopkins University, Baltimore.

Richard T. Johnson, Johns Hopkins University, Baltimore.

Marcus Jacobson, Johns Hopkins University, Baltimore.

Marcel Kinsbourne, Duke University, Durham.

Peter Huttenlocher, Yale University, New Haven.

SOCIETY FOR PEDIATRIC RESEARCH

PLENARY SESSION

Friday, May 26, 1972, 1:45 P.M.

Sheraton Hall

PRESIDENTIAL ADDRESS: Madison S. Spach

1. 2:00 THE GROWTH AND DEVELOPMENT OF NEWBORNS WITH KNOWN HEXACHLOROPHENE (HCP) LEVELS. M. Douglas Cunningham and Nicholas G. Tsoulos, Univ. of Calif., San Diego Sch. of Med., Dept. of Ped., Div. of Perinatal Med., La Jolla, and Dept. of Ped., Naval Hosp., San Diego, (Intr. by Louis Gluck). (p. 171)

2. 2:20 CELLULAR GROWTH CHANGES IN NEWBORN RATS EXPOSED TO PHOTOTHERAPY. Paul Y. K. Wu, Takashi Yoshida, Joan E. Hodgman and Bijan Siassi, (Intr. by Paul F. Wehrle), Dept. of Ped., LAC-USC Med. Cntr. and Univ. of Oklahoma School of Medicine. (p. 171)

3. 2:40 THE UTILIZATION OF MICROWAVE RADIATION IN DEVELOPMENTAL BIOLOGY RESEARCH. Robert L. Brent and Jack Wallace, Jefferson Med. Coll., Depts. of Ped. and Radiol., Philadelphia. (p. 171)

4. 3:00 INTRAUTERINE DIAGNOSIS OF SICKLE CELL ANEMIA AND THALASSEMIA. Yuet W. Kan, Andree M. Dozy, Blanche P. Alter, Fredric D. Frigoletto and David G. Nathan, Children's Hosp. Med. Cntr., Boston Hosp. for Women, and Harvard Med. School, Boston. (p. 171)

5. 3:30 RA27/3 RUBELLA VIRUS STRAIN: THE FINAL SOLUTION TO THE RUBELLA VACCINE PROBLEM? Stanley A. Plotkin, John D. Farquhar and Peary L. Ogra, Wistar Inst., Dept. of Ped., Univ. of Pa., and Dept. of Ped., State University of New York, Buffalo. (p. 172)

6. 3:50 IMPAIRMENT OF PYRUVATE METABOLISM IN PHENYLKETONURIA. M. R. Sutnick, W. D. Grover and M. S. Patel, (Intr. by V. H. Auerbach), Depts. of Ped. and Biochem. Temple Univ. Sch. of Med. and St. Christ. Hosp. Child., Philadelphia. (p. 172)

7. 4:10 DEVELOPMENT OF B-LYMPHOCYTES IN THE HUMAN FETUS. A. R. Lawton, K. S. Self, S. A. Royal and M. D. Cooper, Depts. of Ped. and Microbiology, Univ. of Alabama in Birmingham, Birmingham. (p. 172)

8. 4:30 BILE SALT METABOLISM IN NEWBORN INFANTS. J. B. Watkins, P. O. Klein, D. Ingall and R. Lester, (Intr. by R. Klein), Depts. of Med. and Ped., Boston Univ. Sch. of Med., Boston, and Argonne Nat. Lab., Argonne, Illinois. (p. 172)

9. 4:50 HYPOGLYCEMIA DUE TO FRUCTOSE-1,6-DIPHOSPHATASE DEFICIENCY AND THE TREATMENT OF TWO PATIENTS WITH FOLATE. H. L. Greene, Fred. B. Stifel and R. H. Herman, (Intr. by H. P. Chase), U.S. Army Med. Res. and Nutri. Lab., Denver, Colo. (p. 172)

COMBINED PLENARY SESSION

Ambulatory Pediatric Association; American Pediatric Society; Society for Pediatric Research

CLINICAL COMPETENCE OF CHILD HEALTH ASSOCIATES: COMPARISON OF HISTORY TAKING AND INTERPRETIVE SKILLS WITH THAT OF MEDICAL STUDENTS AND PEDIATRIC RESIDENTS. John E. Ott, John B. Moon, Pavel Machotka. Univ. of Colorado Med. Ctr., Colorado Gen.Hosp., Dept.of Ped., Denver.

Numerous studies have indicated the usefulness and patient acceptance of allied health professionals, but few attempts have been made to determine their competence. This study is one of the first attempts to use objective methods to evaluate and compare skills and performance of various types of health professionals. The ability of child health associate students (CHA) was compared with that of senior medical students (MS) and pediatric residents (PR) in: 1) taking an appropriate initial pediatric history; 2) deriving a clinical impression based on their medical history; 3) ordering relevant laboratory studies; and 4) interpreting their initial impressions to mother and the need for further tests.

Histories were audiotaped. Competence was determined by evaluating: 1) the number of questions relating to the chief complaint (bedwetting) asked by the three groups of health professionals (scores were 17.9 for CHAs, 16.9 for PRs, and 14 for MSs out of a possible 28); 2) the thoroughness in covering the basic aspects of a complete medical history (CHAs and PRs scored 50% higher than MSs); 3) the initial diagnostic impressions and their use of the laboratory (no significant difference among the groups); and 4) the quality of the explanations given to mother (generally adequate for all groups).

This study demonstrates the performance of child health associates in the areas of history taking and interpretation of findings is highly appropriate for clinical practice and is comparable to that of MSs and PRs and demonstrates that one aspect of clinical competence can be evaluated objectively.

THE USE OF PEDIATRIC PSYCHOLOGY PARAPROFESSIONALS IN DIAGNOSING AND PRESCRIBING FOR CHILDREN WITH LEARNING DISORDERS. James T. Heriot, Intr. by P. R. Nader, Univ. of Roch., Sch. of Med., Strong Mem. Hosp., Dept. of Ped., Rochester, N.Y.

The learning disabled child represents an important source of the pressure for pediatric service which is passed on to the psychologist for diagnosis and treatment. Administration of standard psychological tests, their preparation, proofing, and dissemination have traditionally consumed at least eight hours. This precludes the optimal use of the professional's time in counseling, consultation with other professionals and interpretation of results to schools and to other community agencies. The professional pediatric psychologist, then, must serve as data generator, data manager, data interpreter, and must implement some of the services required by his data. The Psychodiagnostic Laboratory (PL) was formed at the University of Rochester in 1969 to allow the professional to be a data manager and implementer. To accomplish this a "job ladder" for Psychodiagnostic Assistants (PA'S) was established. PA training takes four weeks. Three initial PA's have gone on to train eight more staff PA's and 15 volunteers. A computer system was installed to assist in many of the editing and printing requirements for report preparation. Pediatric acceptances of the PL's reports has ranged from 40% to 75% on 11 different dimensions with the bulk of pediatrician reaction being favorable. Cost to the consumer has been drastically reduced. The PA job ladders have led to career and educational advancement. Training, research and service have been provided in a broad variety of public and private settings for over 1200 patients in two years.

AN EVALUATION OF HOME CARE VERSUS HOSPITALIZATION TREATMENT OF BLEEDING *EPISODES IN HEMOPHILIC CHILDREN*. Hanna Strawczynski, M.D., Andrew Stachewitsch, M.D., Gert F. Morgenstern, M.D. and Marjorie E. Shaw, R.N. McGill University, Montreal Children's Hospital, Montreal, Canada.

Medical, economic and social aspects of home care versus hospitalization in treatment of bleeding hemophiliacs were assessed in a 2-year prospective study. 40 children, ages 2 to 16, living within a 15 mile radius of a pediatric teaching hospital, were classified according to the severity of disease and divided randomly into 2 groups. During the first year of study half the patients were hospitalized when bleeding was reported, the other half were treated by Home Care. During the second year groups changed assignments thus serving as their own control. Home care treatment was carried out by a nurse at home or school after initial medical assessment; 24-hour telephone service was available. Self-infusion was not possible in the majority for social or technical reasons.

Results show: 1) Great majority of bleedings do not require hospitalization. 2) No complications were noted. 3) While on Home Care approximately 35% more bleedings were reported and the time of reporting was significantly earlier; school attendance was significantly better. 4) Home Care was preferred to hospitalization by children and parents. 5) Home Care provided an excellent model for mutual teaching-learning experience for doctors,students, para-medical personnel, patients and families; also a new role for a nurse-practitioner. 6) Home Care was provided by: 1/4 time physician (counting all consultants' time), one full time nurse, 1/4 time social worker, 1/4 time secretary. Hospital days in the Home Care groups were 15% of those in the hospitalized groups.

EVALUATION OF A PROGRAM FOR SICKLE CELL SCREENING AND HEALTH EDUCATION. Lawrence D. Robinson, Jr., Cpt, MC, Samuel B. Hunter Maj, MC, John Greenlee, Cpt, ANC, McClain G. Garrett, LTC, MSC, and David G. Doane, LTC, MC. U.S. Patterson Army Hospital, Fort Monmouth, New Jersey 07703 (Intr.by Eugene Kaplan).

A program for sickle cell screening, genetic counseling, and health education has been initiated in a large military post for Army personnel and dependents. The program design provides related health education by group seminar prior to blood screening, and genetic counseling following screening for identified sickle cell trait individuals. The participants varied in socioeconomic background and age. In a continuous three month period of activity the program involved 1428 individuals in prescreen education, 951 accepted blood screening, 71 were identified as sickle trait, and 40 adults received genetic counseling. Our observations indicate, (1) the majority of the black population lacks prior knowledge of sickle cell disorders. (2) identification of sickle cell trait by screening evokes anxiety, confusion, or hostility in many individuals. (3) a program of health education and genetic counseling in support of mass sickle cell screening has a positive impact on a black population of varied socioeconomic background. (4) successful experience with the health education of a limited number of school age children suggests that similar programs are appropriate beginning with the secondary school grades. These findings may have significance in the optimal design of other mass screening programs for sickle cell hemoglobin.

CHILDHOOD LEAD POISONING: A THIRTY CITY NEIGHBORHOOD SURVEY. Roger S. Challop, Edward B. McCabe, U.S. Public Health Service, Cincinnati, Ohio and Cincinnati Childrens Hospital, Cincinnati, Ohio.

In the Spring of 1971 the Bureau of Community Environmental Management sought to conduct a series of neighborhood surveys in a number of cities throughout the country to assess the incidence of elevated blood lead levels in young children between the ages of 1-6 who lived in pre-1949 sub-standard housing. In addition to conducting the surveys in all sections of the country, this survey represented one of the first attempts to link the incidence of elevated blood lead levels with an environmental hazard for each child.

Arrangements were made to obtain capillary blood samples from 50 to 150 children between the ages of 1-6 who lived in high risk dwellings in each city. The blood lead analyses were performed by the anodic stripping voltammetry method. Every child who had a blood lead level of 40 ug/100 ml whole blood or more had a repeat venipuncture sample analyzed by anodic stripping as well as by atomic absorption spectroscopy.

The children who took part in the survey also had their houses tested for the presence of lead in the paint. Both exterior and interior painted surfaces of all houses were tested, using a portable X-ray flourescence analyzer.

In the first twenty cities that have been surveyed, 1622 children have been tested and 670 houses have been evaluated for the presence of lead-based paint. At least 5% of the entire sample have had blood lead values of 40 ug/100 ml whole blood or more on both the initial sampling, as well as the follow-up test. Of the 670 dwelling units tested, 81% had potentially hazardous amounts of lead present on at least one interior surface. If exterior surfaces were included (porch railings, etc.) over 95% of the dwelling units had potentially hazardous amounts of lead-based paint. The availability of potentially hazardous lead-based paint was found to be as prevalent in the South, mid-West, and West as it was in the East.

PEDIATRIC GROUP PRACTICE (PGP): AN EDUCATIONAL SIMULATION MODEL FOR HOUSE *OFFICERS*. B. Duncan, S. Barnett. Univ. Colo. Med. Ctr., Dept. of Ped., Denver.

Pediatric residency programs often fail to prepare graduates as primary care ambulatory physicians with knowledge and experience in the economic, administrative, sociologic, and continuing educational aspects of private practice. When reality replaces the illusion training programs have given to practice, too many physicians return to the security of that which they know.

In July 1970 the Pediatrics Clinic at the UCMC established a PGP to help prepare residents for private practice. The Group consists of 3 third-year residents, 3 pediatric nurse practitioners (PNP), health administration students, an RN, 2 faculty members, and a patient population of 500. Members of the Group have at least one-half day each week to see their own patients, and the 5 physicians rotate night and weekend call, simulating the continuity of private practice. The PGP gives the pediatric resident an opportunity to work at administrative organization and financial details of a practice with the health administration student; work with PNP's in a setting where each can define his respective role in health care delivery; implement his own ideas of health care in a financially protected environment; develop educational literature for patients; develop communication and education systems within the PGP; experience the educational and emotional rewards that come from a continuous doctor-patient relationship.

A questionnaire documented patient satisfaction and accessibility to their own doctors. A missed appointment rate of 10% in this clinic compares with a rate of 32% in the continuity clinics. Graduates of this program feel their experience in the PGP contributed much to prepare them for actual pediatric practice.

COMMUNITY CONTROL OF COMMUNITY HEALTH -- BEYOND THE RHETORIC, Merle C. Cunningham, Univ. of Roch. Sch. of Med., Intro by Barry Pless, Dept. Ped., Rochester, N.Y.

The research objective is to evaluate the differences in program administration and in program "effectiveness" between 5 community-controlled and 5 professionally controlled neighborhood health centers. This 11% sample of all federally-funded comprehensive health care programs was site-visited. Data was collected from interviews with policy and advisory board members and staff members, from observations at board meetings, and from review of annual reports, budgets and center records.

The study reveals few differences in the actual administration of the two types of programs. Community programs have non-physician directors whose responsibilities to a policy board of laymen are well-defined. Professional programs have physician-administrators and token community boards with ill-defined responsibilities. For most of the "effectiveness" parameters studied (appointment-keeping behavior, utilization, range of services, cost, continuity, physician turnover, quality of care), the study reveals no significant differences. Where differences do emerge, however, the findings show that community-controlled programs have more mechanisms of accountability, have services available more hours per week (62 vs. 54), have better after-hours coverage, have 40% greater physician productivity (pts. seen per physician per hour), and have 50% more program staff hired from the geographical area served by the program. Programs under professional control have larger staff and budget appropriations for research and training than programs under community control, and have larger and more active outreach components.

The conclusion is that, other than in the areas noted, there are no major differences in program "effectiveness" between neighborhood health centers under community control and those under professional control.

WHAT HAPPENS TO THE BABIES BORN TO ADOLESCENT MOTHERS? N. Bingol, D.Reininger, H.Rich, S. Iosub, E. Wasserman, Dept. of Ped., New York Med. Col., New York, New York.

Pregnancy in the adolescent has been studied extensively, but developmental assessment of the product of these pregnancies has been neglected.

In this study 107 babies born to 102 mothers, 54 Puerto Ricans (50.4%) and 53 Negro (49.6%) who were 17 years of age or under at delivery have been followed at least 52±2 weeks at which time their growth and development have been evaluated. During the first year, infants were seen at least 6 times and serial measurements of head, chest, length and weight were recorded. Eighteen infants (16.9%) had a head circumference below 2SD.

One hundred and one infants who were born to 100 mothers, with similar socio economic and educational background as the teenagers, who were 20 yrs. of age or older at the time of delivery (57.4% P.R. and 39.6% Negro, 3% White) were evaluated similarly as controls. Only 6 infants (5.9%) had head circumferences below 2SD. The difference is statistically significant ($p < 0.05$). The distribution of the measurement of head circumference for Negroes and Puerto Ricans were relatively similar. But while there is no significant difference in the head size of the offspring of Puerto Rican teenager and controls at 1 yr., there is a significant difference in the percentage of very small size in the products of Negro teenage pregnancies when compared to the infants born to control mothers ($p \simeq 0.05$).

The relationship between head size attained at 1 yr. to birth weight, gestation, maternal nutrition, body length and weight at 52±2 weeks were analyzed according to race and sex. No significant differences were found.

Arrest or slowing of head growth offers a poor prognosis for a child's development and abnormally small head has long been associated with mental deficiency. If one predicts the intelligence quotient attained in later years from the head size taken at one year as reported by several investigators, a significant increase in children who have subnormal intelligence is to be expected from the offspring of the Negro adolescent.

FAMILY STRESS, ILLNESS, AND USE OF HEALTH SERVICES. Klaus J. Roghmann and Robert J. Haggerty. Univ. of Rochester Sch. of Med. & Dent., Depts. of Ped. & Soc., Rochester, N. Y.

Family stress has been positively associated with illness in several studies of selected populations. The present study documents the prevalence of stress in a random sample of families with children, assesses how much illness is stress-related, and analyzes its effect on use of health services. Data on chronic and major stress were gathered by two household interviews. Data on short term and minor stress were collected on a 28-day health calendar. The random sample of 512 families with 2547 members covers 1% of the community's welfare families and 1/2% of its Blue Cross families. 71,316 person days are described in detail for minor events. Markov chains were used in order to identify and describe relations of episodes of short term stress, illness, and care. Most chronic stress situations, like poor housing, are strongly social class related. Most major stress events, such as death in the family, major accidents, divorces, etc., are relatively frequent in all income groups. Stress scores and illness (symptom lists) correlated with r=.16 to .25, medical contacts and stress scores r=.09 to .18, and illness and utilization correlated r=.13 to .42. Family stress is frequent (30%) and so are minor illness (25% of all mother days). Illness is 2.5 times as likely on days with stress than without. Over-all utilization is 50% more likely. Phone calls (+100%) and emergency room use (+150%) are most affected by stress presence, office visits very little (+5%). Whether pediatrics should be organized to cope with such crises and whether such intervention will result in less illness and more effective use of health services requires controlled trials.

REDUCING THE LITERAL AND HUMAN COST OF CHILD ABUSE: IMPACT OF A NEW HOSPITAL MANAGEMENT SYSTEM. Eli H. Newberger, Department of Medicine, Children's Hospital Medical Center, Boston, Massachusetts.

Social service personnel from one public and two voluntary agencies were integrated into a consultation group in an academic pediatric hospital, leading to a reduction in the actual cost of medical services and the rate of reinjury subsequent to the diagnosis of child abuse. In the 1969-1970 hospital year, 62 cases of child abuse were seen, of which 39 were hospitalized. The average hospital stay was 29 days; the average hospital cost $3,000.00. Total hospital costs for the 39 cases were $123,000.00, of which bed costs made up $95,000.00. Nearly all of this cost was paid by the Massachusetts Department of Public Welfare. There were at least three subsequent incidents of child abuse in these 39 cases, and there was one subsequent death; the reinjury rate was 10% for hospitalized cases.

In September, 1970, the Trauma X Group, an interdisciplinary, interagency consultation unit based in the hospital, was formed. Guidelines on the management of child abuse were circulated to the hospital professional staff. With formal consultation and continued surveilance after discharge by the Trauma X group, the following data were obtained for the 1970-71 hospital year. Of 86 cases, 60 were hospitalized. The average hospital stay was 17 days; the average hospital cost $2,500.00. Total hospital costs for the 60 cases was $150,000.00, of which bed costs made up $101,000.00. There was one incident of reinjury and no deaths subsequent to diagnosis in these 60 cases; the reinjury rate was 1.7%.

Outcome data analyzed by calculations of person-months at risk support the dollar-cost impression of effectiveness. Foster placement, furthermore, was infrequent and does not explain the differential impact of the Trauma X Group in the two hospital years.

The personal and political dynamics of forming such a unit in an academic hospital are reviewed in relation to traditional consultative practice and professional ethics.

AMERICAN PEDIATRIC SOCIETY

First Plenary Session

CURRENT APPROACHES AND OUTSTANDING DIFFICULTIES IN PROBLEMS OF DEVELOPMENTAL PHARMACOLOGY. Fabio Sereni, (Intr. by Warren E. Wheeler), Milano University Medical School, Department of Child Health, Milano, Italy.

If the ultimate goal of developmental pharmacology is the definition of correct drug use and dosages in children, we must admit that not much ground has been gained in the last ten years, and only pessimistic conclusions can be derived about the methods used by most investigators in this field.

In light of these premises, and of his own recent studies, the author gives a critical review touching upon the following specific points:

a) - the relevance of animal experiments in developmental pharmacology;
b) - the difficulties inherent in thorough pharmacokinetic studies in humans, and especially in infants and children, and the paucity of our knowledge in this field;
c) - the limited value of data obtained in healthy infants when applied to the sick.

ENZYME CHANGES IN LEUKOCYTES DURING PREGNANCY. J. Metcoff, T.Yoshida, J.W.Coffelt, Depts.Ped. & Biochem., U.Okla, Health Sci.Ctr., Children's Mem.Hosp., Okla.City, A.Bernal, A.Rosado, J.Urrusti, P.Yoshida, S.Frenk, & L.Velasco.Dept.Invest.Cient., Hosp. de Ped., Hosp.Ginec.-Obst. #2, Centro Medico Nacional, IMMS, Mexico, D.F.

Previously we reported that pyruvic kinase (PK) and adenylic kinase (AK) activites were reduced at term in mothers who delivered infants with fetal malnutrition. The ontogenetic pattern for these enzymes during pregnancy was unknown. In the present studies AK and PK activities of maternal leukocytes (ML) were found to rise significantly from the 32nd week of gestation to term in women who delivered normal babies. ADP and ATP contents of ML also increased during this period. DNA-dependent RNA polymerase activity (RNAp), an enzyme essential for protein synthesis, not only increased progressively after the 28th week, but the level attained was directly correlated with birth weight of the baby. Two kinetic orders of RNAp were found. The lower order of activity occurred in leukocytes of mothers who later delivered low birth weight babies. It appears that energy pathways and protein synthesis in ML during pregnancy may be an index of fetal growth.

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INSENSIBLE, SIGNIFICANT AMINO ACID LOSS IN INFANTILE DIARRHEA
Ghadimi, H., Abaci, F., and Jothianandan, D.
Department of Pediatrics, Downstate Medical Center, State University of New York and Methodist Hospital of Brooklyn

A 3-week-old infant with protracted diarrhea underwent parenteral alimentation for 3½ mos. Attempts to introduce oral feeding, even glucose and water, during this time triggered mild diarrhea. 24-hr stool taken in the course of two such diarrheal bouts contained 475 and 608 mg of total amino acids (a.a.) Two stool collections after recovery showed 107 and 140 mg a.a. Two additional 24-hr collections obtained from 2 infants with moderate acute diarrhea of 3 days' duration contained 1,397 and 1,498 mg of a.a. Stool from a comparable control contained only 327 mg. In contrast to control periods, no protein ingestion was allowed during diarrhea; the source of diarrheal a.a. was thus clearly endogenous. (The same applies to protein content of stool, measured separately.)

Diarrhea in early infancy not responding to conventional treatment for more than 2 weeks may be considered intractable. Extrapolation of our figures shows a possible loss of 22,500 mg of endogenous a.a. over a 2-week period in moderate diarrhea. The magnitude of such a loss is striking. It represents double the total serum protein of a 3-month infant, 200 times the free a.a. pool of plasma, about 50 times the free a.a. of liver. It is therefore postulated that protracted diarrhea of early infancy, regardless of cause, may become intractable when a.a. deficit becomes critical, impairing anabolic pathways and enzyme synthesis.

Significant a.a. and protein losses in diarrhea through the stool are probably due to rapid intestinal transit time, impaired absorption of exogenous protein and a.a., as well as impaired reabsorption (from digestive enzymes) of endogenous protein and a.a. Total parenteral alimentation can break this vicious cycle and result in recovery of the patient. Our own experience with 6 patients shows that while parenteral alimentation may be required for as long as 3½ mos, 2 to 3 weeks are generally sufficient to restore digestive function.

NUTRITIONAL IMPLICATIONS OF LACTOSE MALABSORPTION. David M. Paige, George G. Graham, The Johns Hopkins University, Baltimore, Maryland, and Instituto de Investigacion Nutricional, Lima, Peru.

The decreased ability to hydrolyze lactose with its resultant loss of carbohydrate and calories in major population groups is a problem receiving increased attention. Unanswered is whether this intolerance results in incomplete utilization of other nutrients in milk. Balance studies were carried out on 6 healthy subjects, 22 months to 6 years old: 4 were intolerant and 2 tolerant to a lactose load. On a sucrose-casein diet (75 cal/kg; 2 g of protein, 4 g of fat, and 8 g of disaccharide/kg/day), the values obtained in all subjects were consistent with anticipated results in a healthy population of children. The mean values were: 1) stool weight, 38 g/day; 2) stool fat, 3 g/day; 3) apparent nitrogen absorption, 93% of intake; and 4) apparent nitrogen retention, 15% of intake. When the subjects were changed to a lactose-casein diet, the mean values obtained in the lactose intolerant subjects were: 1) stool weight, 147 g/day; 2) stool fat, 5 g/day; 3) apparent nitrogen absorption, 83% of intake; and 4) apparent nitrogen retention, 5% of intake. In the tolerant subjects, the obtained values were consistent with the levels obtained on the sucrose-casein diet, except for nitrogen retention.

Increases in stool water, fat and nitrogen in lactose intolerant subjects suggest that additional nutritional implications may exist over and above lactose loss. (Supported in part by USPHS grant AM-9980-07.)

ACID-BASE PROPERTIES OF "HYPERALIMENTATION" SOLUTIONS. William C. Heird, Ralph B. Dell, and Robert W. Winters. Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, N.Y.

Metabolic acidosis has been observed in infants receiving total parenteral nutrition infusates containing mixtures of synthetic L-amino acids as their nitrogen source. These observations prompted a detailed study of the acid-base properties of all currently available nitrogen sources for such infusates. The physicochemical properties of commercially available fibrin and casein hydrolysates, as well as of both commercially available and experimental synthetic L-amino acid mixtures, were determined--i.e., pH, titratable acidity (TA), inorganic cation-anion patterns and net charge of amino acids and peptides at pH 7.4.

All preparations had a low pH (5.3-6.5). TA of the hydrolysates (32.7 - 50.0 mEq/l) was higher than that of the synthetic L-amino acid mixtures (10.2-11.4 mEq/l). Examination of the inorganic cation-anion pattern of the preparations revealed that, instead of the usual anion gap observed in the hydrolysate preparations, the synthetic L-amino acid mixtures contained a cation gap. In all such preparations, this cation gap, at pH 7.4, was accounted for by the net positive charges of arginine and lysine, both of which constitute a potential load of H^+, regardless of whether they are anabolized or catabolized. This H^+ load can be partially offset if metabolizable anions (acetate, glutamate, asparate) are also included in the amino acid mixture. The anion gaps of the protein hydrolysates are composed of small molecular weight peptides which are probably metabolizable. Titration of these peptides accounts for the high TA of the protein hydrolysates, whereas the lower TA of the synthetic L-amino acid mixtures is explained by titration of histidine and the preservative used in the preparations. To the extent that TA is due to titration of an acid containing a metabolizable anion, it is of no major relevance as regards the overall acid-base effects.

Such knowledge of physicochemical composition of any nitrogen source for parenteral alimentation represents an important factor in the design of an ideal amino acid mixture for use in parenteral nutrition.

CEREBROVASCULAR ACCIDENT (CVA) IN INFANTS AND CHILDREN WITH CYANOTIC CONGENITAL HEART DISEASE (CHD). Charlie Phornphutkul, Amnon Rosenthal, William Berenberg, Alexander S. Nadas. The Children's Hospital Medical Center, Harvard Medical School, Boston, Massachusetts.

CVAs, unrelated to surgery, brain abcess, or subacute bacterial endocarditis, remain a serious and dreaded complication in patients with cyanotic CHD. To determine which patients are most susceptible to CVA, we reviewed our experience with the last 25 consecutive cases. Twelve of the patients had tetralogy of Fallot, 11 D-transposition of the great arteries, and 2 L-transposition of the great arteries and pulmonic stenosis. The group consisted of 17 males and 8 females. The youngest patient was 5 months. Fourteen of 26 episodes occurred in children below 2 years and 18 in those under 4 years of age. The hemiplegia was right-sided in 15 patients, left-sided in 6, and bilateral in 4. It was precipitated by a febrile infection in 6 patients, cardiac catheterization in 2, and a hyperneic spell in 1. Four patients recovered completely and 18 had residual hemiplegia. A seizure disorder developed in 5 cases and mental retardation in 4. Three patients died (mortality=12%). At autopsy superior and saggital sinus thromboses were present in 2 and middle cerebral artery thrombosis in 1. CVA under 4 years of age was associated with hemoglobin of ≤18gm%, hematocrit of ≤58%, and arterial blood oxygen content of ≤17vol.%. By contrast, in older patients the hemoglobin was >18gm%, hematocrit >58%, and oxygen content >17vol.%. Mean arterial blood oxygen saturation for the group was 72.5%(range:56-58%). The data suggests that in patients with cyanotic CHD age 5 months to 4 years maintaining an oxygen content >17vol.% or a hemoglobin of 18gm% by medical or surgical therapy may prevent the occurrence of CVA. Since the cardiovascular malformations in most of the above patients are at present amenable to early surgical correction, an aggressive surgical approach may in the future reduce the incidence of this complication.

AMERICAN PEDIATRIC SOCIETY

Second Plenary Session

URBAN MEASLES IN THE VACCINE ERA; A CLINICAL, EPIDEMIOLOGIC AND SEROLOGIC STUDY. James D. Cherry, Ralph D. Feigin, Louis A. Lobes, Jr., Daniel R. Hinthorn, Penelope G. Shackelford, Richard H. Shirley, Robert D. Lins and Sung C. Choi. St. Louis Univ. and Washington Univ. Med. Sch., Dept. Ped., and St. Louis City Div. of Health.

A measles epidemic, during which 130 children were hospitalized and 6 died, occurred in St. Louis City and County during the winter and spring of 1970-71. From vaccine distribution data and public health surveys, it was estimated that ≥79% of children had either received measles vaccine or had natural disease prior to the epidemic. A questionnaire survey of 10,000 day care and elementary school children, with a 43% response, revealed a measles attack rate of 8.5% in unvaccinated children who had not had natural measles and a rate of 2.4% in children who had been vaccinated (vaccine efficacy 72%). The attack rate in children vaccinated after 1 yr of age was 1.7%, whereas it was 6.3% for children immunized during the 1st year of life. From the survey and census data, it was estimated that there were 10,000 cases of measles; 4400 occurred in vaccinated children. Measles attack rates in vaccinees did not vary significantly with time elapsed since immunization. Twenty-four cases of measles occurred in a school in which 89% of the children were immunized or had natural disease; 19 of these cases were vaccine failures. Of 94 vaccinated children with measles, 29 (31%) had no reduction in their acute serum measles HAI antibody titer with 2-mercaptoethanol treatment. This finding suggests clinical failure but immunologic recall; 8 of these children had mild "modified" illnesses. Twelve children had classic "atypical measles" but surprisingly 6 of these children had received only live virus vaccine. A serologic survey of 248 previously immunized children revealed 10% with HAI antibody titers of <5. Contrary to the reports of others, vaccine failure contributed significantly to the propagation of this epidemic. Although some vaccine failures were apparently associated with waning immunity, the significant majority were primary failures. The magnitude of the problem of vaccine failure has been underestimated in the past. Until it is considered and resolved, measles eradication in the U.S. will not be realized.

REYE'S SYNDROME AND FREE-FATTY ACID-INDUCED COMA. Doris A. Trauner, Ronald B. David, Gordon Madge, Robert E. Brown, and Peter Mamunes, Medical College of Virginia, Richmond, Virginia (Intr. by W. E. Laupus).

The purpose of this study was to observe the effect of short-chain fatty acids (SCFA) on clinical states of consciousness and electroencephalograms (EEG) and to note resultant pathologic changes on post-mortem examination using rabbits as subjects. Eight rabbits (four control and four test animals) were infused with a single injection of either 0.5 cc. of one molar sodium octanoate, pH 7.4 (test animals) or 0.5 cc of one molar sodium lactate, pH 7.4 (controls). EEG electrodes were placed on rabbits restrained and resting. At the conclusion of the experiment (30 minutes post-infusion) the animals were sacrificed. Within one to five minutes following injection, the treated rabbits lost consciousness and developed tachypnea with cyanosis. The EEG showed bursts of high amplitude 9-12 cps activity. Post-mortem light microscopic findings showed fat infiltration in the liver. No similar clinical, EEG, or pathologic findings were demonstrated in the controls with the exception of minimal fat accumulation in the liver of one animal.

The findings of this study confirm the observations of Walker, et al (J. Lab. Clin. Med., 76:569-583, 1970) and Tanaka, et al (Science, 175:69-71, 1972) with respect to the ability of short-chain fatty acids (independent of other metabolic abnormalities) to induce coma. The clinical similarity of Jamaican vomiting sickness and aflatoxin-induced Reye's syndrome to classical Reye's syndrome has been previously described (Reye, et al, Lancet, 2:749-752, 1963), (Bourgeois, et al, Am. J. Clin. Path., 56:558-571, 1971). The elevation of free-fatty acids in the former two disorders has only been recently recognized (Tanaka, et al, see above), (Bourgeois, et al, see above). The presence of clinical, electroencephalographic, and pathologic observations associated with exogenously administered SCFA in our experiment suggests an important role for free fatty acids in the pathophysiology of Reye's syndrome.

THE EFFECT OF CYCLOPHOSPHAMIDE IN CHILDHOOD NEPHROTIC SYNDROME. A REPORT FOR THE INTERNATIONAL STUDY OF KIDNEY DISEASE IN CHILDREN. Adrian Spitzer (intr. by Henry L. Barnett), A. Einstein Col. Med., Bronx, N.Y.

Several clinical studies, all but one uncontrolled, have assessed the efficacy of cyclophosphamide in inducing lasting remissions in children with the nephrotic syndrome who either fail to respond to usual steroid therapy or relapse frequently. The present trial, conducted in 24 clinics, is prospective and based on random allocation of patients to control and experimental groups. Twenty-six of 181 patients failed to respond to a standard course of prednisone (28 days daily, 60 mg/m^2; 28 days intermittent, 40 mg/m^2). The control group was treated with intermittent prednisone. The experimental group received leukopenic doses of cyclophosphamide (2-5 mg/kg) plus intermittent prednisone. Treatment of all patients was maintained for 90 days. Two of the 14 patients in the control group and 5 of the 12 patients in the experimental group cleared their urine of protein. The average time from initiation of therapy to response was 104 days for the control and 24 days for the experimental group. All the patients that eventually responded to either of the two treatment regimens had minimal changes or mild proliferative glomerulonephritis. Among the frequent relapsers, the 20 children in the control group received 180 days of intermittent prednisone. Twenty-two patients received cyclophosphamide alone for 42 days. Thirteen of the controls (65%) and only 7 of the experimental group (32%) have relapsed ($p<.05$). Half of the controls relapsed while on treatment; the overall relapse rate per patient month was 0.18. No patient in the experimental group relapsed on treatment; the relapse rate was significantly less, 0.07 ($p<.01$). It appears, therefore, that cyclophosphamide is superior to prednisone in inducing remission in patients who fail to respond to initial steroid therapy, but is ineffective in patients with different forms of progressive glomerular disease. In addition a short course of cyclophosphamide reduces significantly the incidence of relapse in steroid-responsive, frequently-relapsing patients.

A COMPARISON OF NORMOCOMPLEMENTEMIC AND HYPOCOMPLEMENTEMIC PATIENTS WITH ACUTE POST-STREPTOCOCCAL NEPHRITIS. C. Frederic Strife, A. James McAdams, Paul T. McEnery and Clark D. West, Department of Pediatrics, University of Cincinnati College of Medicine and Children's Hospital, Cincinnati.

Although normocomplementemic patients with acute post-streptococcal nephritis have been described, none of the available data show differences from hypocomplementemic patients other than in serum complement levels. To look for other differences 20 normocomplementemic patients have been compared with 162 who were hypocomplementemic. The difference in complement levels could not be explained by a delay in measurement of C3 levels in the normocomplementemic group. In the hypocomplementemic group 80% had an upper respiratory infection in the four weeks preceding onset and 16%, a skin infection whereas 90% of the normocomplementemic group had respiratory and 5% had skin infection. The ASO titer was elevated at 85% of the hypocomplementemic and 89% of the normocomplementemic patients. There was no significant difference in incidence of hypertension, anemia or elevated sedimentation rate. Renal biopsies of 9 normocomplementemic patients studied by light and fluorescence (labeled antibody to IgG, IgA, IgM and C3) microscopy could not be distinguished from biopsies of hypocomplementemic patients and preliminary study has shown no differences by electron microscopy. However, the incidence of mild chemical nephrotic syndrome was greater in the normocomplementemic group. Their serum albumin levels were significantly lower ($P=<0.01$) and serum cholesterol higher ($P=<0.05$) although the incidence of edema (weight loss of 4 lbs. or more) was greater in the hypocomplementemic group. In the normocomplementemics, serum albumin levels remained low for 2-3 weeks rising more slowly than in hypoalbuminemic patients in the hypocomplementemic group. This difference aside, the results suggest that the factor producing the glomerular lesion in acute nephritis is not related to the mechanism responsible for the hypocomplementemia.

HOW USEFUL ARE THE NEW CYTOGENETIC TECHNICS?
H.A. Lubs, L. Ewing and S. Merrick, University of Colorado Medical Center Denver, Colorado (Intr. by F. C. Battaglia)

This study was aimed at answering the following question: How many clinically significant cytogenetic abnormalities can be detected in an abnormal population if a battery of the currently available technics are used routinely? A series of 25 patients with mental retardation referred to the Kennedy Center were studied by several of these technics and compared to 25 normals. Homologues were identified in 10 cells per person by QM fluorescence. These cells were also stained with giemsa, measured with an X,Y digitizer and analyzed for significant between homologue differences. C banding was employed only in selected cases. Dual karyotypes were prepared routinely in 2 cells for detailed visual analysis of the banding pattern. Six abnormalities were found; only one would have been clearly detected without the new technics. In 4 of the patients a small but significant abnormality was found; in each case both a small arm length difference and small QM difference was observed. Quantitative studies were particularly valuable in determining the presence or absence of borderline length differences, and in one patient (in addition to the 4 described above) led to the detection of a small 6q+ abnormality which was not detected by any of the other studies. No instance of a banding difference between homologues without a difference in arm length was found. The following conclusions have been reached: 1) Homologue identification is essential for routine cytogenetic study, 2) A significant proportion of cytogenetic abnormalities were likely missed two years ago, and the number ascertained at present is probably proportional to the number and quality of the technics employed. Optimal cytogenetic study, therefore, includes the use of several technics.

INCREASED INCIDENCE OF DIABETES MELLITUS IN PATIENTS WITH HASHIMOTO'S THYROIDITIS. Orville C. Green and Robert J. Winter (Intr. by Wayne H. Borges). Northwestern Univ. Med. School, The Children's Memorial Hospital, Dep't. Pediatrics, Chicago

In the past four years in the Endocrine Clinic, 21 patients have been followed with the diagnosis of chronic thyroiditis. Four have developed juvenile diabetes mellitus at intervals from one month to three years after the diagnosis of thyroiditis. From the remaining 17 patients, nine were selected for study in the Clinical Research Center. An oral glucose tolerance test was performed on each patient with analysis of blood glucose and plasma insulin every 30 minutes for five hours. Thyroid status was re-evaluated at the time of study and all patients were euthyroid. One patient with a markedly abnormal glucose tolerance test progressed into ketotic diabetes mellitus during the project period and was evaluated twice; insulin resposiveness disappeared in the four month interval between tests; glucose/insulin ratios from the first test were predictive of diabetes mellitus. Two of the other seven patients demonstrated glucose intolerance and poor insulinogenic reserve as judged by 2-hour glucose values and glucose/insulin ratios. Of the remaining five patients studied, two had elevated 2-hour blood glucose values, but glucose/insulin ratios appeared normal. The increased incidence of thyroid dysfunction in patients with diabetes mellitus has been reported previously. These studies indicate that children with chronic thyroiditis are at an increased risk of developing diabetes mellitus when compared with the normal childhood population.

BEHAVIORAL SCIENCE

BEHAVIORAL AND DEMOGRAPHIC CHARACTERISTICS OF DRUG DEPENDENCY IN THE ADOLESCENT 16 AND UNDER

Robert A. Kramer, Univ. of Connecticut Sch. of Med., Dept. of Ped., Hartford, Connecticut. (Intr. by Milton Markowitz).

The syndrome of drug dependency in children 16 and under has characteristics which can be applied to therapeutic, rehabilitation, and preventative programs. The following data are derived from an analysis of 87 drug dependent adolescents ages 11-16 admitted to a pilot program at Univ. of Connecticut Hospital.

Heroin drug dependency manifests with the same level of social morbidity in the young adolescent as in adults, i.e. stealing, dealing and prostitution. The youngest prostitute in the group was 12. The youngest dealer was 13. The heroin dependent adolescent has comparable physical morbidity to adults.

Socio-cultural factors are related to the type of drug dependency observed. Innercity youth use heroin as the drug of choice, tend to reject other chemicals and rarely use more than one or two drugs. Suburban youth use hallucinogens, stimulants, depressives more than heroin and tend to use many drugs at the same time.

All patients in the study group were seeking help on a voluntary basis or under pressure of the juvenile court. In either case, the length of experience with drugs was over 6 months in 85%, over 1 year in 65% and over 2 years in 45%.

Motivation for seeking help included: fear, parental pressure, legal pressure, "mind messed up," bad trip or can't afford it. None objected to the drugs per se. Rather, behavioral patterns necessary to obtain drug or the persistent personality changes disturbed the patients most.

Intelligence levels as measured by the WISC indicate that these youth are above average in IQ although most were doing badly in school.

Proposals for treatment and rehabilitation programs based on these data will be presented.

THE EARLY DEVELOPMENT OF INFANTS OF HEROIN-ADDICTED MOTHERS. Geraldine S. Wilson, Murdina M. Desmond, and Willie M. Verniaud. Baylor College of Medicine, Harris County Hospital District, Department of Pediatrics, Houston.

The effect of maternal heroin use upon the infant during the immediate neonatal period and acute withdrawal phase has been extensively reported. However, little information on the subsequent course and development of such infants is available. This paper presents a study of early development in 28 infants of heroin-addicted mothers followed up to two years. Patients were divided into two subgroups on the basis of maternal pattern of drug abuse. Group A consists of 15 infants of chronic addicts continuing heroin use throughout pregnancy; the mothers of the 13 infants in Group B received multiple agents for attempted withdrawal during pregnancy. Five Group A infants (33%) and four Group B infants (40%) were undergrown at birth.

Infants were evaluated periodically during the first 24 months by Gesell developmental testing. The most prominent findings were a trend toward delay in adaptive behavior during the first 4-6 months followed by generally normal values, a discrepancy between gross and fine motor activity during the first year, and the presence of behavioral disturbances in 25% of the infants (Group A-5, B-2) who were seen after one year of age. These disturbances included hyperactivity (7), brief attention span (2), and violent temper outburst (2). Somatic growth was variable; weight at the last visit was below the 10th percentile for 25% of Group A and 50% of Group B infants. Half of each group showed length below the 10th percentile. It is concluded that although the majority of infants show normal development, maternal heroin and its associated adverse effects during pregnancy may continue to exert an unfavorable influence after the symptoms of acute withdrawal have subsided.

THE BLACK PREGNANT TEENAGER, WHAT BECOMES OF HER AND HER OFFSPRING? Rosalind Y. Ting, Monica H. Wang. The Children's Hospital of Philadelphia, Department of Pediatrics University of Pennsylvania.

Approximately 8,000 Black mothers were enrolled in the Collaborative Perinatal Study in Philadelphia. Of these 31% were 19 years or under and 4% were 15 years or under. A total of 191 of the latter were chosen for study who were unwed and primagravidas. These were matched with an equal number of primagravida unwed women between 20 and 24 years of age who had delivered infants of the same sex within the same 3 months period. Our data show that teenage mothers give birth to more female babies than male (56% to 44%). Their pre-pregnant weight is lighter, they gain more weight during pregnancy. Obstetric complications show only higher incidence of a prolonged 2nd stage labor (≥ 100 min.) Duration of prenatal care incidence of anemia, toxemia, caesarian section, premature delivery, complications of labor, show no significant difference between the two groups. The infants of the teenagers did not differ from those of the older women in the distribution of gestational age, birthweight, height, head circumference, incidence of abnormal Apgar Scores at 1 and 5", hematocrit and bilirubin levels. Physical growth up to 7 years of age is similar in the two groups as were the results of Psychological tests at 4 and 7 years. Among the socio environmental factors reviewed the only noticeable difference was that the teenage mother tended to break her follow up appointments and move more often and to have more children than mothers of the older group. In contrast to what has previously been reported, our data show that Black teenage mothers living in a low socio economic environment are not more liable to major obstetric hazards than a matched control group, nor do their children differ in growth and development from those of older mothers.

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MATERNAL BEHAVIOR ONE YEAR AFTER EXTENDED POST-PARTUM CONTACT. John Kennell, Richard Jerauld, Harriet Wolfe, David Chesler, Willie McAlpine, Nancy C. Kreger, Meredith Steffa, and Marshall Klaus. Case Western Reserve University School of Medicine, Department of Pediatrics, Cleveland, Ohio.

As reported to the Society last year, a study was undertaken to determine the consequences of present hospital practices for mothers and newborns. 28 primiparous women were randomly placed either in an Extended or Routine Contact group. The Routine group saw their babies briefly 6-12 hours after delivery and for 20-30 minutes every 4 hours for feeding. In addition to this usual practice the Extended Contact mothers were given their nude babies in bed for 1 hour during the first 3 hours and for 5 additional hours on each of the first 3 days. Observations during a physical examination, a standardized feeding, and an interval history one month after delivery revealed that the Extended Contact mothers showed significantly greater soothing and fondling behavior, eye-to-eye contact, and reluctance to leave their infants.

To examine if differences persist one year after birth, quantitative observations of these mothers and infants were made from sequences consisting of: an interview, a separation and reunion, a developmental test, a physical examination of the infant, and a feeding. Those Extended Contact mothers who returned to work or school were more preoccupied with their babies than Routine Contact mothers who returned to work or school ($p=.02$). During the physical examination Extended Contact mothers spent more time at the tableside assisting ($p<.05$) and soothing the infant when it cried ($p=.05$) and were more likely to kiss their babies. The observers and raters were unacquainted with the mothers and babies. It is surprising that measurable differences in maternal behavior remain 1 year after the addition of only 16 hours of extra physical contact in the first 3 days of life.

THE PSYCHOLOGICAL EFFECT OF SUMMER CAMP ON THE PERSONALITIES OF JUVENILE DIABETICS AND THEIR PARENTS. Ron McCraw*, Luther B. Travis, Warren F. Dodge and Harvey Bunce*. Departments of Pediatrics and Preventive Medicine, University of Texas Medical Branch, Galveston, Texas.

Children with diabetes mellitus (JD) have long been known to experience various emotional and psychological problems which directly affect their basic disease. Most studies have shown that they and their parents have increased manifest anxiety (MA) and low self-esteem (SE). Numerous articles attest to the merits of special summer camps for JD in altering some of these personality traits. Objective investigations of their value, however, are limited. This report describes a study designed to evaluate such a camp and its effect on several psychologic variables. The experimental group (JD-E) consisted of 35 children between the ages of 6 and 14 who were attending camp for the first time. They and their parents were interviewed in their home (by R.M.) prior to camp and given a battery of psychological tests (Children's Manifest Anxiety Scale, Coopersmith's Self-Esteem Test, Children's Report Parental Behavior Inventory, Taylor's Manifest Anxiety Scale, Porter's Parental Acceptance Scale, Family Goal Consensus Scale). All were then re-tested by the same examiner between three and eighteen weeks after conclusion of the camp. There were highly significant increases in the child's self-esteem ($p<0.001$) and in the mothers acceptance of the child and his disease state ($p< 0.05$); and a significant decrease in the child's manifest anxiety ($p< 0.01$). A control group of twenty-five diabetic children (JD-C) who had never attended camp and who were closely matched with the experimental group, were also tested, on two occasions, with the interval time being similar. The JD-E children showed a significantly increased self-esteem when compared to JD-C ($p< 0.05$) and the mothers acceptance of the disease state was greater in the former group ($p< 0.07$). On the other hand there was no statistical difference between the two groups in the manifest anxiety scale or in the parents self-esteem.

LONG-TERM FOLLOWUP ON KIDNEY TRANSPLANT PATIENTS AND THEIR FAMILIES. Barbara M. Korsch, James E. Gardner, Richard N. Fine, and Vida F. Negrete, Univ. of Southern California Sch. of Med., Dept. of Peds., Childrens Hosp. of Los Angeles.

Followup on 30 children 1-5 years after kidney transplant is presented to provide objective data on the controversy regarding financial, ethical and psychological aspects of kidney transplantation in childhood and to advance methodology for psychosocial study of sick children.

Thirty transplant recipients and their families were assessed by an interdisciplinary team utilizing a battery of tests for which data are available from populations of sick and well children. These include standardized interviews with child and family, activity lists, California Test of Personality, Sarason's Anxiety Scale, Self-Esteem Inventory and Draw a Person. Coding was designed for computer processing. Scores obtained by these tests were compared to global ratings by clinicians who overestimated the extent of rehabilitation in some children and their families. On the California Test of Personality the study group was not significantly different from a matched healthy control group of children ($p>.05$ on t test). Low scores were more frequent in social than in personal adjustment. Only 6 children were low in both, an additional 4 in social adjustment only. Self-esteem tended to be low compared to normal controls. Anxiety ratings were generally high. Long range effects on family equilibrium were: 3 increased cohesiveness; 7 sibling problems and 13 mild maternal depression. Temporary marital discord was mentioned in 11, but there were no separations or divorces. Overprotection was infrequently reported by parents or children and appropriate discipline including physical punishment was the rule. All except two attend appropriate schools. The greatest illness related remaining worry for child and parent was fear of kidney rejection, with emotional problems, obesity and finances ranking next. Future concerns focused on employment barriers.

DOUBLE BLIND CLINICAL EVALUATION OF THE ANOREXIC ACTIVITY OF MAZINDOL AS COMPARED TO A PLACEBO IN CHILDHOOD OBESITY. Platon J. Collipp, Raj K. Sharma, Joseph Thomas, Iraj Rezvani, John Strimas. Nassau County Medical Center, East Meadow, New York.

A double blind study comparing the safety and efficacy of Mazindol (42-548) 2 mg. tablet once a day and placebo in 153 obese adolescent patients was conducted. All patients received a fixed daily dose of one tablet, one hour before the noon meal for twelve weeks. Diet was prescribed initially with optimal caloric intake and patients were instructed to remain on this diet, but no additional pressure was exerted on patients to prevent consumption of additional food. Efficacy of the drug was measured in terms of weight loss and skin-fold measurements as listed below:

	Weight Loss	Skin-fold Loss in Triceps	Skin-fold Loss in Subscapular
Mazindol	-18.9 lbs.*	- 3.24 mm	- 2.84 mm
Placebo	-11.8 lbs.*	- 3.62 mm	- 2.81 mm

* $p<0.01$

There were no statistically or clinically significant differences observed between the two treatment groups in laboratory and physical parameters. 37% of the patients in Mazindol group (28/76) and 13% placebo group (10/76) reported adverse experiences. The side effects reported were drowsiness, weakness and nausea and were primarily limited to first six weeks of the therapy. This drug has less psychostimulant effect than amphetamines and could be useful in long-term treatment of childhood obesity.

ATTITUDES TOWARD HOSPITALS, PERCEIVED SEVERITY OF ILLNESS AND PHYSICIANS' ESTIMATES OF SEVERITY OF ILLNESS IN CYSTIC FIBROSIS (CF). Maarten S. Sibinga, C. Jack Friedman, Nancy H. Huang and Harry Markow. Dept. of Ped., Temple Univ. Sch. of Med. & St. Christopher's Hosp. for Child., Phila., Pa.

In illness situations, reality is often less important than the perception of the facts of illness by the patient and his family. Perception, as such, can give an indication of the way in which people will react.

This study was an attempt to determine the relationship between parental perception of the hospital as a positive opportunity or negative authority institution and the course of the illness. A 48 item rating scale was developed. In addition, ratings of the state of health of the patients with CF were obtained from fathers, from mothers and from the physician in charge of the patient. Several discrete variables were intercorrelated.

For fathers, there was a non-significant correlation between positive perception of the hospital and their rating of severity of illness of their child.

For mothers, however, the sicker they rated their child, the more negatively they rated the hospital. In contrast, there was no significant relationship between either fathers' or mothers' perceptions of the hospital and the ratings of the child's health by the physician. There was a non-significant correlation between the parents' ratings of the child's state of health and the rating of the physician. In addition, parental attitudes toward the hospital were unrelated to parental understanding of CF. Those parents who felt that the health of their child could be influenced by their own behavior and was not just determined by luck or chance tended also to see hospitalization as more positive. Finally, parents who regarded their physician as relatively more competent also had more positive attitudes towards the hospital.

Supported in part by the Children's Cystic Fibrosis Fund.

STUDENT HEALTH PROGRAM FOR MIGRANT FARM WORKERS AND RURAL POOR

S.E. Barnett and H.P. Chase, Univ. Colo. Med. Center, Denver, Colo.

For the past two summers health students (medical students, child health associates (CHA) have worked in a service and education program in rural Colorado caring for children from migrant farm labor families. The purpose of the program is to expose students to the organization and delivery of health care in a rural area of medical scarcity and to provide service to a needy population. The program has been a multi-dimensional coordinated effort of the UCMC, State Health Department (SHD), Colorado Migrant Council (CMC), and rural physicians and communities. The students functioned optimally, working through the CMC Head Start Centers as a team with SHD migrant nurses, migrant advocates, and local physician preceptors. Each student did an average of 44 screening exams (physical, visual, auditory, dental, plus hematocrit, U/A, tine test, throat culture) on Head Start children, saw 139 patients in evening and week-end clinics, made a mean of 96 home visits (average 9 persons/living unit), saw 60 children with local physician, and assisted in 41 instances of patient transportation. Total patient encounters/ student/summer were 352. Five rural hospitals have opened limited facilities to migrant families in the past two summers. Out of 14 students, one who has completed internship is working in a rural federally funded clinic, and two have changed their career plans toward rural practice. A fourth student (CHA) is serving as a consultant to the CMC Health Committee representing the allied health professions. This project suggests that health students can fill a needed role in the delivery of rural health care and that an educational experience during the formative years of their medical training can provide a stimulus in this area.

EPIDEMIOLOGY OF ELEVATED BLOOD LEAD LEVELS IN RURAL AND URBAN 1-5 YEAR OLDS

Carol Cohen*, Martha L. Lepow, Univ. of Connecticut Sch. of Med. (Ped. and med. student), Hartford, Connecticut.

Quantitative lead determinations were performed on venous blood samples from 230 rural 1-5 year olds attending well child clinics and 330 urban children of the same age attending the Univ. of Connecticut clinics. Ninety-one percent of the rural children were Caucasian, while 95% of the urban children were Black or Puerto Rican.

Demographic data were obtained for each rural child. Samples of paint and water were tested in houses where children had elevated levels in both groups.

Eight percent of the rural children had blood lead levels of 40 μgm-60 μgm but none higher than this level. Twenty-two percent of the urban children had levels $>40\,\mu$gm and $\frac{1}{2}$ of these were $>60\,\mu$gm. All the rural children with elevated blood lead levels lived in housing >25 years of age. Paint samples from these dwellings were found to contain from 5-50% lead on indoor and outdoor surfaces. All of the urban children with elevated levels are living or have recently lived in dwellings >25 years old.

The mean blood level among rural groups living in houses >25 years was significantly higher than in children living in newer housing regardless of socioeconomic status. It is concluded that presence of lead paint on accessible surfaces is the major factor in pediatric lead posioning and that this problem is not limited to urban ghetto areas.

THE USE OF A GRADED PROBLEM ORIENTED RECORD TO EVALUATE PEDIATRIC TEACHING

Carmi A. Margolis, William T. Stickley and T. Joseph Sheehan. (Intr. by C. D. Cook). Yale Univ. Sch. of Med., Dept. of Ped., New Haven, Case-Western Univ. Sch. of Med., Div. of Res. Med. Ed., Cleveland, and Univ. of Conn. Sch. of Med., Dept. of Res. Health Ed., Farmington, Connecticut

Three cognitive skills, data collection, chart recording, and problem solving, were chosen from ten skills felt by two pediatric faculties to be suitable instructional objectives for pediatric clerks. It was proposed that a student's facility with these skills could be measured by grading his problem oriented record (POR). The POR was divided into fourteen sections (Chief Complaint, Present Illness, etc.), each of which was graded for structure and completeness; maximum possible total score was 162 points. Eight full time faculty members at two institutions graded a single write-up with grades ranging from 110 to 119 points. In two observed workups there was a high correlation between observed data and data recorded in the POR. Six groups (A-F) of 9 to 16 students each, submitted 67 POR's; the mean score was 101.75 points (range 10 to 152 points). When the 14 sections of the graded POR's (GPOR) were correlated and reduced by a principal component analysis to uncover which independent sections might cluster together, 5 underlying variables emerged, and alone accounted for 72% of the total covariance. All groups were taught the same POR. Groups A and B were composed of students at the beginning and middle of a clerkship at institution 1 who had no teaching resident (TR) and who averaged 81.0 and 83.0 respectively. Groups C, D, and E included students at the beginning, middle and end of a clerkship at institution 2, who had a TR, and averaged 110.7, 129.0 and 129.9 respectively. F was a group of students at the middle of a clerkship at institution 2, who had no TR, and averaged 87.5. The GPOR can measure facility at data collection, recording, and problem solving as they are used in a real workup. A TR can improve student facility with the above three cognitive skills.

ATTACHMENT* BEHAVIOR IN INFANTS WITH DOWN'S SYNDROME

Leon Cytryn, M. D. (Intr. by Robert H. Parrott, M.D.)
Children's Hospital, Washington, D. C. and the Dept. of Child Health and Dev. (Psychiatry), George Washington University Medical School.

The onset of attachment behavior was studied in 76 infants with Down's syndrome. This investigation was carried out over a four year period as part of a larger study of personality development of children with mental retardation. The onset of attachment behavior characteristic of the first six months of life was only slightly delayed as compared with normal infants. However the attachment behavior normally ocurring in the second half of the first year of life did not begin until close to the end of the second year in about 85% of the sample. In the remainder, the onset of this behavior was only slightly delayed. The investigation of this sub-group revealed in each case an exaggerated maternal involvement with the baby due to exceptional life circumstances such as life threatening disease of the child, marital crisis or a strong feeling of guilt. The analysis of our findings throws light on the respective roles of intellectual functioning, maternal involvement and parental attitudes in the origin of human attachment patterns.

*Attachment is one of the terms commonly used in psychiatric and psychological literature to denote a number of species-characteristic behaviors, serving to bind the child to his mother.

BEHAVIORAL SCIENCE

Read by Title

A CONCEPTUAL MODEL OF THE CHILD WITH A PSYCHOSOMATIC PROBLEM.

L. Baker, S. Minuchin, L. Milman, R. Liebman and T. Todd. Children's Hospital of Philadelphia and Child Guidance Clinic.

Management of children with severe psychosomatic problems has been hampered by the lack of a conceptual model. We have developed the hypothesis that severe psychosomatic symptoms in a child are related to 3 major variables: 1) Family interactional characteristics which encourage organ choice; 2) Involvement of the child in parental conflict; and 3) Physiological vulnerability.

To test these hypotheses: 1) A standardized family task interview evaluates family interactional characteristics; 2) A standardized family stress interview allows for induction of parental conflict and assessment of the role of the index child in that conflict; and 3) Physiological vulnerability is evaluated by tests of autonomic nervous system reactivity in children with known target organ dysfunction (diabetes and asthma in our preliminary studies). Free fatty acid levels (FFA) are measured during the course of the stress interview. Psychological rating systems have been devised.

Eight families have been studied in a prospective manner. A prediction of the direction of the child's FFA during the recovery phase was based on psychological analysis of the role of the child within the family during the stress interview; there was an 8/8 correlation between predicted and actual direction of FFA. A direct test of the conceptual model was made by having raters who did not know the clinical diagnosis of the child evaluate the family task and the family stress interviews; based upon these scores, a prediction was then made as to whether the child would or would not be "psychosomatic". A 100% correlation between prediction and actual diagnosis was seen.

BEHAVIOR DISTURBANCES IN CHILDREN WITH DOWN'S SYNDROME

Leon Cytryn M.D. and Helen K. Rubin (Intr. by Robert H. Parrott M.D.)
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The stereotype of placidity, cheerfulness and relative absence of behavior disturbances in children with Down's syndrome has recently been challenged by several investigators who claim that these children carry a similar risk of behavior disturbances as the children with other forms of mental retardation. This controversy is complicated by the frequent use in such studies of biased samples, consisting of institutionalized patients or those referred to a psychiatric clinic. In this study an entire population of a private nursery school system for the mentally retarded (m.r.) (n=46; Down's syndrome - 21, other forms of m.r.-25) has been rated by the teaching staff on a 4 point scale on seven types of behavioral disturbances, commonly seen in m.r. children: hyperactivity, aggression, lack of cooperation, withdrawal, lack of relatedness, irritability and impulsivity. The speech development was similarly rated on a 4 point scale.

The children with other forms of m.r. showed significantly more disturbance than those with Down's syndrome on 4 of the 7 variables: withdrawal ($p<0.01$), lack of relatedness ($p<0.05$), impulsivity ($p<0.01$) and irritability ($p<0.02$).

These differences may be due to constitutional factors, social learning patterns or a combination of the two.

TEACHING OBJECTIVES OF A PEDIATRIC CURRICULUM FOR A DEVELOPING COUNTRY. Donald A. Hillman, Elizabeth S. Hillman and Alan Ross, McGill Univ. - Montreal Children's Hosp. and Univ. of Nairobi, Kenya.

Since 1968, 8 members of the department of pediatrics, McGill University and 4 residents have developed a pediatric curriculum for a new medical school in Kenya. The African students receive their pediatric training following 2 years pre-clinical instruction and a year of systems-oriented clinical training with minimal pediatric content. It was necessary to develop a program that could readily be applied by a series of different teachers, to ascertain the skills and attitudes not taught in the clinical "systems teaching" and to teach intelligent problem solving and quality pediatric care in the African scene. The students were pre-tested to determine the status of their pediatric and public health knowledge. The pediatric core curriculum was divided into ten major topics. A precise statement of the objectives in each topic was prepared. Each major topic became the basis for one or more student-presented seminars with the faculty providing resource assistance prior to seminars.

The establishment of the pediatric instructional objectives facilitated the integration with the programs in obstetrics and public health and served to encourage and orient the students reading and general interest during the pediatric training period. The structured presentation of core material requiring approximately an hour and a half daily was enthusiastically received by the students. For the teachers it provided the re-assurance that stated minimum instructional objectives were well covered. To augment teaching we made liberal use of films, slides and tapes prepared in Montreal. It was possible to give more personal attention to individual students who worked as clinical clerks on the wards and clinics of the hospital. The students were taken on field trips to community child care facilities and introduced to the functions of the paramedical personnel who provide most of the primary medical services in the country.

THE PARENTAL ESTIMATE OF DEVELOPMENT SCALE (PEDS) J.T. Heriot, Intr. by G. Forbes, Univ. of Rochester, Sch.of Med. and Dentistry, Strong Memorial Hosp., Dept. of Pediatrics, Rochester, N.Y.

A scale was developed at the Psychodiagnostic Lab., Univ. of Rochester, which asks parents to rate their children in four dimensions: mental age, intellectual level, occupational projection, and a projection of education level attainable. The parental estimates can be converted to mental ages and I.Q. equivalents for each of the above dimensions as well as averaged to yield a general I.Q. estimate. The PEDS can then be compared to the child's general level of functioning as well as to his specific strengths and weaknesses.

Contrary to general opinion, parents of children with potential learning disorders estimate their children's ability with remarkable accuracy. Their estimates correlate 0.83 with prorated I.Q. The PEDS is an invaluable tool for parent counseling and in terms of understanding parental expectations and attitudes towards their children. Both over and underestimates lead to useful counseling in-roads in helping parents to be more realistic concerning their children's capabilities. Furthermore, it gives the parent a feeling of contributing to and taking part in the diagnostic process.

Among the variables affecting accuracy of the PEDS are the presence of behavioral symptoms and neurological symptoms. There does not appear to be a relationship between accuracy of the PEDS and a number of demographic variables such as race, sex, and social-economic level.

PEDIATRIC ACCEPTANCE OF A PSYCHO-EDUCATIONAL SCREENING INSTRUMENT USING PARAPROFESSIONAL EXAMINERS AND COMPUTER SUPPORTED REPORT WRITING-J.T. Heriot, Intr. by S.B. Friedman, Univ. of Roch., Sch. of Med., Strong Mem. Hosp., Dept. of Pediatrics, Rochester, N.Y.

The vast majority of school children with learning disorders are deprived of adequate diagnostic services. A Psychodiagnostic Lab. (PL) has been formed to deal with manpower shortages, excessive time lags, and inordinate costs in the diagnosis of children with learning disorders. Sub-professionals are used as testing technicians, and a computer used to speed the process of report writing. Testing, report writing, and counseling take 3 hours or less (about 1/3 of the time required to perform standard psychological tests and prepare narrative reports). Such a program, to be viable, must be accepted by the professional community. All reports generated by the PL were therefore accompanied by a "Reader Acceptability Check List (RACL)." The RACL asked the referrer to compare the PL reports to standard psychological reports generated by Doctoral level examiners. The report reader was asked to make this comparison in terms of 11 different dimensions. Among these dimensions were "relevance," "specificity," "precision," and "success in identifying etiologic factors." 85% of the first 170 readers returned the RACL, the majority of whom (65%) were pediatricians. An average of 55% of the readers compared the PL report favorably on the 11 dimensions, ranging from 42% who thought the PL reports were less verbose to 75% who thought they were more meaningful. The acceptance of this approach in the professional community and the speed of testing and report processing would suggest application in a broad variety of proprietary and non-proprietary pediatric settings.

MECHANISM OF REVERSALS IN READING AND WRITING. Marcel Kinsbourne, Duke University Medical Center, Department of Pediatrics, Durham, North Carolina.

Beginning readers and older dyslexics commonly reverse letters they read and write. Do they fail to discriminate, remember, or attend to orientation of visual stimuli? In order to determine the locus of the orientation difficulty, kindergarteners were asked to identify one of two mirror image shapes in two ways: when both alternatives were presented on each trial (simultaneous discrimination); when only one alternative is shown at a given trial (successive discrimination). If the limitation in performance is at the level of discrimination or memory, the learning is faster under simultaneous presentation. However, successive presentation has the advantage of focussing attention on the relevant dimension, orientation. In the event, children learned faster in the successive paradigm. This supports an attentional model of reversals: they occur when childrens' attention is pre-empted by other aspects of visual stimuli, so that orientation is ignored. Similar results will be reported for older children with developmental delay in learning to read. Of visual processes basic to reading, defective retention of orientation best discriminated normals from developmentally delayed readers aged less than eight (though not older children). The model suggests how reversal tendency might be overcome.

EARLY DEVELOPMENT OF CHILDREN WITH ABNORMALITY OF THE SEX CHROMOSOMES

Gail Landy and Martha F. Leonard (Intr. by Albert J. Solnit), Yale University Child Study Ctr., New Haven

The development of 11 children discovered at birth to have chromosomal abnormalities without obvious clinical signs has been periodically assessed. These subjects were identified in a study by Lubs and Ruddle (Science 169: 495, 1970) by chromosomal studies of 4500 newborn infants delivered at Yale-New Haven Hospital during one year, 1967-8. One infant had an XO pattern, three XXX, four XXY, and three XYY. A control group was formed of infants with normal karyotypes born at about the same time. Developmental evaluations were performed at the age of 1-1 1/2 years and again at 2 - 2 1/2 years by two specialists in child development who had no knowledge of the karyotypes until the evaluations were completed. The parents also were not informed whether their child has a chromosomal abnormality.

Although the sample is small, the developmental trends are of interest. Only one child with a chromosomal abnormality was functioning in the retarded range, and two subjects had DQ's above 100 at the second evaluation. The mean DQ was 94 with a range of 72 to 119. Comparable data for the controls showed a mean of 107 and a range of 87 to 131. The most striking difference between the two groups was in language development. Although there was little difference at the first evaluation, by 2 1/2 years the language sector of the profile, on the basis of a quotient of 100 as average, showed a mean of 79 for the subjects and 114 for the controls. Since language development is especially vulnerable to many environmental as well as intrinsic influences, psychosocial as well as genetic factors must be considered in evaluation of these results. No consistent trends in personality development were observed in any of the groups. More prospective studies of this type are needed to establish the range of developmental potential of children with abnormalities of the sex chromosomes.

SERVICES DESIGNED TO FACILITATE THE COPING CAPACITY OF PARENTS WITH DOWN'S SYNDROME (D.S.) INFANTS, Jane Lawrence, Theodosia Myertholan, Gertrude Kohn, Eileen Rawnsley, Mary Ames, William J. Mellman, Children's Hosp. of Phila.

Since 1966 special social service and genetic counselling programs have been provided for parents of infants with D.S. Parents actively participated in an evaluation of the effectiveness of services as provided for 3 groups of parents exposed to different social service approaches: Gr. I: Parents of 10 infants with D.S. who were hospitalized for 2 weeks at birth as part of a research project. Frequent staff contacts were made with individual parents during the hospitalization, and follow-up contacts occurred thereafter at 6 month intervals, when these parents met as a group. Gr. II: 44 additional families of children with D.S. from ages newborn to 3 years, referred for genetic counselling over a 3 year period, were invited to join the meetings of Gr. I. Gr. III: 28 families of children with D.S. who were seen in a flexible program that included monthly group meetings during infancy as well as individual contacts with the social worker as indicated.

Gr. III was formed because of staff awareness that the results with Gr. II were unsatisfactory, in sharp contrast with the positive experience of Gr. I parents. To identify the components of the program responsible for this difference in results, a committee of parents was invited to assist the staff in devising a "family adjustment" questionnaire. 50 families were interviewed with the aid of this questionnaire: Gr. I - 6, Gr. II - 16, Gr. III - 28.

80% of interviewed families indicated that frequent early contacts following their child's birth were most valuable in promoting their ability to cope with the impact of the diagnosis of D.S. There was a strong desire by parents in Gr. I and II (19 of 22 interviewed) for continued contact with each other. The high dropout rate of Gr. II (30%) indicated the ineffectiveness was a consequence of the infrequent contacts that were offered. Those in Gr. III were equally divided in their preference for individual over group social service contact. This experience emphasized the need for a flexible program that provides both individual and group service for parents of children with a single diagnosis, best handled in a centralized community service.

CORRELATION OF DEVELOPMENT WITH TREATMENT OF METHYLMALONICACIDURIA. Martha F. Leonard and Y. Edward Hsia, Yale Univ. Child Study Center and Yale Univ. Sch. of Med., Depts. of Ped. and Med., Div. of Med. Genetics, New Haven,Conn.06510

Many inborn errors of amino acid metabolism are known to cause brain damage and developmental retardation. Such retardation has generally been irreversible.

Developmental evaluation in a patient with vitamin B_{12} dependent methylmalonicacidiuria, who had severe ketoacidosis in infancy, (Ped.46:497,1970) showed unequivocal evidence at the age of 10 months of retarded function in all sectors of development, with a DQ of 51. Treatment with a protein restricted diet and vitamin B_{12} injections protected him from ketoacidosis,and lowered his urinary methylmalonate production markedly. Concomitant with stabilization of his metabolic derangement, a steady and dramatic acceleration of his development has been demonstrated by serial evaluations, up to the average range (DQ 94) by the age of 2 years. On the only occasion subsequently when his developmental evaluation, at the age of 4 1/2, showed definite slowing in his rate of progress, his urine methylmalonate output had also increased 5 to 10 fold. This may indicate his brain development is still sensitive to excessive methylmalonate production despite freedom from recent attacks of ketoacidosis, so treatment is being intensified.

Careful and repeated developmental evaluations in this patient have therefore proven to be of clinical value in the management of this condition. Furthermore, since the delayed mental development in this condition has proven to be reversible, the pathogenesis of neurochemical damage here may prove to differ from the mechanisms in conditions such as phenylketonuria, in which retardation, once established, is not responsive to treatment.

A COMPUTER ALGORITHM FOR EVALUATING GROWTH AND DEVELOPMENT. Charles P. Schade, Carlos Vallbona, and Charles L. Moffet. Baylor College of Medicine, Department of Community Medicine, Houston, Texas.

A plan for supporting paramedical staff in the routine developmental screening of children in an out-patient well-child clinic is proposed. Physical parameters to be measured are head circumference, height and weight. A computer-selected subset of the Denver Developmental Screening Test (DDST) appropriate for the child's age will be used to evaluate neurological development. These data will be obtained repeatedly during the child's first five years and compared to the predictions of a mathematical model implemented on a digital computer.

The set of evaluative standards for these parameters are based on current pediatric practice, statistical observations, and the assumed characteristics of the population to be followed. Derived measurements, primarily percentile ranks, will be used to detect abnormal growth or development patterns. The ranking system has been extended to low birth weight children. These derived values include 1) percentiles for height, weight, and head circumference; 2) the value of the weight divided by the square of height; and 3) performance on the DDST. Detected deviations from the predicted normal values are then classified for further workup which will frequently be performed in part as a direct response to actions proposed by the computerized algorithm.

Validation of the screening program will be a retrospective process. The records of raw data, derived parameters, classifications, and proposed actions will be compared with clinical decisions and modifications to the evaluative standards within the program made as necessary.

THE DEVELOPMENTAL ROOTS OF RACISM Reginald S. Lourie, Introduced by Robert H. Parrott, Children's Hospital of D.C.

Racism has been described by some as the number one public health problem of this country. Available research and clinical observations confirm that its origins begin in the first year of life during the phase of stranger anxiety. Attitudes towards differences in color, hair, and social status are consolidated in the first three years as the child develops self-image, identifications and the first steps in value systems. These attitudes become intertwined with later stages in personality development, particularly those involving fears, and can thus be locked in place. Pediatricians can be of assistance in preventive approaches to racist concepts through awareness of the times in development when such distortions commonly occur and alertness to a parent's prejudices. Calling attention to these danger points is useful for motivated parents in both majority and minority segments of the population. It's "All in The Family."

A MULTIDISCIPLINE DIAGNOSIS OF FIRST GRADE STUDENTS IN A PUBLIC SCHOOL. Rita E. Scott, Olive J. Morgan, Allan Heffler, Joseph Rudolph, William Morrison and Valarie Ivey, (Intr. by Doris A. Howell), Medical College of Penn., Dept. of Ped., Philadelphia, Penn.

A first grade in an urban school was studied by a multidiscipline team representing pediatrics, neurology, psychology, psychiatry, audiology-speech, pathology and social work to determine the nature and extent of learning and/or adjustment problems in school. The population consisted of 94 children; 25 white boys, 31 white girls, 13 negro girls, and 25 negro boys. The average education of the white mothers was grade 11.4, the white fathers 11.5, the negro mothers 11.4, and the negro fathers 11.3. The income levels ranged from $2,700 to $20,000 annually. The examination included a pediatric evaluation. All children did not have each evaluation: 81 had neuro-development; 88 psychologicals; 74 audiologic and speech; 64 psychiatric and 73 social service evaluations. 42/81 of neuro-development evaluations were normal; 1/81 had cerebral palsy. 9/81 had poor motor coordination with associated perceptual deficits. 29/81 had anxiety. Of these 17/29 had perceptual deficits. The psychological evaluations revealed 55% of white and 27% of black children had IQ's over 110 with marked variability between verbal and performance quotient. 31% of white and 51% of negro children revealed perceptual inadequacy; 18 different types of maladaptive behavior were found. 16/74 or 21.6% had hearing defects; 36.5% had speech defects. The most frequent defect was interdental lisp. 16/64 had normal psychiatric evaluations; the remainder showed sufficient deviant psycho-development to be placed in a suspect or definite psychopathological group. According to social service evaluation 64% negroes and 58% whites had above marginal economic status. 0/73 had "maximum" parental emotional support, 12% had "moderate" and 88% "minimal". Many questions were implied as a result of this study. Why the large percentage of perceptual deficits? Is it due to lack of experience, social factors, emotional stress, maturational lag, mothering patterns? How can it be prevented, identified and programmed?

THE FOSTER GRANDPARENT PROGRAM IN A CITY HOSPITAL-A 6 YEAR APPRAISAL. Elizabeth M. Mazyck (Intr. by Richard W. Blumberg). Emory Univ. Sch. Med., Grady Mem. Hosp., Dept. Ped., Atlanta, Ga.

The Older Americans Act of 1965 established a Foster Grandparents Program in which low-income persons over 60 years could be paid to work 20 hours a week with disadvantaged children, primarily performing such tasks as bathing, feeding, and "mothering" children in an institutional setting. Since this act was passed, 67 such programs in 40 states and Puerto Rico have been instituted; the program at Grady Memorial Hospital was begun in 1966 and now includes approximately 20 foster grandparents for a 94-bed pediatric ward. Numerous reports have dealt with the benefit of this program to the aged. The purpose of this report is to evaluate the degree to which the foster grandparent aids in the care of the child in a large metropolitan hospital.

Questionnaires were administered to the pediatric house staff members to determine their evaluation of the Foster Grandparent Program. 73% of the house staff considered the program "very helpful" in patient care, and 27% considered it "moderately helpful". Interviews were conducted with all R.N.'s and L.P.N.'s on pediatric patient care areas and it was estimated that the performance of child care duties by the foster grandparents allowed the nursing personnel to allot 30% more of their working day to directive, administrative, and instructive duties. Both nurses and house staff considered the foster grandparents most valuable in dealing with chronically ill children, emotionally deprived children, and children with failure to thrive.

THE NEW PRIMARY PEDIATRICIAN (A PHYSICIAN WHO IS NOT A DOCTOR) AND IMPLICATIONS FOR EDUCATION IN THE HEALTH PROFESSIONS. Henry K. Silver. Univ. of Colorado Sch. of Med., Dept. of Ped., Denver

There is a continuing need for additional primary physicians capable of delivering high quality comprehensive primary health care to children. I hold that the single most effective way of meeting this need is through the preparation and utilization of a new type of allied health professional--an individual capable of functioning as a primary pediatrician, but one who would not require a doctorate of medicine to do so.

The prototype of the new primary pediatrician is the child health associate, a graduate of the program the author originally developed, who is prepared for practice in as little as five years after graduation from high school. The child health associate has the knowledge, clinical proficiency, competence, and problem-solving and decision-making capabilities to assume a direct, responsible, and independent role in the diagnosis, prevention, and treatment of patients in sickness and in health. Presently, he only lacks one essential ingredient necessary to function optimally as an independent primary physician--his acceptance in the role of a non-doctor physician by others and by himself.

I recommend: 1) that many of the functions and activities performed by doctors in an ambulatory practice setting be delegated to this new category of health professional; 2) that the course of study for most doctors of medicine should be intensified and remain at its present length rather than decreased; 3) that new primary pediatricians, as well as other primary physicians and health workers of all types ideally should be prepared in a unified college of health sciences; and 4) that the preparation of doctor physicians should place greater emphasis on their being health planners as well as skilled diagnosticians and therapists.

AVERSIVE TREATMENT OF INFANT RUMINATION. Richard P. Toister, Colin J. Condron, Lee M. Worley, and David Arthur. (Intr. by William W. Cleveland) Dept. of Peds., Univ. of Miami Sch. of Med., Miami, Florida and Univ. of London, London, England.

The problem of infant rumination has seen various prescriptions for therapeutic intervention. While the etiology is unclear and may vary for individual cases, the characteristics of the syndrome are clearcut and consistent in all reports. Previous treatment has included: thickening of feeds; anti-emetics; sedation; sitting the infant in an upright position after feeds; and the fostering of a "warm" caretaker-infant relationship.

An eight month old infant hospitalized for four weeks was unsuccessfully treated by thickened feeds; upright positioning, parental counseling and frequent handling and attention by nursing staff. At this point aversive faradic therapy was instituted following a procedure reported by Lang (1969). There was an immediate suppression of rumination and a weight gain of almost two pounds in five days. The condition was completely eliminated in six days at which time the child was discharged from the hospital. In addition, a decrease in "hospitalisms" such as stereotyped rocking and motor movements was observed with a concomitent increase in social behavior and vocalizations.

The infant was followed by home and clinic visits for 6 months and social and motor development was normal. No detrimental effects of the therapy were noted. This study underscores the use of aversive therapy as an effective treatment in certain cases of maladaptive physiological conditions in infants and children.

DEVELOPMENTAL BIOLOGY

First Session

COMPONENTS OF THE "CRITICAL" WEIGHT AT MENARCHE AND AT INITIATION OF THE ADOLESCENT SPURT: ESTIMATED TOTAL WATER (TW), LEAN BODY MASS(LBM) AND FAT, Rose E.Frisch, Roger Revelle, and Sole Cook. Harvard Center for Population Studies. (Intr. byT.E.Cone, Jr.)

Estimations were made for each of 181 girls whose heights and weights at each event were determined from longitudinal data of 3 growth studies. Mean TW at menarche, estimated by the regression equations of Mellits and Cheek (1970) and F.D. Moore et al. (1963) was 26.2 ± .18, S. D. 2.4 liters, and 26.8 ± .16, S.D. 2.2 liters, respectively. Mean LBM at menarche was 36.3 ± .29 kg, S.D. 3.3 kg; mean fat, 11.5 ± .29 kg, S.D. 3.9 kg. At menarche (mean age 12.9 ± .09 years) early and late maturers have the same amount of TW, but late maturers have a slight but significant ($p<.02$) increase in percent TW/Body Wt. since they have about 1.3 kg less fat than early maturers. During the interval from spurt initiation to menarche both early and late menarcheal girls gained about 8 liters of TW, 11kg of LBM and 6 kg of fat. This is a 120% increase in fat (mean fat was 5.1 ± .17 kg at spurt initiation) and a 44% increase in LBM (mean LBM was 25.6 ± .18 kg at initiation), a change in ratio of fat/LBM from 1:5 at spurt initiation to 1 : 3 at menarche. Mean percent TW/Body Wt decreases from 60.4 ± .28, S.D. 3.8% at spurt initiation to 55.1 ± .27, S.D. 3.6%, at menarche. The latter CV, 6.5%, is 55% less than that of the critical weight at menarche (47.8 ± .51, S.D. 6.9 kg; CV= 14.4%). The CV of mean TW or LBM at menarche (9.2%) is 35% less than that of mean weight at menarche. Both reductions in variability are consistent with the hypothesis that the critical weight relates to a critical metabolic rate. Of 169 girls, 138 (82%) remained in the same percentiles of TW/Body Wt. from initiation of the spurt to menarche, compared to only 79 (47%) remaining in the same percentiles of weight from initiation to menarche, and 66 (39%) remaining in the same percentiles of TW from initiation to menarche.

IRON, NUTRITION AND GROWTH. Ray Hepner, Norma Maiden and Prasanna Nair, (Intr. by Marvin Cornblath) Sch.of Med.,Univ.of Md.Hospital,Dept.Ped.,Baltimore

More accurate data on iron (Fe) requirement for growth during infancy and childhood are needed. Others have shown that Fe content of the human fetus is a constant fraction of the fat free dry weight from conception to birth. From birth through 8 yrs., the body composition is constant, and each Kg of weight added requires 35 mgms Fe. Gorten and Hepner reported both Fe_{59} absorption and Fe utilization are proportionate functions of growth rate.

An 8% sample(862) of 10,775 Baltimore Inner City subjects registered in C&Y Project 606A, revealed a dietary pattern from birth through 8 yrs. characterized by adequate intakes of protein and calories (>85% ate>66% of the Recommended Daily Dietary Allowances (RDA) of the Nat. Research Council) but inadequate intake of Fe (>70% ate <66% RDA). Each of the registered subjects (10,775) had the following measurements of Fe nutrition: hem., hct., MCHC, calculated total body Fe, and body Fe concentration. The prevalence of Fe deficiency as defined by these parameters was greater during growth spurts (43% at 1 yr. and 8.4% at 5½ yrs.) than during slow growth periods (4% at 4 yrs. and 1.5% at 8 yrs.) and was greater in faster growing subjects (>90th%-ile) than in those <10th%ile (P= <0.01).

These data suggest that Fe requirement should be calculated from growth rates by age. The data reveal major differences from the current RDA. At 4 mos. of age, the requirement for growth alone is greater than the RDA (16 vs. 10mg/day), and at 8 mos. and thereafter, is 1/3 to 2/3 of the RDA. These differences explain the variations in prevalence of Fe deficiency anemia from those expected from intake as a % of the RDA.

Age (yrs.)	4/12	8/12	1½	4	5½	8
Intake Fe(mgms)	(9.2 ± 10.3)		(6.9 ± 5.25)		(6.0 ± 3.0)	(8.2 ± 3.0)
RDA (mgms)	10	15	15	10	10	10
Hem.<10gms.%	18%	30%	24%	4%	8%	3%
Calculated (assuming constant 10% absorption, and X 2 to reach final values for growth only)	16±2.7	11±2.7	5±1.3	4±1.3	6±2	5±2

TRIMETHADIONE INHIBITION OF DRUG METABOLISM; POSSIBLE ROLE IN TERATOGENESIS. A. B. Rifkind. Cornell University Medical College and the Rockefeller University, New York, N.Y. (Intro. by M. I. New)

Trimethadione (TMD) has recently been implicated as a human teratogen. We studied the effect of TMD and its metabolite dimethadione (DMO), on developmental morphology and hepatic drug metabolizing activity in chick embryos. When injected at 72 hours of development or earlier, both TMD and DMO caused dose related increases in the number of fetal resorptions and in the occurrence of gross congenital anomalies, particularly failure to close the abdominal wall. When injected in vivo in 17 day old chick embryos, TMD (3 mgm) caused 4 to 10 fold increases in the hepatic activity of delta aminolevulinic acid synthetase (ALAS) but inhibited cytochrome P-450 and aminopyrine demethylase by 30% and 75% respectively. Therefore, TMD stimulated ALAS and inhibited microsomal oxygenase activities. Anticonvulsant therapy frequently includes a combination of TMD and barbiturates. Barbiturates normally increase the activities of both ALAS and microsomal oxygenases. In embryos pretreated with TMD, seconal stimulation of ALAS was enhanced, while its stimulation of cytochrome P 450 and aminopyrine demethylase was blocked. Thus, by altering drug metabolism, TMD can alter the effect of a drug that is administered together with it. In addition to its effects on other drugs, TMD may also block its own metabolism. TMD is converted to DMO which circulates in humans for more than 3 weeks. By inhibiting microsomal oxygenase activity, TMD may prevent the further metabolism of DMO and thus account for its unusual persistence. TMD inhibition of drug metabolism may therefore result in the accumulation of either TMD or DMO themselves, both of which are teratogenic, or of some other potentially teratogenic metabolic product. These studies show that TMD has potent effects on liver metabolism as well as on cerebral activity. TMD inhibition of microsomal oxygenase activity may have clinically significant consequences when TMD is administered with other drugs, and may also have a role in TMD caused teratogenesis.

THE EFFECTS OF HEROIN ON LUNG MATURATION AND GROWTH IN FETAL RABBITS. H.William Taeusch, Jr., Stephen Carson*, Nai S. Wang*, and Mary E. Avery, McGill University-Montreal Children's Hospital Research Institute and Department of Physiology, McGill University, Montreal.

The absence of hyaline membrane disease (HMD) in low birth weight infants of heroin addicted mothers (Glass, et al., Lancet, Sept., 1971), suggested the possibility that heroin accelerated lung maturation. Cortisol and thyroxin have previously been shown to increase lung maturation of the fetal rabbit when injected on day 24-26 of gestation (term = 31 days), with sacrifice 48 hours later. In the same rabbit model, heroin has no effect on lung maturation (using as indices: minimum surface tension, deflation pressure-volume curves, distensibility, and histology) when 2 mg/kg BID x 3 days is injected intravenously in the doe. Heroin has an equivocal effect on lung maturation when injected directly into the fetus and amniotic fluid (92 ug/kg) A significant reduction in body weight occurs in the heroin injected fetus when compared with littermate controls, and in litters of heroin injected does when compared with saline injected does. ($p<0.05$). The data suggest that heroin has a direct inhibitory effect on fetal growth that is not attributable to maternal malnutrition, and that the reduction in body weight for gestational age is associated with underrepresentation of HMD in addicts' infants.

	n	fetal wt	V_4*
A Maternal injection saline	61	25.3 g	25
B Maternal injection heroin	56	23.1	26
C Littermates of D	27	20.6	42
D Heroin injected fetuses	14	19.8	45

*V_4 indicates volume in lungs at a deflation pressure of 4 mm Hg expressed as % of the total lung capacity. Higher values are characteristic of increased lung maturity. Fetuses in groups A-D are all 27 days gestation. $p<0.001$ when A and B are compared with C and D.

THE ACCELERATION OF NEUROLOGICAL MATURATION IN HIGH STRESS PREGNANCY AND ITS RELATION TO FETAL LUNG MATURITY. Jeffrey B. Gould*, Louis Gluck and Marie V. Kulovich*, Univ. of Calif.,San Diego Sch. of Med., Dept. of Ped., Div. of Perinatal Med., La Jolla, Calif.

Lecithin/sphingomyelin (L/S) ratios in amniotic fluid, demonstrate accelerated development of pulmonary surfactant in some high stress pregnancies, e.g., hypertension, toxemia, etc.(see abstract by Gluck et al). An evaluation of CNS maturation in these pregnancies was done. The products of 25 high risk pregnancies with L/S ratios greater than 1.5 were examined. Gestational age (GA) was determined by maternal history, by averaging the 50th percentile values for length, head circumference and birth weight, and by physical criteria. These were compared to neurological age determined by modification of the method of Dubowitz et al. Five infants with a neurological age at least 2.5 weeks older than GA by LMP are shown in Table I. Patients 1, 2 and 3 have a physical age less than the GA by LMP. Advanced physical age of patient 5 probably reflects maternal diabetes. These results suggest that intrauterine factors which accelerate the biochemical maturation of pulmonary surfactant may also accelerate neurological maturation.

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	Sex Wgt	GESTATIONAL AGE Hist.	Physical Meas.	Physical Crit.	Neur. Crit.	History	L/S	Hosp. course
#1	♀1400	30	30.5	30	34	tox. + convulsions	1.7	min. RDS
#2	♀1049	31.5	29*	31	34	toxemia	2.8	normal
#3	♂2183	34	33	33	38	PROM	1.8	min. RDS
#4	♀2218	36	34	39	40	pylo.	3.5	normal
#5	♂4494	38	>40	42	42	IDM-PROM	3.9	normal

*Wgt.<10%ile for GA by LMP

TRANSFER OF METHIONINE AND CYST(E)INE ACROSS THE HUMAN PLACENTA AND THE ROLE OF CYST(E)INE IN FETAL GROWTH. Gerald E. Gaull, Niels C. R. Räihä, J. Saarikoski and John A. Sturman. Dept. Ped. Res., N.Y. State Inst. Basic Res. in Mental Retd., Staten Island; Dept. Ped., Mt. Sinai Hosp. Sch. Med. of the City Univ. of New York, and I & II Clinic of Obstet. & Gyn., Helsinki Univ. Central Hosp., Helsinki.

Cystathionase is absent from human fetal liver and brain. Its product, cysteine (cysh), may be essential. The plasma fetal/material gradient and the transfer of amino acids into human fetuses with intact placental circulation was investigated by I.V. infusion into the mother. Methionine (met) accumulated in fetal plasma against a 3-fold gradient. Leucine, transported by the same carrier system in most tissues, behaved similarly. Cystine (cys), equal or lower in conc. in the fetus at zero time, showed a slower increase in conc. in fetal plasma and was always lower than maternal plasma conc. Ornithine, which is transported by the same carrier as cys in most tissues, was similar to met and leucine. Measurement of cys and cysh following infusion of each alone gave results similar to cys. Experiments with S^{35}-cystine in the pregnant Rhesus monkey (whose transfer of met and cys across the placenta resembles the human) have ruled out the possibility that the low fetal plasma cys concentration is due to rapid uptake and/or metabolism by the fetal organs or placenta.

Thus, cyst(e)ine is not transferred across the placenta by active transport, but is transferred by simple or facilitated diffusion.

Cysh, but not GSH, is a potent inhibitor of methionine-activating enzyme, the first step in conversion of met to homocysh. We present evidence elsewhere that inability to synthesize cysh in human fetus conserves homocysh for conversion of N^5-methyltetrahydrofolate to 5,10-methylene tetrahydrofolate, a precursor of the DNA-specific nucleotide, thymidylate. We postulate cysh exerts negative feedback control and that the slower transfer of cyst(e)ine across the placenta may be an adaption to more rapid DNA synthesis in the fetus.

CYTOCHALASIN B: EFFECTS ON MUCOPOLYSACCHARIDE SYNTHESIS AND MORPHOGENESIS. Merton R. Bernfield, Ronald H. Cohn and Shib D. Banerjee. Stanford Univ. Sch. of Med., Dept. of Ped., Stanford, Ca.

Many motile cellular processes, including morphogenetic changes in tissue shape, are reversibly inhibited by the drug cytochalasin B (CB). Ultrastructurally, CB appears to disrupt contractile intracellular microfilaments and has been proposed as a diagnostic tool for microfilament contractility (Wessells, et.al. Science 171:135, 1971). CB causes mouse embryo salivary epithelia to flatten and lose their lobules; removal of CB is followed by thickening of the epithelium and resumption of morphogenesis. Since normal epithelial morphology and organogenesis require the presence of acid mucopolysaccharide (MPS) within the epithelial basal lamina (Bernfield, Banerjee & Cohn, J.Cell Biol., March, 1972), the effect of CB on the distribution and synthesis of MPS was studied. CB does not alter the ultrastructure of the basal lamina, or the nature and amount of its MPS as determined by light and electron microscopic histochemistry. Studied autoradiographically, CB reversibly inhibits the incorporation of ^{3}H-glucosamine into basal laminar MPS, but has no discernable effect on $^{35}SO_4$ incorporation. To quantitate these effects, mouse 3T3 fibroblasts were used. The fibroblasts become highly arborized in CB, but promptly revert to normal morphology after CB removal. Amino acid incorporation into protein is unaffected by CB. However, ^{3}H-glucosamine incorporation into both sulfated and non-sulfated MPS is inhibited 95%, while $^{35}SO_4$ incorporation is reduced only 15%. These data suggest that CB does not substantially alter MPS synthesis, but prevents either the transport of glucosamine into the cell or the utilization of glucosamine for MPS synthesis. Analysis of the soluble pools and measurement of glucosamine uptake demonstrate that CB rapidly and reversibly inhibits the intracellular transport of glucosamine. The relationship between the inhibition of transport and the biologic effects of the drug are unknown, but these studies indicate that the anti-morphogenetic effects of CB may not be solely due to interference with microfilament contractility.

ALTERATIONS IN THE GROWTH PATTERN OF FETAL RHESUS MONKEYS FOLLOWING THE INUTERO INJECTION OF STREPTOZOTOCIN. Donald E. Hill, Alan B. Holt, Richard Reba, and Donald B. Cheek. Johns Hopkins Univ., School of Med., Dept. of Pediatrics, Baltimore, Md.

Investigation of the role of insulin in fetal growth was undertaken in rhesus monkeys. Twenty-four pregnant monkeys had hysterotomies at 110 days gestation (full term = 165 days) and a fetal leg was exposed. Streptozotocin was given intravenously to each fetus in a dose of 75 mgm/kg. At 158 days gestation the surviving fetuses (12/24) were delivered by C-section and analyzed. Three animals were more than 2 S.D. below the mean body weight for gestational age while the remaining animals were of appropriate body weight. Seven animals of the latter body weight group had significantly larger adrenals for body weight or age. The small animals had normal size adrenals. The fetal pancreatic insulin content was extremely low in the animals with large adrenals. The fetal plasma insulin was similar in all groups as was the maternal insulin. In the muscle of the small animals, the total DNA (cell number) was low while the protein/DNA ratio (cell size) was increased. In addition, the percent water and the total muscle mass were both significantly low. In the normal size animals with large adrenals, the total DNA was unchanged, and the protein/DNA ratio was increased. The muscle mass was increased as was the skeletal mass. A group of sham operated animals had an increase in adrenal weight but no increase in muscle mass or skeletal mass. In the liver, the small animals had normal body composition, but reduced in total amounts. The total DNA and protein/DNA ratio were normal. In the group with large adrenals, total DNA and total protein were proportionally increased. The total RNA was markedly increased. Two patterns of tissue growth have therefore emerged. If the animal responded to the stress with adrenal enlargement, body size was normal with increases in some of the cellular components. If the adrenals were normal or small, three of the animals were small and had reductions in cell number. Variation in response to the Streptozotocin could be responsible for these findings.

ISOLATION OF SERUM MACROMOLECULE STRINGENTLY REQUIRED FOR THE MITOSIS OF DIPLOID HUMAN FIBROBLASTS. John C. Houck and Richard F. Cheng, Children's Hospital, Washington,D.C. and George Washington Univ., Washington,D.C.,20005.

Serum has been known for years to be enormously helpful in maintaining fibroblasts in vitro. Within the last few years serum has been shown to be stringently required by diploid human fibroblasts for cell division. We have been unable to substitute any mixture of human growth hormone, cortisol, parathyroid for serum in permitting diploid human fibroblasts to divide.

We have isolated from the sera of horse, cow, pig and human a macromolecule of molecular weight between 100,000 and 200,000 daltons with an iso-electric point of 5.2 which is electrophoretically homogenous in acrylamide gels. This material can completely substitute for serum in terms of the mitosis of diploid human fibroblasts and represents as much as a half percent of the total serum protein. This fraction contains essentially all of the mitotic stimulating activity of serum for fibroblasts and is approximately 150-fold purified. Diploid human fibroblasts from both embryonic lung and adult skin have survived at least 12 doublings using only this macromolecule instead of serum.

The isolation and purification procedures involved firstly, molecular sieving using Amicon Diaflo filters; secondly, iso-electric focusing and thirdly, preparative acrylamide gel electrophoresis.

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INDUCTION OF RENAL DYSPLASIA IN HUMAN EMBRYONIC KIDNEYS IN WHOLE ORGAN CULTURE:
John F. S. Crocker (Intr. by Richard B. Goldbloom) Dept. of Pediatrics, Dalhousie University, Halifax, Nova Scotia, Canada.

Perey et al (Science, 158:1,494,1967) found that adrenal steroids injected into rats and rabbits shortly after birth induced cystic changes in kidneys. Later studies suggested that (a) hypo-potassemia was a major causal factor, (b) the resulting cysts were dilated, blind-ending, collecting ducts.

Crocker and Vernier (Science, 169,485,1970) previously reported on 1000 fetal mouse kidneys grown in culture at various potassium concentrations. They noted defective branching of the ureteral bud and straight tubules (collecting ducts) which grew to the capsule without inducing nephron formation when the K^+ of the media approached maternal levels at this crucial stage of development. These tubules often bent toward the hilus upon contact with the capsule and failed to induce nephrons.

We have studied the effect of various K^+ concentrations on the development of 26 paired controlled human embryonic kidneys of 5 to 10 week gestation and grown in organ culture. All kidneys grown in K^+ concentration of 8 to 10 mEq/L grew normally while all kidneys grown in K^+ concentration of 4 to 6 mEq/L (normal maternal levels) grew with defects similar to those noted previously in mice. These findings demonstrate that alterations in potassium concentration in the environment of the developing human kidney may play a critical role in the induction of morphological defects.

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DEVELOPMENTAL BIOLOGY

Second Session

BIOCHEMICAL STUDIES OF CELLULAR DIVISION: NUCLEIC ACID BIOSYNTHESIS IN ISOPROTERENOL STIMULATED SALIVARY GLANDS. Nicholas J. Hoogenraad*, Jean M. Roux,* and Norman Kretchmer. Dept. of Ped., Stanford Univ. Sch. of Med., Stanford, and Center of Neonatal Research, Hospital Port-Royal, Paris.

Pyrimidine nucleotides required for RNA and DNA synthesis can be obtained by two biochemical pathways -- by de novo synthesis from CO_2, ATP and glutamine as a source of nitrogen, and by phosphorylation of preformed nucleosides. The relative importance of these two mechanisms to the process of cellular division is still unknown. Isoproterenol, a sympathomimetic drug, stimulates cellular proliferation in the salivary gland which can then serve as a system to evaluate critically the relationship between the two pathways. It has a further application in the study of the effects of neural stimuli on basic cellular phenomena. After 20 hours, according to Baserga (1966), a single injection of isoproterenol caused a marked increase in DNA synthesis in the salivary glands of mice. This event is followed by cell division. The mechanism by which isoproterenol results in synthesis of DNA is not defined. In our studies, there was a sharp increase in the activity of the first two enzymes of the de novo pyrimidine pathway (carbamyl phosphate synthetase and aspartate transcarbamylase) and in uridine kinase (an enzyme utilizing pre-formed nucleosides) within the first hour after the injection. Using ^{14}C-labelled compounds, it was shown that isoproterenol stimulated the incorporation of the de novo pathway intermediate, orotic acid, into RNA, whereas ^{14}C from pre-formed nucleosides was incorporated almost exclusively into DNA.

From these studies, it appears that when salivary glands are stimulated with isoproterenol, de novo synthesis provides pyrimidine nucleotides for RNA synthesis whereas pre-formed nucleosides are utilized for DNA synthesis.

ISOLATION OF SUBCELLULAR PARTICLES ON A MICROSCALE: MITOCHONDRIAL ENZYME ACTIVITY IN SUBCUTANEOUS ADIPOSE TISSUE OF HUMAN NEWBORNS. Milan Novak, Ellen Monkus, Victoriano Pardo, and David Alzamora, Univ. of Miami Sch. of Med., Dept. of Ped. and Veterans' Administration Hospital, Miami, Fla.

A method for the separation of isolated subcellular particles on a microscale has been developed, using a column constructed of a series of Millipore filters of appropriate pore size. Intant organelles,such as mitochondria, unfixed and in a good state of preservation, can be isolated from samples of subcutaneous adipose tissue (10 to 40 mg) obtained by a needle biopsy.

The method is adapted to an amount of tissue as small as 10 mg and can be used for the isolation of more than one organelle from a single sample. The technique was applied to the study of metabolism of mitochondria obtained from human newborn infants. It is also suitable, however, for the investigation of other subcellular particles and other aspects of tissue metabolism at a subcellular level.

The activity (μM DPNH converted/g mitochondrial protein/min) of mitochondrial beta-hydroxyacylCoA dehydrogenase (HAD), which is an important unidirectional enzyme in the combustion of fatty acids, was directly correlated with age in hours ($y=9.44x+7.43, r=0.822$, $p<0.001$) in normal fullterm infants in the first week of life and parallels the known increased dependency of older newborns on fatty acids as an energy source. Mitochondrial L-malate dehydrogenase (M-MDH) (μM DPNH converted/g mitochondrial protein/min) was increased at 4 to 7 days over values at 3 to 12 hours of age ($p<0.05$) in healthy fullterm neonates. M-MDH measured 4 to 7 days after birth was decreased in prematurely born in comparison with fullterm neonates ($p<0.01$) and was directly correlated with the length of gestation ($p<0.01$). These findings regarding M-MDH activity in human subcutaneous (white) adipose tissue are in agreement with those of others in fetal and newborn rabbit liver and guinea pig brown adipose tissue. This suggests that all these tissues may be subjected to similar regulating mechanisms during the fetal and neonatal period.

BIOGENESIS OF MITOCHONDRIA, AND THE EFFECT OF CHLORAMPHENICOL, DURING NEONATAL RENAL COMPENSATORY GROWTH. Charles E. Mize and Howard G. Worthen. Univ. of Texas Southwestern Med. Sch., Dept. Ped., Dallas 75235

Unilateral nephrectomy dramatically produces an increase in kidney mass in the contralateral kidney, progressively increasing from approximately 8% at 1-day post nephrectomy to 120% at 6-days, compared to sham controls. Morphologic assessment by electron microscopy suggests greater compaction and increased numbers of mitochondrial profiles within 24 hours after nephrectomy, which precedes general compensatory renal hyperplasia. Enzymic assays utilizing whole kidney mitochondria at this time interval suggest preferential early increase in specific activity of mitochondrial inner membrane enzymes (cytochrome oxidase, succinate-cytochrome c reductase) compared to outer membrane (monamine oxidase) or soluble enzymes. Compensatory hypertrophy also stimulates quite early incorporation of radioactivity into mitochondrial inner membrane from ^{3}H-leucine and ^{14}C-glycerol. These changes in enzymic activities and rapid incorporation of small molecular-weight membrane precursors are sensitive to inhibition by chloramphenicol at the earliest stages of compensatory hypertrophy while not readily demonstrable at later stages. These several results will be discussed relative to mitochondrial formation and antibiotic inhibition of membrane genesis in neonatal kidneys during rapid growth.

CHANGES IN MITOCHONDRIAL AND MICROSOMAL FATTY ACID ELONGATION DURING DEVELOPMENT OF THE RAT. Joseph B. Warshaw and Robert E. Kimura, Harvard Med. Sch., Mass. Gen. Hosp., Shriners Burns Institute, Boston.

The developing rat undergoes a number of metabolic adaptations during the postnatal period. After birth there is increased dependence on mitochondrial aerobic oxidations and a corresponding increase in mitochondrial number. The activities of enzymes generally associated with the hepatic endoplasmic reticulum also rise during the postnatal period. Since fatty acids are important membrane components of these organelles, we have investigated fatty acid elongation by heart homogenates and hepatic microsomes as a function of development. Mitochondrial fatty acid elongation is the only pathway for fatty acid synthesis in the mammalian heart. Both mitochondrial and microsomal fatty acid elongation involve the addition of 2 carbon units to preexisting long chain acyl-CoA primers. Fatty acid elongation by the developing heart was determined by measuring acetyl-CoA incorporation into long chain fatty acids extractible with pentane. The activity of fetal rat heart homogenates was very low but during the first week of life increased from less than 1 to approximately 5 nmoles of acetyl-CoA incorporated per mg per hr. Heart activity dropped approximately 50% after weaning presumably because of a decrease in fatty acid intake. Cytochrome oxidase activity, an index of mitochondrial number, increased only twofold in the postnatal period indicating that the changes in activity could not be totally attributed to an increased mitochondrial number. Fatty acid elongation by microsomal fractions of developing liver determined by malonyl-CoA incorporation into long chain fatty acids was also very low during fetal development. Activity increased from 0.3 to 5.0 nmoles per mg per hr., by 10 days of age. In contrast to mitochondrial fatty acid elongation, microsomal activity increased approximately 50% after weaning. This suggests an increased synthesis of a fatty acid product previously supplied in the milk. It is concluded that the changes in these activities are related to functional and structural adaptations of the cell to the postnatal environment. (Supp. by Mass. Heart Assoc. Grant #1074).

COMPARISON OF RNase ACTIVITY AND PLACENTAL RNA CONTENT DURING NORMAL AND RETARDED GROWTH. Elba G. Velasco, Jo Anne Brasel & Myron Winick. Cornell Medical Center, Department of Pediatrics, N.Y., N.Y. 10021.

Alkaline RNase (pH 7.8) has been postulated to affect the rate of RNA catabolism and thereby regulate RNA levels. Since tissue RNA changes with normal growth and is altered by growth retarding stimuli, we have measured RNase activity of placenta under these conditions and correlated this activity with tissue RNA levels. Normally total RNA content of rat placenta increases slowly from 11 to 14 days and more rapidly thereafter. By contrast RNase activity declines from high levels at 12 and 13 days of gestation to a nadir at 14 days and then plateaus from 15 to 19 days. Thus there is, in general, an inverse relationship between levels of RNase activity and the net accretion of RNA. Uterine artery ligation predictably retards placental and fetal growth most severely in conceptuses proximal to the ligature. Ligation at 16 days of gestation reduces proximal placental weight by 34% and fetal weight by 20% 72 hours later; placental RNA is reduced by 37%. In contrast proximal placental RNase activity increases within 24 hours, reaches 2-3 times control levels by 48 hours and is declining by 72 hours. The elevated RNase activity in the face of a reduced RNA per cell results in RNase activity per mg RNA which is proportionally even greater than the elevation of activity per cell. Thus in both normal and retarded placental growth there is an inverse correlation between net RNA synthesis and RNase activity. These data reinforce the concept of a catabolic regulatory role for RNase and open to further exploration the possible use of this enzyme as a marker for retarded tissue growth.

ENHANCEMENT OF LECITHIN SYNTHESIS AND PHOSPHORYLCHOLINE GLYCERIDE TRANSFERASE ACTIVITY IN THE FETAL RABBIT LUNG AFTER CORTICOSTEROID ADMINISTRATION. Philip M. Farrell and Richard D. Zachman, (Intr. by Charles C. Lobeck), Univ. of Wis. Dept of Ped., Madison, Wis.

Kotas and Avery (J. Appl. Physiol., 30, 358, 1971) and Motoyama et al (Ped. 48, 547, 1971) reported that rabbit fetuses treated with corticosteroid showed evidence of increased pulmonary maturation as determined by pressure-volume curves and surface tension properties. In the present study, the effect of steroid on lung lecithin and its synthetic enzymes was measured in premature rabbits. Rabbit fetuses of 23-24 days gestation were injected with 9-fluoroprednisolone acetate or saline. Three days later, the animals were delivered into saline by C-section. In agreement with Kotas and Avery, the steroid treated rabbits showed a slight (15%) decrease in body weight and a moderate (37%) reduction in lung weight. In addition, it was found that the lecithin content of lung parenchyma was elevated in this group from the control value of 70 mg/gm dry weight to 96 mg/gm dry weight ($p < 0.005$). Preliminary studies suggest that the lecithin synthesized is acetone precipitable, and therefore is presumably surface active.

The activities of four enzymes in two lecithin biosynthetic pathways were also examined, namely choline kinase and phosphorylcholine-glyceride transferase (PCGT) of the choline incorporation pathway and methionine adenosyltransferase and phosphatidyl methyl transferase of the methylation route. Of these enzymes, the only significant change in the steroid treated group involved PCGT which was elevated 45%. General protein synthesis was unaffected. These findings suggest that lung PCGT is induced by corticosteroid, leading to increased synthesis of lecithin through the choline incorporation pathway.

THE EFFECT OF FETAL THYROIDECTOMY ON GROWTH OF THE OVINE FETUS. A. Erenberg, K. Omori, W. Oh and D.A. Fisher, UCLA Sch. of Med., Harbor Gen. Hosp., Dept. of Peds., Torrance, California.

The role of the thyroid on fetal growth has been investigated in several species, and the results have suggested that thyronines may not be required for fetal somatic growth. In many of the experimental designs, other factors than thyronine deficiency were involved; therefore, the present study was designed to minimize the non-thyroid variables. Five fetal sheep were thyroidectomized (Tx) at 90 to 110 days gestation (normal gestation = 150 days); hypothyroidism was confirmed by serum T4, T3 and TSH levels of <1 μg%, <30 ng%, and 300-1500 μU/ml respectively. The animals were sacrificed at 119 to 140 days gestation (19 to 43 days post Tx). Body weight and length, organ weight, and RNA, DNA and protein content of the liver, spleen, kidney, heart, cerebrum, cerebellum, lung and thymus were determined and compared with 8 matched control fetuses. Mean body weight in the Tx fetuses was not significantly less than in control animals, (2.00 kg vs 2.86 kg), while mean body lengths were similar (42.8 cm vs 38.9 cm). Of the major organs measured, however, only the lungs of the Tx fetuses weighed significantly less than controls (48 gm vs 98 gm). The total RNA content of these lungs was also less than controls (258 mg vs 491 mg); however, mg RNA/gram lung (5.3 mg/g vs 5.6 mg/g), total DNA content (1730 mg vs 2387 mg), mg DNA/gram lung (33.6 mg/g vs 24.3 mg/g) and RNA/DNA ratio (0.24 vs 0.30) were similar in the two groups. All other organs investigated had similar RNA and DNA content and RNA/DNA ratios in Tx and control groups. It therefore appears that thyronine deficiency does not affect somatic growth; and except for the lungs, does not appear to have a role in specific organ growth. Even in the instance of the lungs, the RNA and DNA content and protein composition were not abnormal.

DEFICIENCY OF THYROID HORMONE AND DEVELOPMENT OF THE FETAL RHESUS MONKEY. George R. Kerr, Ian Tyson, James R. Allen, Jon H. Wallace and Guenther Scheffler. University of Wisconsin, Departments of Pediatrics, Radiology, Pathology, and the Regional Primate Research Center, Madison, Wisc. 53706

Endocrine relationships between the pregnant human female and her fetus are not fully defined. Species differences in placental and fetal growth limit the value of most experimental animals in clarifying these relationships. The processes of fetal growth in a few subhuman primates are generally comparable to those of humans. Pregnant (70-90 day) rhesus monkeys were injected with 2 mc. sodium iodide (I^{131}), and the fetal consequences evaluated at 150 days gestational age. I^{131} fetuses showed several peculiarities, broad maxillae, prominent tongue, respiratory depression and cerebral edema. Thyroid or parathyroid tissue were not found in the I^{131} fetuses. The thymus was significantly smaller, and the body weight, pancreas, spleen, liver, and adrenals were somewhat smaller in I^{131}fetuses than in controls. The pituitary gland was significantly heavier in I^{131} fetuses.

A marked delay in epiphyseal ossification was apparent in the I^{131} fetuses (2-4 centers ossified in the upper and lower extremity compared with a range of 26-47 centers in controls). Significant reduction in diaphyseal ossification was found in all tubular bones. Characteristic patterns of change in PBI, T_4 and "T_3 index" followed I^{131} administration to the pregnant female: all values showed an immediate marked increase, then a gradual reduction to levels significantly below those of controls. Levels in cord blood at 150 days gestation were also significantly lower in I^{131} fetuses than in controls (T_4 in cord blood - .58 µg% in I^{131} fetuses; 7.2 µg% in controls). Combined fetal and maternal hypothyroidism in this species results in an easily recognizable clinical syndrome: the absence of such findings in most athyreotic human newborns suggests that an appreciable amount of maternal thyroxin reached the fetus via the placental circulation or swallowed amniotic fluid.

EFFECT OF HUMAN GROWTH HORMONE (HGH) ON RNA SYNTHESIS IN RAT LIVER MITOCHONDRIA. George Bren, Vaddanahally T. Maddaiah, Raj K. Sharma, Joseph Thomas, Platon J. Collipp, and Shang Y. Chen. Nassau County Medical Center, East Meadow, New York.

It has been shown that a significant proportion of injected labeled human growth hormone accumulates in mitochondria of hypoxed rat liver. Further, hypophysectomy reduced and HGH increased mitochondrial protein synthesis. We have now measured the in vivo rate of incorporation of [5-^{3}H] uridine (^{3}HU) into mitochondrial RNA. Incorporation (cpm/mg protein) into mitochondrial RNA plateaued 30 minutes after an intravenous injection of ^{3}HU into normal (N) and hypophysectomized (Hy) rats. Results of incorporation of ^{3}HU (30 min. after I.V. injection) into N, Hy + saline and Hy + HGH (100 ug/rat, 5 days) are given below:

	Incorporation (cpm/mg protein) Acid Insoluble Pool			Incorporation (cpm/mg protein) Acid Soluble Pool		
	N	Hy + Saline	Hy + HGH	N	Hy + Saline	Hy + HGH
Nuclear	229 ± 29	177 ± 15	242 ± 26	80 ± 17	108 ± 17	128 ± 25
Mitochondrial	253 ± 33	157 ± 12	220 ± 15	114 ± 20	116 ± 41	135 ± 29

Incorporation into acid insoluble fraction was significantly reduced after hypophysectomy, and was significantly increased after HGH treatment. There was no significant difference in the incorporation into acid soluble pools. It could therefore be concluded that GH has a direct effect on macromolecular synthesis in liver mitochondria which may play a significant role in the action of HGH.

EFFECTS OF ACTH ON THE SYNTHESIS OF RAPIDLY LABELLED ADRENAL CYTOPLASMIC RNA. Salvador Castells, Nicholas Addo and Kwaku Kwateng, Dept. of Ped. State University of New York, Downstate Medical Center, New York

ACTH has been shown to stimulate adrenal RNA synthesis in vivo. In an attempt to define which species of RNA are primarily effected by ACTH, rat adrenal cortices were incubated in a continuous flow system with constant removal of secreted steroids. Adrenal response to ACTH was measured by corticosterone determination in the effluent medium. Duplicated control and experimental flasks containing 24 adrenals each were incubated in a buffer containing bentonite. The flow of incubation medium was 1ml per min. and contained 1 uC of uridine-5-6-H^3 per ml for 15,30 and 45 min. ACTH was added to the continuous flow medium at 24 mU per ml. over the same periods. Total cytoplasmic RNA was treated with sodium dodecyl sulfate, extracted with aqueous phenol and purified by Sephadex-G 50 column. Cytoplasmic RNA fractions were separated by electrophoresis in 2.4% acrylamide gels, scanned by U.V. and radioactivity of total and 2mm gel slices determined. ACTH did not affect the distribution and electrophoretic pattern of RNAs sufficiently for changes to be detected by U.V. scanning. ACTH increased the incorporation of labelled precursor in those electrophoretic fractions equivalent to 28S, 18S, 5S and 4S with a pronounced increase of radioactivity of the 18S fraction at 30 minutes. Also rapidly labelled were minor species of heterogeneous 4-16S material which manifested a considerable increase in radioactivity at 45 min. Thus, ACTH increases the synthesis of rapidly labelled cytoplasmic RNAs with a marked effect on molecules with a sedimentation coefficient of 18S, followed by an increase in radioactivity of heterogeneous 4-16S material. The effect in 4-16S could be due to increase synthesis of these fractions or increase degradation of 18S RNA to smaller, more rapidly sedimenting fragments. These data suggest that the effect of ACTH on the adrenal gland may be mediated by increased synthesis of specific RNA molecules.

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DEVELOPMENTAL BIOLOGY

Read by Title

GLUCOCORTICOID RECEPTORS IN THE FETAL LUNG. Philip L. Ballard and Roberta A. Ballard (Intr. by William H. Tooley). Cardiovascular Research Inst. and Depts. of Bio-chem. and Ped., Univ. of California, San Francisco.

Studies indicate that administration of glucocorticoids to fetal lamb and rabbit accelerates lung maturation with precocious appearance of pulmonary surface active material in lung fluid. Since a variety of steroid hormones interact with specific receptor proteins in their respective target tissues and then bind to the nucleus as early requisite steps in their mechanism of action, we examined fetal rabbit lung and other fetal tissues for the presence of glucocorticoid receptors using ^{3}H-Dexamethasone (Dex) in a charcoal assay developed by Baxter and Tomkins (P.N.A.S. (U.S.), 68, 932, 1971). Receptor activity was found in the soluble cytoplasmic fraction from all fetal tissues studied, including lung, liver, small intestine, skeletal muscle, heart, thymus, brain, skin and placenta. Fetal lung contained the greatest concentration of receptor sites ($\sim$6 x 10-^{13}M/mg protein); other fetal tissues contained 17-56% of this level. In the rabbit the concentration of receptor sites remained nearly constant during the last 12 days of gestation (term 30 days). The dissociation constant was 4.2 (range 2.3-6.6) x 10-^{9}M for Dex in the lung and 3.0-11.5 x 10-^{9}M in other tissues. Binding of labeled Dex (10-^{8}M) to receptor was abolished by the presence of competing unlabeled cortisol or corticosterone at 10-^{5}M, but was unaffected by the presence of inactive steroids such as epicortisol or androstenedione. When receptor-bound Dex was incubated with fetal lung nuclei, a significant transfer of bound Dex to the nucleus occurred.

These studies indicate that lung and most other fetal tissues contain specific macromolecular receptors for glucocorticoids in a concentration and with properties similar to those receptors of glucocorticoid-responsive adult tissues and cultured hepatoma cells. The capacity of fetal lung to both bind Dex and transfer it to the nucleus is consistent with a direct role for glucocorticoids in both normal and accelerated pulmonary development.
(Supported in part by Grant N.I.H. HEO 6285.)

THE DEMISE OF ANOTHER VESTIGIAL ORGAN. Robert L. Brent, Christopher Leung, William London and David Wittingham. Jefferson Med. Col., Dept. Ped., Phila.; NIH, Bethesda; Physiol. Lab., Cambridge

The teratogenic effect of heterologous rat nephrotoxic serum was reported from this laboratory in 1961 and it was also demonstrated that antiserum against rat chorioplacenta was teratogenic. Radioactive labeling and fluorescent localization of teratogenic antisera revealed that these antibodies localized in the glomeruli and the yolk sac. Based on these findings, an antiserum was prepared against yolk sac which also proved to be teratogenic. In the rat and related species the yolk sac is a vital organ during the period before the development of the chorioplacenta. In the rat yolk sac dysfunction during this early period of differentiation can result in congenital malformations, growth retardation and/or embryonic death. Since the primate embryo never develops the yolk sac placenta that is present at term in the rodent, question has arisen as to the role of the yolk sac in human development, since the yolk sac appears as a shortlived outpouching which quickly diminished in size and becomes incorporated into the umbilical stalk. Both the Rhesus monkey and ferret have "vestigial" yolk sacs so there is a theoretical possibility that nephrotoxic antiserum might not affect the developing embryo in these species. When nephrotoxic antiserum was prepared and injected into pregnant monkeys in the mid trimester of gestation, maternal nephritis was produced, but no effect was observed on the developing embryo. If the same antiserum were injected on the 24th day of gestation, interruption of pregnancy occurred. In the ferret, nephrotoxic antiserum produced embryonic death and congenital malformations when injected on the 17th, 18th or 19th day of pregnancy. The malformations which were produced in the rat, namely hydrocephaly, anopthalmia and amphalocele were also produced in the ferret. It is likely that the yolk sac has a role in embryonic development during a short period of early primate development and that yolk sac dysfunction may result in embryonic death or malformation.
(NIH HD 630; Travelling Fel. Roy. Soc. Med.)

POST-FERTILIZATION CHANGES IN PROCESSING OF NUCLEIC ACID PRECURSORS. Donna L. Daentl and Charles J. Epstein, Univ. of California, Dept. Pediatrics, San Francisco.

Crucial to its further growth and development after fertilization, the mammalian ovum contains the metabolic machinery responsible for conversion of precursors to nucleic acids. Because the activities of these enzyme systems do not change upon fertilization, it appears that they are at least initially under control of the maternal genome. After the first cleavage, the activities of kinases and phosphoribosyltransferases increase. Concurrently transport systems for nucleic acid bases and nucleosides become active, but subsequently follow at least five independent patterns of developmental change, suggesting the existence of separate carriers for purines, pyrimidines, purine nucleosides, pyrimidine nucleosides and pyrimidine deoxynucleosides. Despite relatedness of function, all these biochemical changes appear to occur independently of one another. Since transcription occurs at the 2-cell stage, these developmental phenomena could be under control of the embryonic genome. However, the relative contributions of maternal and paternal genes and the mechanisms which control their expression remain to be determined.

MATERNAL-FETAL TRANSFER OF GENTAMICIN. Salvador Garcia, C. Ballard, C.B. Martin, D. Ivler, A. Mathies, B. Bernard. (Intr. by Paul F. Wehrle). Depts. of Pediatrics and Obstetrics, Los Angeles County-USC Med. Ctr.,Los Angeles.

Twenty-five pregnant women (11 in first trimester, 11 in second trimester and 3 at term) were given a single IM dose of 1 mg or 2 mg/kg gentamicin sulfate (GMS) prior to hysterectomy for therapeutic abortion (22 patients) or term delivery (3 patients with premature rupture of membranes). GMS was administered 1/2 to 10-3/4 hrs. prior to termination of pregnancy. GMS microbiological assay was determined in maternal serum (zero, 1,2,4 hrs. and delivery time), myometrium, placenta, amniotic fluid, and fetal cord and heart serum, kidney, urine, lung, liver, brain and CSF. Maternal serum half life was independent of dose and gestational age. At 1 mg/kg, maternal serum GMS concentrations were 3.02 ug/ml at 1 hr, 1.76 ug/ml at 2 hrs, and 0.87 ug/ml at 4 hrs. At 2 mg/kg, GMS concentrations were 7.69 ug/ml at 1 hr, 5.16 ug/ml at 2 hrs, and 1.95 ug/ml at 4 hrs. GMS concentration in myometrium varied directly with maternal serum concentrations and was not detected after 5 hrs at 1 mg/kg dose or after 6 hrs at 2 mg/kg dose. The concentration of GMS in placenta and fetal kidney exceeded that in maternal serum after 6 hrs and remained elevated to 11 hrs. The concentration of GMS in fetal kidney was related to the dose administered, but its concentration in placenta was not dose dependent. GMS was concentrated in fetal kidney as early as 13 weeks gestational age. GMS was detected in all 3 fetal urine samples obtained. In fetal cord and heart serum, detectable concentrations of GMS were 15% of maternal serum levels at 2 hrs, and 50% at 4½ hrs and none after 6 hrs. GMS was detected in lung tissue in 4 of 7 fetuses 15 weeks gestational age or less, and none of 7 beyond this time. GMS was present in only 1 of 13 fetal livers assayed, and in only 1 of 15 fetal brains. GMS was not found in CSF of any fetus when the mother had received 1 mg/kg. Following the 2 mg/kg dose, GMS was present in 4 of 8 fetal CSF samples examined; all of these fetuses were less than 15 weeks gestational age.

TRANSIENT TYROSINEMIA IN THE TERM NEONATE. Peter Mamunes, Department of Pediatrics, Medical College of Virginia & Bureau of Child Health of Virginia State Health Department, Richmond, Virginia. (Intr. by W.E. Laupus)

Transient neonatal tyrosinemia (TNT) in the premature is a frequent and well described entity, but its occurrence in the term infant has not been well evaluated. From 1967-1971 (when 97% of Virginia's 410,000 live births were screened for phenylketonuria) 36 term neonates with moderate to severe tyrosinemia (mean level 33.5±15, range 15-50mg%) were uncovered because of positive initial Guthrie tests (4mg% or greater) performed at a mean age of 14±6 days. All TNT cases had been placed on an evaporated milk (EM) formula (2-3x protein content of proprietary formula) after hospital discharge, and only one had received vitamin C prior to Guthrie testing and subsequent serum quantitation (by spectrophotometric method of Ambrose) of tyrosine and phenylalanine. Tyrosine levels returned to normal (<3.5mg%) or near normal within 24-48 hours after lowering the protein intake or within 7-14 days after the administration of vitamin C (100mg%).

Biochemical studies of recent cases before treatment have revealed a marked urinary excretion of p-OH-phenylpyruvic acid (6/6 cases) and a generalized aminoacidemia (2/3 cases). No TNT infants were symptomatic, and physical and neurological exams were within normal limits. However, in the only two cases studied with EEG's, abnormal recordings (generalized delta grade I in one and biparietal dysrhythmia grade III in the other) reverted to normal shortly after the tyrosine level returned to normal; these findings, coupled with the report of Menkes et al (APS-SPR meetings, April,1971) suggest that TNT may be injurious to the developing central nervous system.

If further investigations substantiate this preliminary evidence, the true incidence of TNT in the term neonate taking an EM formula should be established. By present screening procedures those infants who might develop tyrosinemia because of the high protein content of an EM formula begun after discharge would not be detected because they would have already had a negative Guthrie test in the nursery while receiving a proprietary formula.

SPECIFIC ENDOGENOUS MITOTIC INHIBITORS FOR LEUKEMIC LYMPHOCYTES IN VITRO. Hiltje C. Irausquin and John C. Houck, Children's Hospital and George Washington University, Washington, D.C. 20005.

The mitotic rate of human lymphoid tumor cells in culture is determined by the amount of tritiated thymidine incorporated by these cells after 4 hrs. incubation. The rate of thymidine incorporation by these cells was remarkably depressed (50-90%) when they were exposed to dialyzed, lyophilized aqueous extracts of lymphoid tissues from cow, swine and rat. Extracts of the spleen thymus or lymph node of these various three species all possessed the ability to markedly depress the H^3 thymidine uptake after 4 hrs. incubation by these cancer cells in vitro. The cytotoxicity of these fractions judged by the cytology and the exclusion of vital dye was significant but not considerable during this time period. However, most of the cytotoxicity could be removed by molecular sieving using Amicon Diaflo filters. The cytotoxic-free inhibition of the mitosis of human lymphoid tumor cells in culture was associated with a factor weighing between 30,000 and 50,000 daltons. The inhibitory activity could not be extracted from non-lymphoid tissue, i.e., muscle, or WI-38 fibroblasts. Further, this inhibitory fraction had no effect upon the mitotic rate of either HeLa cells or WI-38 fibroblasts in culture.

This mitotic inhibitory activity was thermolabile, destroyed by trypsin and soluble in 70% ethanol. This inhibition could also be demonstrated for normal human lymphocytes when they were transformed by either phytohemagglutinin or in mixed leukocyte culture.

These aqueous extracts of lymphoid tissue were dialyzed against water, which both removed small molecular weight nucleotides which could dilute out the tritiated thymidine pool size and precipitated euglobulins, including the thymidine phosphorylase activity which is present in uniquely high concentrations in lymphoid tissue.

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CYSTATHIONASE: IMMUNOCHEMICAL EVIDENCE FOR ABSENCE FROM HUMAN FETAL LIVER. Theresa A. Pascal, Bruce M. Gillam, and Gerald E. Gaull. Department of Pediatric Research, New York State Institute for Basic Research in Mental Retardation, Staten Island, New York, and Department of Pediatrics, Mt. Sinai Hospital School of Medicine of the City University of New York.

Cystathionase in human liver does not appear until after birth, and its early absence suggests that cyst(e)ine, a product of cystathionase, may be an essential amino acid in the human fetus and premature infant (Sturman, J.A., Gaull, G.E., and Raiha, N.C.R., Science 169: 74, 1970). It was thus of clinical and theoretical interest to determine whether the human fetus is competent to synthesize cystathionase. Such data might be relevant to attempts at facilitating the metabolic adjustment to premature extra-uterine existence. Immunochemical studies were initiated to determine whether the virtual absence of cystathionase activity is because of the presence in the fetus of a precursor enzyme protein, as yet inactive but immunochemically related to the adult enzyme, or whether the fetus is incompetent at this stage to synthesize the intact enzyme protein.

Purified human liver cystathionase was obtained by ammonium sulfate fractionation (45-65%) saturation, and starch block and disc gel electrophoresis Antibodies to the human enzyme were induced in the rabbit using as antigen, cystathionase in polyacrylamide gel. A pooled homogenate from 14 human fetuses (5.7 to 20 cm crown-rump length) obtained at therapeutic abortion was compared by agar double diffusion analysis with an homogenate from normal human adult liver. A specific enzyme stain, using cystathionine as substrate, was used to detect cystathionase activity in the immune precipate.

The presence of an enzymatically inactive immune precipitin band uniting with the catalytically active band formed with the adult liver was not detected with the fetal liver giving evidence that the human fetus is not competent to synthesize more than trace amounts of the intact enzyme. The absence of active or precursor fetal liver cystathionase immunochemically related to the adult form was confirmed by absorption and immunotitration studies.

DERMATOGLYPHIC STUDIES IN LEUKEMIC CHILDREN

Norman Jaffe, Mary A. Whelan, Lakshmi Das, Miriam Manning and Demetrius G. Traggis, Children's Hospital Medical Center, Children's Cancer Research Fndn. and Harvard Medical School, Boston, Mass. (Intr. by Sidney Farber).

Conflicting reports relating to the prevalence of simian and Sidney lines in leukemia prompted a study of 82 children of whom 71 had been diagnosed as acute lymphoblastic leukemia (mean age 94 mths.) and 11, leukemias of other types (mean age 105 mths.). There were no apparent congenital anomalies in these patients and no children with congenital leukemia. As an independent control, 11 patients with Wilms' tumor (mean age 61 mths.), 10 with neuroblastoma (mean age 63 mths.) and 131 normal siblings comparable in age and sex were also studied.

The following characteristics were examined: 1) Presence or absence of simian lines, Sidney lines, thenar, hypothenar or interdigital patterns; 2) ATD angle (measured in degrees), and 3) distribution of fingerprint patterns (classified as ulnar loops, radial loops, arches and whorls). The results were analyzed separately by disease category and sex.

There were no significant differences between index and control children. The findings also failed to establish an event at the appropriate stage of embryological differentiation reflecting itself in dermatoglyphic shifts in this group of leukemic children. (Supported by NIH Grant C-6516).

KINETICS AND SUBCELLULAR DISTRIBUTION OF GROWTH HORMONE IN HUMAN AND RAT LIVER SLICES. Iraj Rezvani, Vaddanahally T. Maddaiah, Platon J. Collipp, Joseph Thomas, Raj K. Sharma and Shang Y. Chen. Nassau County Medical Center, East Meadow, New York.

Human (autopsy) and hypophysectomized or normal rat liver slices were incubated at 37° in Kreb's bicarbonate buffer with ^{3}H-acetyl human growth hormone (^{3}H-HGH) or ^{3}H-acetyl bovine growth hormone (^{3}H-BGH). Uptake of both labeled hormones into liver slices increased sharply up to 10 min. and plateaued off at 20 min. Uptake by rat liver slices with increasing concentrations (up to 50 ug/ml) of ^{3}H-HGH or ^{3}H-BGH followed a sigmoid (S-shaped) curve. With human liver slices kinetics was sigmoid with ^{3}H-HGH, but followed a simple saturation curve with ^{3}H-BGH. ^{3}H-HGH uptake was significantly reduced when incubated with unlabeled hormone but not with either nitrated hormone (biologically inactive and immunologically active) or inactive fragment of BGH (Sonnenberg). Percent subcellular distribution (Homogenate=100) labeled hormones in human liver slices are as follows:

Hormone	^{3}H-HGH						^{3}H-BGH	^{3}H-Albumin
Time	2	5	10	20	40	60	20	20
Nucl.	26	26	29	33	38	38	31	10
Mito.	18	21	20	20	24	25	24	7
Micro.	15	16	14	13	14	15	13	5
Cyto.	41	37	37	34	23	20	32	76

Time course of distribution with ^{3}H-HGH was different from the in vivo distribution in hypophysectomized rats. Distribution of ^{3}H-HGH and ^{3}H-BGH were identical but were different from that of ^{3}H-albumin.

GAS CHROMATOGRAPHIC ANALYSIS OF CONCENTRATIONS OF 16 AMINO ACIDS IN AMNIOTIC FLUID FROM EARLY, MIDDLE, AND LATE PERIODS OF HUMAN GESTATION.
Joseph D. Schulman, M.D., John T. Queenan, M.D. and Larry Doores, Cornell University Medical College and New York Hospital-Cornell Medical Center, Departments of Pediatrics and Obstetrics and Gynecology, New York City.

28 early (14-20 wks gestation), 10 middle (21-36 wks), and 23 late (37-41 wks) amniotic fluid samples were analyzed for amino acid concentration by gas chromatography of the n-propyl-N-acetyl derivatives. The amino acids and the alpha-amino adipate internal standard were eluted from short Dowex 50 columns, then propylated and acetylated in a Packard derivatizer. Mean values in micromoles/10 ml are given in the table.

	Al	Val	Gly	Iso	Leu	Pro	Thr	Ser	Asp	Met	Phe	Glu	Tyr	Orn	Lys	Tryp	
Early	3.2	1.7	1.5	.34	.74	2.3	1.7	.46	.47	.26	.82	2.9	.50	.40	2.0	<.028	
Middle	2.4	.72	-	-	.40	2.4	1.1	.48	.24	.14	.68	1.9	.38	.40	1.7	<.007	
Late	1.3	.51	1.2	.13	.26	1.2	.84	.60	.32	.09	.36	1.3	.26	.38	.94	<.004	

Mean concentrations of almost all amino acids declined with increasing gestational age, but serine concentrations increased. The difference in the means for each amino acid in early and late fluids was statistically significant ($p<.05$) except for ornithine ($p=.4$). Tryptophan levels were very low, the means were calculated excluding fluids with less than 1 nanomole/10 ml, and statistical analysis was not attempted for this amino acid.

This report documents the feasibility of gas chromatographic analysis of amino acids in biological fluids using an automated, commercially available derivatizer. Advantages of the method are: lower cost than ion-exchange systems; instrument flexibility and ease of maintainence; 2 hour analysis time; sensitivity in the nanomolar range; ability to measure tryptophan. Disadvantages include: need for additional sample preparation to measure cystine, histidine, and arginine; some loss of precision and accuracy due to need for sample preparation and derivatization; lack of full automation, so that certain manual operations are required before and after derivatization.

EFFECT OF COLD EXPOSURE UPON GROWTH OF THE NEWBORN RABBIT. Myron Sokal (Intr. by Robert W. Winters). Department of Pediatrics, Columbia University College of Physicians & Surgeons and Babies Hospital, New York, N.Y.

The effect of cold exposure upon newborn rabbits has been investigated in order to study the interrelationships of food intake, growth and metabolic rate. Rabbits were divided at birth into "warm" and "cold" groups. The "warm" group was raised for the first week at 35°C and for the second week at 32°C, temperatures which were shown to be in the thermoneutral zone. The "cold" group was raised at 30°C for the first week and 27°C for the second week, temperatures which were shown to increase oxygen consumption by 50 to 100%. Rabbits were returned to the mother for 5 to 15 minutes per day for feedings; milk intake was measured accurately by the body weight before and just after feeding. Half of the rabbits were killed at the end of one week and the remainder at the end of two weeks. Liver, kidney, heart, brain, lung and muscle were removed, weighed and analyzed for nucleic acid and protein contents.

The two groups grew at rates which were not significantly different nor were significant differences found with respect to milk intake. Differences in organ weight, nucleic acid or protein contents attributable solely to the influence of temperature were not found; however, multivariate analysis revealed a significant interaction of environmental temperature and increasing age upon growth of heart and kidney of the "cold" versus the "warm" animals. The apparent paradox of a similarity of weight gain between the groups in the face of a similar intake of milk but a different oxygen consumption may be explained by a difference in gastrointestinal utilization of ingested calories or by some other unmeasured parameter of body composition. (Supported by HD-03993).

PHYSICAL AND CHEMICAL CHARACTERISTICS OF AMNIOTIC FLUID
Daniel Stowens, Robt. L. Smith & William H. Sanders
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The characteristics of amniotic fluids obtained from pregnancies of from 8 to 40 weeks were determined. The values for term fluids were: osmolality, observed 258 mOsm; calculated 243 mOsm; (in meq/l) Na 125; Cl 105; K 4.3; (in mgm/100 ml) glucose 31; urea N 15; creatinine 2.2; uric acid 9.3; cholesterol 27; Ca 6.2 Phosp. 1.8; bilirubin 0.2 (in Gm/100 ml) protein 0.44; alb 0.25 glob. 0.19; (in mU./ml) alk. phosph. 139; LDH 175; OGT 39. ∝ - fetoprotein was present in samples from gestations of less than 11 weeks. Ammonia- traces. Statistically significant differences are present between term observed and calculated osmolalities; for creatinine at term and at all times before; and for values of enzymes, uric acid, glucose and sodium in early and term specimens. Differences between amniotic fluid osmolality and those of maternal and fetal serum and of urine aid in explaining the rapid turnover in amniotic fluid and correlated with the largely "juxtamedullary" anatomy of the fetal kidney. The composition of the fluid indicates it is the product of an active, selective fetal physiologic function.

CORD BLOOD CHOLESTEROL AND PARENTAL TRIGLYCERIDE. R. Tsang, R. Fallatt, P. Steiner, C.J. Glueck (intr. by J. Sutherland). Univ. of Cincinnati, College of Medicine, General Clinical Research Center, Cincinnati

Parental and neonatal lipids were measured in 2000 live births; follow-up studies were done in selected complete kindred (mother, father, baby). Umbilical cord blood cholesterol (UC) was elevated above an arbitrary upper normal limit of 95 mg% in 84 neonates. Eighteen of these neonates (mean UC±SD, 112±22) had parents with primary triglyceride (TG) elevations (mean TG 286±98, range 214-576), normal plasma cholesterol (C) 212±34), and Type IV hyperlipoproteinemia. Mean umbilical cord blood triglyceride (UTG) (22±13) in these neonates did not differ from UTG (22±20) in 26 normal neonates (UC 67±10) who came from normal kindred. Normocholesterolemic neonates (UC 72±13) coming from 56 kindred with elevated parental TG (283±181, range 202-1580 mg%), had UTG (31±18) similar to UTG of hypercholesterolemic neonates of Type IV parents. In 19 neonates from Type II kindred (parental C 282±32, range 244-368), elevated UC (117±30) and cord blood "beta" lipoprotein cholesterol (UC-BLP, 67±25) did not differ from UC (112±22) or UC-BLP (67±29) in the 18 hypercholesterolemic neonates from Type IV kindred. In normo- or hypercholesterolemic neonates whose parents had primary elevations of TG, UTG did not correlate with TG of the abnormal parent. In normal neonates with normal parents, UTG did not correlate with TG of either parent. In normal or hypercholesterolemic neonates with Type IV parents, UC did not correlate with TG of the abnormal parent. Neonates in 47 kindred had elevated UC (110±19) with normal maternal C and TG (186±30, 86±43) and normal paternal C, TG (177±31, 98±52). Screening of UC identifies neonatal familial Type II and hypercholesterolemic, normotriglyceridemic infants from Type IV kindred. Longitudinal follow-up of such neonates and those with "false positive" hypercholesterolemia, may contribute to further understanding of Type II and Type IV hyperlipoproteinemia in childhood.

BLOOD VOLUME IN THE HUMAN FETUS Alice C. Yao and Therese Lu, Departments of Pediatrics and Obstetrics-Gynecology, Downstate Medical Center Brooklyn, New York (Introduced by Elizabeth M. Smithwick)

The purpose of this study was to determine the blood volume of the developing human fetus during the previable stage. Blood volume was measured by the radioisotope dilution technique (RIHSA-125) in seven human fetuses during hysterotomy for therapeutic and/or legal abortions. Maternal complications included diabetes, liver cirrhosis, epilepsy and hypertension. Gestational ages ranged from 12-20 wks; fetal weights, 80-687 gms. (mean 266 gm); placental weights, 84-202 gm. (mean 138 gm.).
Results:

	No. of cases	Hct. %	BV ml/kg*	RCV ml/kg*
Midterm fetus	7	33 (29-39)	77 (60-100)	22 (13-30)
Term infant	111	48-65+	90 (86-110)	44 (36-52)

Our results are in agreement with others' studies which have shown that the hematocrit of the midterm human fetus is significantly lower than those of term and near term infants. Furthermore, our findings suggest that the blood volume and red cell volume of the midterm fetus are also significantly lower.

BV= blood volume, RCV= red cell volume, Hct.= hematocrit, Mean (range), *fetoplacental weight in kilogram, +values for early and late cord clamped infants.

CARDIOLOGY

First Session

THE EFFECT OF 17, β-ESTRADIOL ON THE MAGNITUDE AND DISTRIBUTION OF UTERINE BLOOD FLOW IN PREGNANT AND NONPREGNANT EWES. Charles R. Rosenfeld, Allen P. Killam, Giacomo Meschia, Edgar L. Makowski, and Frederick C. Battaglia, Div. Perinatal Medicine, Univ. of Colorado Medical Center, Denver.

Abnormalities in uterine blood flow (UBF) have been suggested as possible causes of retarded fetal growth. As there appears to be no direct effect of changes in respiratory gas tensions on the control of UBF, its regulation may be hormonal. The administration of exogenous estrogen has been shown to cause a rise in UBF in both pregnant and nonpregnant ewes. We have utilized a new biologic preparation which permits measurement of the magnitude and distribution of UBF by means of electromagnetic flow probes and radioactive microspheres before and after a 2-minute IV infusion of 17, β-estradiol into nonpregnant and pregnant unstressed ewes. In the former, UBF increased ~ 13 times the control values, from flows of 20-30 ml/min. to 300-400 ml/min. The myometrium, endometrium, and specialized sites of implantation (caruncles) of the nonpregnant uterus each accounted for ~ 33% of the increase in UBF. The mean flow per gm. of tissue to the caruncles and endometrium was much greater than that to the myometrium, 9.00 ± 1.49 ml/gm/min. and 7.19 ± 1.02 ml/gm/min. vs. 1.55 ± 0.40 ml/gm/min. respectively. In pregnant animals, the estradiol response was related to gestational age and limited to endometrium and myometrium without significant changes in placental flow. The effect of surgical stress in altering blood flow to reproductive tissues was clearly demonstrated. When estrogen-stimulated UBF in surgically-stressed and in unstressed ewes were compared, the maximum UBF attained in the stressed group was ~ 100 ml/min. less than in the unstressed group. This occurred despite mean arterial pressures in the stressed vs. unstressed ewes of 131 vs. 104 mm Hg respectively. These observations support the hypothesis that UBF is under hormonal regulation and demonstrate that large changes of UBF in the pregnant animal can be limited to tissues other than the placenta.

PULMONARY CIRCULATION IN FETAL LAMBS: Abraham M. Rudolph and Michael A. Heymann
Univ. of California-San Francisco, Cardiovascular Research Inst. and Dept. of Ped.

Previous observations of phasic flow in the fetal pulmonary circulation have been made in acute exteriorized open chest preparations. Although O_2 is known to dilate fetal pulmonary vessels, the exact pattern of response to changes in PO_2 in the fetal range have not been delineated. Since patterns of flow and vascular responses may be drastically altered in acute preparations, we examined the pulmonary circulation in intact fetal lambs in utero. Using methods described previously a left thoracotomy was performed in 3 fetal lambs with gestational ages of 115-135 days. A precalibrated electromagnetic flow transducer (Statham SP 2202) was placed on the artery supplying both lungs (PA). In fetal lambs this arises from the main pulmonary trunk as a single vessel before dividing into the left and right pulmonary arteries. Polyvinyl catheters were inserted into the PA and systemic arteries. Studies were performed after a 4-5 day recovery period. PA flow and PA and systemic arterial pressure were monitored continuously. Flow velocity peaked in early systole, fell rapidly by midsystole with a further gradual fall and prominent reversal of flow in early diastole. Decreasing pulmonary vascular resistance by acetylcholine infusion into PA markedly decreased negative flow. Without changing pH and P_{CO2} PA P_{O2} was altered from control levels of 18-21 mm Hg by either increasing or decreasing O2 concentration in maternal inspired air. These studies were performed repeatedly over several days in the same fetus. Calculated pulmonary vascular resistance was related to PA P_{O2} and showed a progressive rise as P_{O2} was reduced from 27 to 8 mm Hg. In the 115 day fetus there was only about a 3-fold rise in resistance but in the 135 day fetus there was a 10-20 fold increase. The constrictive effects of hypoxia were not altered by alpha or beta adrenergic blockade. There is suggestive evidence that pulmonary vascular responses to O_2 vary with gestational age.

Supported by HE 06285

AN INTRAVASCULAR ELECTRODE FOR CONTINUOUSLY MONITORING ARTERIAL OXYGEN TENSION. Edwin G. Brown, Chung C. Liu, Francis E. McDonnell, Michael R. Neuman, Avron Y. Sweet. Dept. of Pediatrics and the Perinatal General Clinical Research Center, Case Western Reserve Univ. at Cleveland Metropolitan General Hospital, Cleveland.

A miniature electrode (cathode) which can be embedded in the wall of a #5 F polyvinylchloride (PVC) arterial catheter has been designed to continuously monitor aortic blood oxygen tension (PO_2) of neonates. PO_2 is determined polarographically at the cathode when molecular oxygen is reduced to hydroxyl ions by combining with water and electrons. The net cathode current is proportional to PO_2. The cathode consists of an epoxy insulated gold wire covered with a thin membrane of PVC which reduces motion artifact and eliminates direct contact of the electrode with the blood. The circuit is completed by a silver-silver chloride electrode. A current pre-amplifier provides a constant polarizing voltage of 0.6 V across the electrodes. Cathode current is linearly related to PO_2 and variations due to temperature are predictable and can be compensated. Cathode current is not affected by changes in pH, PCO_2 or by gas sterilization.

Electrodes operated in vitro under conditions of constant temperature and PO_2 for 96 hours have shown no more than 5% variation in output. Prompt and accurate detection of changes in PO_2 has been observed in dogs subjected to various environmental oxygen concentrations. Changes in PO_2 are recorded and serve to indicate the need to obtain blood samples for more precise, traditional measurements. This system is unique in that blood samples may be obtained at any time to check calibration and measure other important parameters while the electrode is operating.

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THE IN VITRO RESPONSE OF THE LAMB DUCTUS ARTERIOSUS TO PROSTAGLANDINS
Peter M. Olley and Flavio Coceani (Intr. by Andrew Sass-Kortsak)
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A series of experiments was undertaken to test the possibility that prostaglandins, a group of naturally occurring vasoactive lipids, may be implicated in functional closure of the ductus arteriosus at birth. Circular and longitudinal strips of ductus arteriosus from near term lamb foetuses were suspended in an organ bath and their mechanical activity was recorded isotonically. Under anoxic conditions, prostaglandin E_1 (PGE_1) produced a profound and persistent relaxation of ductal tissue over a dose range from 10^{-9}M to 10^{-5}M. Upon exposure to oxygen, the ductus developed a sustained contraction and became less sensitive to PGE_1. At times, no effect by PGE_1 could be elicited in the O_2-treated tissue. A similar pattern of activity was observed with prostaglandin E_2 (PGE_2) whereas prostaglandins A_1 (PGA_1) and F_{1a} (PGF_{1a}) produced no responses. PGE_1 and PGE_2 had little effect on the anoxic tissue depolarized by excess potassium. Papaverine, 10^{-5}M, relaxed the ductus to the same degree before and after exposure to oxygen. Separate experiments showed that PGE_1 and PGE_2 are natural constituents of ductal tissue during foetal life. The results suggest that E-type prostaglandins may have a role in maintaining patency of the ductus arteriosus prior to birth. An additional suggestion from these findings is that functional closure of the ductus at birth may not occur if tissue sensitivity to prostaglandins is unaffected by the rise in blood oxygen tension.

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VENTRICULAR PERFORMANCE, CORONARY FLOW, AND MVO_2 IN THE HYPERTROPHIED RAT HEART. Walter J. Gamble, Charlie Phornphutkul, and Amy Kumar (Intro. by Richard Van Praagh). Harvard Medical School, The Children's Hospital Medical Center, Boston, Massachusetts, 02115.

This study was undertaken to determine whether there was an increase in oxygen consumption in the hypertrophied heart. Left Ventricular Hypertrophy (LVH) was produced in Charles River rats by incompletely ligating the aorta above the renal arteries to a small, relatively consistant cross section. As compared to age matched sham operated controls, there was significant ($p < .005$) LVH as measured by the ratios of left ventricular/body weight or of left ventricle/right ventricle. No significant difference was found for right ventricle/body weight. The hearts were rapidly excised and perfused with arterial blood from an anesthetized support rat. Fifty-five steady state determinations of left ventricular systolic and diastolic pressures, heart rate, coronary flow, and myocardial oxygen consumption were made at systolic pressures from 50 to 200 mm Hg. in 6 hypertrophied hearts. Forty-eight similar sets of data were obtained from 7 control hearts. No control heart could sustain systolic pressures above 175 mm Hg. where as 4 of the 6 hypertrophied hearts maintained 195 mm Hg. or better. No significant difference in diastolic pressures or coronary flows were found. Myocardial oxygen consumption/gram/beat was significantly less ($p < .01$) in the hypertrophied hearts at systolic pressures of 75 mm Hg. or more. Thus one may conclude that at a given pressure, the oxygen requirements are less, presumably because in the hypertrophied heart the tension per unit cross section of myocardium is less at a given pressure.

INCIDENCE AND TREATMENT OF PATENT DUCTUS ARTERIOSUS IN THE LOW BIRTH WEIGHT NEONATE. Richard D. Zachman; Marion K. Ledbetter; Richard J. Botham; George P. Steinmetz; and Stanley N. Graven, Univ. of Wis., Dept. of Peds., St. Marys Hosp. Med. Ctr., Madison, Wis.

Twelve to 15% of patients admitted to a Neonatal Intensive Care Unit developed a patent ductus murmur. In a 3 1/2 year period, of 82 patients with the clinical diagnosis of a persistent patent ductus arteriosus, confirmation was made in 43% - by surgery alone (28%), autopsy (10%) or aortography (5%).

Of 28 patients without failure, 3 (11%) had severe respiratory distress syndrome, 16 (57%) had transient respiratory distress, 5 (18%) were $\leq$ 29 weeks gestation and 17 (60%) were $\leq$ 33 weeks gestation.

The remaining 54 patients (66%) went into congestive heart failure in the nursery and required digoxin and diuretic therapy. Twenty six (50%) had severe respiratory distress syndrome, 21 required respirator therapy. Transient respiratory distress occurred in 10 other patients and 11 (20%) were $\leq$ 29 weeks gestation. Forty seven (87%) were $\leq$ 33 weeks gestation.

Twenty three of those in congestive failure underwent surgical ligation of the ductus. All 23 were under 34 weeks gestation, 80% were $\leq$ 32 weeks. One weighed over 2.0 Kg, 75% weighed less than 1.5 Kg. Seventy per cent survived surgery, their clinical course improved, and they were discharged. The surgical survival rate in those over 1.0 Kg was 85%. Thirty one patients were treated for failure only medically. There were 11 deaths in this group, 4 attributed to refractory congestive failure from shunting through a patent ductus arteriosus.

Congestive heart failure from a persistent patent ductus arteriosus in the low birth weight neonate with respiratory distress has occurred in 20-25% of our cases. Surgical repair has yielded good results and is undertaken when severe congestive failure fails to respond medically.

LEFT VENTRICULAR ISCHEMIA IN SEVERE VALVAR AND SUPRAVALVAR AORTIC STENOSIS: A COMMON MECHANISM. William R. Vincent, Gerald D. Buckberg, Julien I.E. Hoffman. UCLA Sch. of Med., Depts. of Ped. and Surg.; and Cardiovascular Research Institute and Dept. of Ped., Univ. of California, San Francisco.

Severe valvar aortic stenosis (VAS) and supravalvar aortic stenosis (SVAS) can cause left ventricular (LV) subendocardial ischemia and infarction with unobstructed coronary arteries. While LV ischemia in VAS has been related to reduced coronary perfusion relative to raised metabolic requirements, ischemia in SVAS has been considered to be on some other basis because coronary perfusion pressure is high. Since LV subendocardial coronary blood flow is diastolic a diastolic pressure time index (DPTI) (area between aortic and LV pressure curves in diastole) was used to estimate it. LV oxygen requirements were estimated from the tension time index (TTI). The ratio DPTI:TTI (supply:demand) was used to estimate the adequacy of subendocardial flow. We constricted the supravalvar aorta in 10 dogs and measured phasic left coronary blood flow (CBF) with an electromagnetic flow meter and LV subendocardial and subepicardial blood flow with 8-10 μ radioactive microspheres. Flow was homogeneously distributed (inner:outer 1:1) and predominantly diastolic (80% of total CBF) before aortic constriction. Although total CBF rose significantly following aortic constriction ($p < .01$), diastolic flow fell to 38% of total CBF ($p < .01$) and the proportion of flow delivered to subendocardial muscle fell 63% ($p < .01$). Systolic coronary flow always increased but did not improve subendocardial underperfusion. Changes in flow distribution were predictable from the ratio DPTI:TTI; values below 0.7:1 were always associated with relative subendocardial underperfusion. DPTI:TTI values were calculated for one patient each with severe VAS and severe SVAS. In both DPTI was reduced by shortened diastole and high diastolic pressure. TTI was raised by high systolic pressure and prolonged systole. Both had ECG changes of LV ischemia and DPTI:TTI values below 0.7:1. The mechanism of subendocardial ischemia is the same in both diseases and its presence is predictable from pressure measurements which are readily obtainable at cardiac catheterization.

EFFECT OF AUTONOMIC DRUGS ON EXCITATION AND CONTRACTION IN NORMAL AND DEPRESSED MYOCARDIUM, Henry Gelband, Arthur L. Bassett and Brian F. Hoffman. Dept. of Pharmacology, College of Physicians and Surgeons, New York, and the Dept. of Pediatrics, University of Miami School of Medicine, Miami. (Intro. by W. W. Cleveland).

The effect of acetylcholine (ACh) and epinephrine (Epi) on cardiac muscle contractility depends, in part, on the degree of membrane polarization. To determine the importance of altered resting potential (RP) in relation to force generation, we studied the actions of these drugs on normal myocardium and cardiac muscle partially depolarized by chronic congestive heart failure, toxic concentrations of acetylstrophanthidin (ACs), and acute overstretch. Standard microelectrode and isometric recording techniques were used to measure electrical and mechanical activity. ACh caused membrane hyperpolarization and decreased developed force (P) in normal dog, cat, and human atrial muscle, obtained at cardiac surgery, while Epi had little effect on resting potential but increased P. Both ACh and Epi increased RP, action potential (AP) amplitude, AP rate of rise, and P for partially depolarized right atrial muscles removed from animals in chronic experimentally induced right heart failure. Epi increased P and simultaneously improved RP, AP amplitude for right ventricular papillary muscles (RVPM) from cats in chronic right heart failure; Epi had little effect on RP in normal RVPM. ACh reversed the negative inotropy (increased P), decreased resting force, simultaneously increased RP, AP amplitude in dog and human atrial muscles partially depolarized by excessive concentrations of ACs and digitalis. ACh also reduced resting force and increased RP in unstimulated ACs poisoned dog atrial muscles. These effects were blocked by atropine. ACh and Epi caused membrane hyperpolarization and increased P in dog atrial muscles partially depolarized by excessive stretch. These data suggest that, under certain clinical circumstances, the positive inotropic effect of catecholamine may result, at least in part, from hyperpolarizing actions, thereby recruitment and more synchronous activation of contractile cells. (Supported by NHLI Grant 12738)

CARDIOVASCULAR EFFECTS OF PROPRANOLOL IN PUPPIES. Nestor J. Truccore and C.Robert Levine. Columbia Univ.Coll.of Phys.& Surg. Dept. of Ped., New York, N.Y.

The acute cardiovascular effects of propranolol were studied in 7 intact adult dogs, and in 7 intact mongrel puppies 3 to 6 wks old weighing 0.7 to 1.4 kg. Morphine-chloralose anesthesia was used, with artificial ventilation via endotracheal intubation. Cardiac catheters were passed into the right atrium via the jugular veins, and into the left ventricle (LV) via a carotid artery. A tipmanometer catheter was also passed into the LV to measure the rate of LV pressure development (dP/dt). Cardiac output (CO) was determined by indocyanine green dye dilution, using a continuous flow system in the puppies. Measurements were made of heart rate (HR), CO, LV peak systolic pressure (LVPSP), LV end-diastolic pressure (LVEDP), and LV dP/dt, and were repeated 5 mins after intravenous administration of propranolol, 0.5mg/kg.

In the adult dogs there was a significant fall in cardiac index (CI) and peak dP/dt ($p<.01$), an increase in LVEDP ($p<.05$), and no statistically significant change in HR, stroke index (SI), LVPSP, systemic resistance index (SRI), or dP/dt at 40 mmHg LV pressure (P_{40}dP/dt). In the puppies there was a significant fall in HR ($p<.01$), CI ($p<.05$), LVPSP ($p<.05$), peak dP/dt ($p<.05$) and P_{40}dP/dt ($p<.01$), an increase in LVEDP ($p<.05$), and no significant change in SI or SRI. The control peak dP/dt in the puppies averaged 20% of the adult value ($p<.01$); the control P_{40}dP/dt was not significantly different between the two groups. The percent fall in mean HR, CI, LVPSP, peak dP/dt and P_{40}dP/dt after propranolol was 2 to 4 times as great in the puppies as in the adult dogs.

This study suggests that the sympathetic nervous system is more important for maintenance of normal resting cardiovascular performance in puppies than in adult dogs.

EARLY ARTERIAL CALCIFICATION IN INFANCY AND CHILDHOOD AND ITS RELATION TO THE ARTERIAL GROWTH. Wladimir W. Meyer and John Lind, Karolinska Institute, Department of Pediatrics, Stockholm, and University of Mainz, Institute of Pathology, Mainz.

Calcific deposits represent a common and early lesion of the human arteries. With an appropriate technique, calcifications of the internal elastic membrane have been demonstrated grossly in the common and internal iliac arteries in half of all 25 autopsied newborns and infants in the first four weeks of life, in 10 of 13 infants aged 1-11 months and nearly in all 31 children aged 1-12 years. The early selective development of calcific deposits in the common and internal iliac arteries is probably related to their position and function in fetal circulation. During fetal development these arteries unite the abdominal aorta with the umbilical arteries and are therefore subject to the full impact of the large blood volume in the placental circuit. This results in accelerated growth of the iliac arteries and some structural characteristics which probably favor the calcific deposits. The siphon of the carotid artery is another common site of early calcifications in infancy and childhood. In this tortuous arterial segment calcific deposits have been demonstrated grossly in all 22 children aged 1-16 years. In half of these cases the children died after accidents and were probably healthy before. The tortuosity of the siphon, which increases during fetal development, the high rate of prenatal and postnatal growth of the brain and its supplying arteries, as well as some general factors may be responsible for the early development of calcifications in this arterial segment.

CARDIOVASCULAR RESPONSES TO HYPOXEMIA AND TO ACIDEMIA IN UNANESTHETIZED FETAL LAMBS. Herbert E. Cohn, Edmond J. Sacks, Michael A. Heymann, and Abraham M. Rudolph.

Previous studies of fetal circulation during asphyxia were done acutely and did not separate the effects of hypoxemia from acidemia. We studied circulatory responses during these states in 10 late gestation fetal lambs in utero. Vinyl catheters were placed in various fetal and maternal vessels as previously described. The fetuses were studied 48 hours post-operatively. Fetal heart rate, arterial pressure, pH, PO_2, PCO_2, were obtained during a control period and while the standing ewe breathed 7-10% O_2 and 3% CO_2 for 20-60 minutes. Cardiac output and its distribution were measured during control and hypoxemic states using labelled microspheres. Two groups of fetuses were studied: those that became hypoxemic(H) mean PO_2 13, pH 7.35, and those that also became acidemic(HA) mean PO_2 12, pH 7.27. Fetal PCO_2 values were normal throughout. During hypoxemia, fetal arterial pressure increased and fetal heart rate decreased. In all but one, cardiac output decreased. Blood flow to the fetal body decreased, but umbilical flow was maintained or increased. Organ blood flows changed markedly and there were differences in the H and HA groups. The percentage increases from controls were: cerebral(H+86,HA+28), and myocardial(H+156,HA+42). The percentage decreases from controls were: renal(H-26,HA-76), gut(H-28,HA-83), splenic (H-48,HA-92), and carcass(H-47,HA-85). These studies demonstrate the redistribution of cardiac output that occurs during fetal hypoxemia. Although the directional changes of blood flow are similar, there are marked differences in the magnitude of change in organ blood flows with hypoxemia alone, and with combined hypoxemia and acidemia.
Supported by NIH Grant HE 06285

CARDIOLOGY

Second Session

THE TRICUSPID VALVE IN DOUBLE-INLET LEFT VENTRICLE (DILV), NATURALLY OCCURING IN THE HUMAN, EXPERIMENTALLY PRODUCED IN THE CHICK
Gessner, Ira H., and Van Mierop, L. H. S.; Univ. of Fla., Coll. of Med., Dept. of Ped., Gainesville, Fla. 32601

DILV is an unusual congenital heart defect in which both the mitral and tricuspid valves open into the left ventricle. The right ventricle consists only of an outflow chamber and complete transposition of the great vessels usually is associated. Early in cardiac development, the entire atrioventricular (A-V) canal opens only into what will become the left ventricle. If this relationship is maintained after normal division of the A-V canal, DILV results. DILV can be produced experimentally in the chick by temporarily placing a small wire device under the outflow portion of the 3-day chick embryo, displacing the cono-truncal area rightward and anteriorly. The human tricuspid valve is derived in major part from right ventricular muscle and is liberated from the ventricular wall by a process of diverticulation and undermining. If the right-sided portion of the A-V canal does not shift medially, the tricuspid valve must form from whatever surrounding ventricular structures are available to it. We have reviewed the tricuspid valve in 6 clinical cases of DILV and have found that the valve generally has two leaflets and supporting structure which are in mirror image to the normal mitral valve. The tricuspid valve in the chick is normally a muscular flap valve consisting of a single lateral leaflet. We have observed 23 instances of experimentally produced DILV in the chick, in which the tricuspid valve anatomically resembles the mitral valve. It is formed of two cusps, fibrous rather than muscular, and may have some chordae tendineae whereas the normal tricuspid valve has none. These observations support the contention that the anatomic characteristics of the tricuspid valve are determined by the ventricular structures surrounding the right A-V orifice. In DILV the right A-V orifice opens into theleft ventricle. Thus the tricuspid valve forms in a manner similar to the mitral valve and therefore closely resembles it anatomically.

EFFECT OF OXYGEN-HEMOGLOBIN AFFINITY ON OXYGEN CONSUMPTION AND CARDIAC OUTPUT OF NEWBORN PIGLETS FOLLOWING EXCHANGE TRANSFUSION. Maria Delivoria-Papadopoulos, Ronald J. Martens, Frank A. Oski and Robert E. Forster,II. University of Pennsylvania, School of Med.

Previous studies of piglets 3 hours after exchange transfusion with fresh heparinized maternal blood showed an increased P_{50} (P_{O_2} for 50% HbO_2 saturation at pH 7.40 and 39.6C°)and increased mixed venous P_{O_2} ($P_{\bar{v}}O_2$). The present studies were designed to investigate the importance of varying the hematocrit (Hct) of the donor blood on oxygen consumption (V_{O_2}) and cardiac output in 27 newborn piglets of mean weight 1.350g. Nine piglets were exchanged with blood of comparable Hct (30%), 10 piglets were exchanged with blood of higher (50%) Hct and 8 piglets served as controls. Measurements of blood gases, including $P_{\bar{v}}O_2$, P_aO_2, P_{50}, and $\%HbO_2$ saturation, 2,3-Diphosphoglycerate (2,3-DPG) levels and total V_{O_2} were determined before, 2 and 24 hours after exchange. Arteriovenous oxygen content differences (AVD) and cardiac output were calculated. In the exchanged piglets mean P_{50} was 27.0, 33.0 and 34.5 mm Hg respectively, 2,3-DPG was 4230, 9400 and 11600 mμM/ml RBC respectively, while in the control group those values did not change. Oxygen consumption was the same in all. In those piglets exchanged with normal Hct (30%) cardiac output first increased slightly 2 hours after exchange but decreased from a control value of 130 ml/min/Kg before exchange to 110 ml/min/Kg in 24 hours. In contrast, in those piglets exchanged with high Hct (50%) blood, cardiac output decreased from a control of 130 to 90 ml/min/Kg, in 2 hours and rose slightly to 105 ml/min/Kg 24 hours after exchange respectively. These studies indicate that the decrease in oxygen affinity following exchange transfusion results in a decreased cardiac output. By increasing O_2 capacity in addition a further reduction of cardiac output can be achieved.

CHANGES IN BLOOD PRESSURE AND FLOWS DURING SCIATIC NERVE STIMULATION IN NEWBORN PIGS UNDER HYPERCAPNIA AND HEMORRHAGE. G. Dasaradharama Reddy, N. Buckley, N. Gootman and P. Gootman, Long Island Jewish Med. Ctr., Dept. of Ped., New Hyde Park, N. Y. (Intr. by P. Lanzkowsky)

Previously we showed that changes in blood flow do occur in newborn pigs to peripheral and central nervous stimulation. (Circulation 44:111-114, 1971). Here we report the effects of hypercapnia and hemorrhage on blood pressure (BP), left ventricular pressure (LVP), heart rate (HR) and regional blood flows in 13 piglets (13 hours to 2 days) anesthetized with a mixture of 0.25-1.0% halothane in 50% N_2O-O_2, paralyzed with decamethonium. Respiration, ECG and arterial blood gases were monitored. Combinations of flows were recorded using calibrated electromagnetic flow probes on renal (RF), carotid (CF) and femoral (FF) arteries. Sciatic nerve stimulation (SNS) was used as a test of responsiveness of the central nervous system. Low frequency SNS resulted in decreased BP, RF and FF, unchanged CF, and increased HR. High frequency SNS produced increases in all. Hypercapnia ($PaCO_2$ = 53-91 mm Hg) by breathing 10% CO_2 increased BP, HR, CF, RF and FF; threshold for responses to SNS was higher, and the responses were smaller. Hemorrhage (20-30% of blood volume) produced marked tachycardia, hypotension and reduction in RF and FF, but CF was maintained. These results constitute evidence that adjustments of flow by the controlling system do occur in the newborn animal under conditions of stress.

LIMB BLOOD FLOW IN CHILDREN WITH TETRALOGY OF FALLOT AND NORMAL HEARTS FROM INFANCY TO CHILDHOOD.

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Experimentally induced hypoxia has been shown to produce an increase in limb blood flow. No information is available regarding the effect of long-standing hypoxemia on the peripheral circulation. Total systemic blood flow in Tetralogy of Fallot (TF) as measured by the Fick and dye dilution techniques is usually normal, slightly or moderately increased. To assess the peripheral blood flow in children with long standing hypoxemia we have obtained upper and lower limb blood flow by venous occlusion plethysmography in 10 children with TF and 31 normal children between one month to 12 years of age. Normal blood flow progressively increased with age from 1.49 $\pm$ 0.19 to 2.18 $\pm$ 0.44 in the calf and from 0.52 $\pm$ 0.07 to 1.41 $\pm$ 0.23 ml/min/100 ml tissue in the forearm. Whereas normal mean calf blood flow in all age groups was 1.88 $\pm$ 0.13 it was 1.07 $\pm$ 0.18 in 10 children with various degrees of TF (mean arterial O_2 saturation 80.04 $\pm$ 3.3%) and 0.56 ml/min/100 ml tissue in 5 severe cases of TF with known history of spells (O_2 saturation 73.1 $\pm$ 4.5%). While mean normal forearm blood flow was 0.98 $\pm$ 0.09 for all ages it was reduced to 0.38 $\pm$ 0.03 ml/min/100 ml tissue in the 5 severe cases of TF. This finding of abnormally decreased limb blood flow in children with TF is contrary to those seen in experimentally induced hypoxemia. This marked decrease in limb blood flow in severe TF as compared to total systemic flow measured by the Fick technique suggested the presence of a significant diversion of blood flow to more vital organs such as the brain and/or decreased oxygen consumption of the limbs. It is postulated that in children with TF these adaptive mechanisms to hypoxemia, at rest, may be altered during exercise because of peripheral arterial vasodilatation. The ensuing increase in peripheral blood flow may result in a redistribution of blood from the vital organs to the limbs and may explain the vulnerability of these children to cyanotic spells.

QUANTITATIVE ECHOCARDIOGRAPHIC MEASUREMENTS IN NORMAL NEONATES

University of Michigan - Wayne County General Hospital, Department of Pediatrics, Ann Arbor and Eloise, Michigan

Sundar Rajan, V., Vinay K. Duggal, Bruce D. Doust, and Ruth H. Strang (Intr. by William J. Oliver)

Qualitative echocardiography has been used diagnostically in neonates and small infants but most of the quantitative work has been done only in adults. The various standard measurements, i.e., cardiac chamber measurements, valve mobility, have not been determined in various pediatric age groups.

50 full-term normal neonates (25 males, 25 females) aged 48 hours to 15 days were selected for measurements. Three additional neonates with left to right shunts were studied. Values are tabulated:

	Normals		L to R Shunts		
	Mean (mm)	Range (mm)	A*	B**	C**
1) Right ventricular wall thickness	4.4	3-5	8	3	6
2) Mobility of anterior tricuspid leaflet	7.1	6-12	16	8	8
3) Left ventricular wall thickness	4.6	3-6	5	5	3
4) Mobility of anterior mitral leaflet	10.0	9-11	12	10	10
5) A.P. diameter of RV cavity	12.0	10-15	14	12	12
6) A.P. diameter of LV cavity	15.0	10-20	18	14	14
7) Thickness and motion of interventricular septum	2.7	2-5	6	2	3
8) A.P. diameter of left atrial cavity	7-0	6-9	10	6	10

***A was a full-term infant; **neonates B & C were prematures. Full-term infant A showed greater than normal RV wall thickness, greater diameter of LA cavity, and increased mobility of tricuspid leaflet.**

Previously quantitated echocardiographic measurements in adults have shown that the ratio of RV diameter to LV diameter is 1:3; our measurements in normal neonates recorded a ratio of 1:1. Also the ratio of RV wall thickness to LV wall thickness was 1:1.

EFFECT OF CONTRAST MEDIA USED IN ANGIOCARDIOGRAPHY ON OXYHEMOGLOBIN DISSOCIATION. Amnon Rosenthal, S. Bert Litwin, and M.B. Laver. The Children's Hosp. Med. Center, Mass. Gen. Hosp., and Harvard Med. Sch.,Boston.

Adverse reactions induced by contrast material in infants with cyanotic congenital heart disease (CHD), e.g. bradycardia and ischemic electrocardiographic changes, prompted us to investigate the effect of sodium and meglumine diatrizoate (Renovist-II) on the affinity of hemoglobin for oxygen. Serial hemoglobin-oxygen dissociation curves (HODC) were obtained prior to and after a bolus injection of 0.7 - 1.6 ml/kg of Renovist-II in 15 patients with CHD at the time of cardiac catheterization. HODC was performed by the method of Duvelleroy et al (J. Appl. Physiol. 28:227, 1970). A significant increase ($p < 0.01$, paired t test) in the hemoglobin affinity for oxygen (leftward shift of the HODC) occurred in 13 patients and in 2 there was no significant change. P50 (pO_2 at 50% oxyhemoglobin saturation, pH 7.4, 37°C) decreased by an average of 1.4mmHg 10 minutes after injection (range: 0.2 - 2.2mmHg); a maximum value of 3.2mmHg was seen after 20 minutes. A leftward shift occurred as early as 3 minutes after injection, reached maximum at 10 - 20 minutes, and returned to control levels at approximately 40 minutes. The injection was accompanied by a decrease in mean hematocrit of 5% ($p < 0.01$) and mean hemoglobin of 0.8gm% ($p < 0.05$). There were no significant changes in blood pH, PaO_2, $PaCO_2$, or erythrocyte 2,3-Diphosphoglycerate concentrations. In vitro incubation of heparinized fresh whole blood from two cyanotic and two normal patients with Renovist-II added to a concentration of 2 and 4% demonstrated a decrease in mean P50 of 2.6 and 5.1mmHg respectively. Incubation of blood with 0.9 and 3% saline had no effect. We conclude that an injection of Renovist-II in doses commonly used in angiocardiography reduces hemoglobin affinity for oxygen in vivo and in vitro. This change may be related to an interaction between the organic iodinated compound and hemoglobin. The physiologic consequences of this leftward shift in patients with severe hypoxemia, low cardiac output, and myocardial ischemia remain to be established.

CARDIAC ULTRASONOGRAPHY; A NEW STOP-MOTION TECHNIQUE: APPLICATION IN THE DEMONSTRATION OF TRANSPOSITION OF THE GREAT VESSELS. **Carl N. Steeg, Donald L. King and Kent Ellis (Intr. by Welton M. Gersony). Div. of Pediatric Cardiology, Depts. of Pediatrics and Radiology, Col. of Physicians & Surgeons, Columbia Univ. & Babies Hospital, Columbia-Presbyterian Medical Center, New York.**

Cardiac ultrasonography is the production of two-dimensional cross-section stop-motion images of cardiac anatomy by compound scan pulse-echo ultrasound. This differs from conventional echocardiography which is a single plane display system. The technique also differs from conventional ultrasonic imaging utilized in visualization of relatively motionless organs; an ECG-triggered gating circuit is used to eliminate blurring of the image by cardiac motion. By cross-sectional imaging of cardiac anatomy it is possible to demonstrate the size, shape and orientation of the great vessels. Observations were made in nine infants and children known by previous catheterization and angiocardiography to have transposition of the great vessels (TGV). A control group of similar aged patients were also studied. In all cases of TGV the technique demonstrated the abnormal relationships of the great vessels. The arteries were seen to be in parallel alignment and/or the anterior vessel was noted to be displaced medially as it arose from the ventricle. These findings represent a characteristic pattern specific for the TGV group. Control individuals displayed patterns consistent with normal great vessel outflow anatomy in each instance. Ultrasonography is a promising new non-invasive diagnostic technique which may also be applicable in the evaluation of other congenital heart defects.

CARDIOLOGY

Read by Title

THE NATURE AND SIGNIFICANCE OF MOBITZ II RHYTHM IN CHILDREN. Joseph M. Bordiuk, Richard J. Golinko (Intr. by Welton Gersony) St. Vincent's Hosp. & Med. Ctr., Dept. of Ped., New York. Brookdale Hosp., Dept.of Ped.,Brooklyn.

Mobitz II rhythm (M II) is second degree heartblock with a uniform PR interval in complexes preceding the non-conducted P. Conduction delay may be above or below the bundle of His (H). Delay below H is felt to be a prelude to complete heart block (CHB). Recent studies in the adult suggest that conduction delay above H is a benign arrhythmia and may not require cardiac pacing.

Three children are reported with M II due to pre H block. Two patients developed CHB. The third had symptomatic bradycardia.

C.M. was noted to have antinatal bradycardia. She developed M II by 48 hours and progressed to CHB with junctional rhythm, requiring cardiac pacing. She was later documented to have Transposition of the Great Vessels.

R.G. was noted to have M II at the time of admission for elective surgery. She developed CHB with junctional rhythm following induction of anesthesia with ketamine. Second degree block returned after surgery.

L.T. was admitted to the hospital because of symptomatic bradycardia. Her ECG documented M II. His bundle cardiography demonstrated a pre H block with Wenckebach phenomenon. Conduction distal to H was normal.

These patients demonstrate that M II in children is frequently due to pre His block. Moreover, it is a serious arrhythmia and may lead to CHB.

EFFECTS OF PROPRANOLOL ON PATIENTS WITH TETRALOGY OF FALLOT AND SURGICAL SHUNTS by Guy A. Carter and Roger A. Hurwitz (Intr. by Robert L. Baehner) from Dept. of Ped., Indiana Univ. Med. Sch.

Although beta-adrenergic blocking agents have been shown to generally increase the aortic oxygen (O_2) saturation in tetralogy of Fallot (TOF), it has been suggested that such drugs may produce a decreased O_2 saturation in patients with TOF and a surgically created shunt. To test this, we have studied the effects of Propranolol, a beta-adrenergic blocker, on ten patients with TOF and aorta-pulmonary artery shunts. During cardiac catheterization the following were measured before and after IV infusion of Propranolol in a dose of 0.15 mg/kg: % right-to-left shunt, aortic pressures, O_2 saturation, and heart rate.

Mean right-to-left shunt at rest was 47%; at maximal effect the shunt decreased to 33% ($p < 0.002$). The major effect occured within ten minutes. Mean aortic O_2 saturation increased from a resting level of 85.5% to 87.1% within ten minutes. Mean heart rate decreased 8.7% (101.5 to 88.0 beats/minute) by five minutes post-injection and then remained constant. No change was noted in aortic pressure.

These results were consistent with published data on the effect of Propranolol in patients with TOF and no previously created shunt. No deleterious effects were noted in the hemodynamic or clinical condition of these children following Propranolol infusion. This data suggests a possible use for Propranolol in the management of children with TOF and a sub-optimal surgical shunt.

EFFECT OF DIBUTRYRL CYCLIC AMP ON MYOCARDIAL PERFORMANCE
Anthony F. Cutilletta, Chung-Yuan Lin and René A. Arcilla
The University of Chicago, Department of Pediatrics, Chicago, Illinois

ß-adrenergic drugs exert their cardiac inotropic effects via adenyl cyclase and cyclic AMP. Whereas the inotropic effect of cyclic AMP has been shown on isolated papillary muscles, this has not been clearly demonstrated in vivo. The dibutyryl derivative of cyclic AMP (dcAMP) was infused (100 mg) into the left coronary artery of 6 dogs. Left ventricular (LV) performance was evaluated using catheter microtransducer in LV and aortic electromagnetic flow probe. Parameters included: contractility index (using isovolumic maximal dP/dt/P), dP/dt max, cardiac output (CO) and stroke power (SP). Vector loop display of phasic LV pressure versus dP/dt or aortic flow facilitated the performance analyses. Data were obtained every 5 min. during consecutive 15 min infusion of saline, dcAMP and saline. No significant changes in heart rate, LV pressure, CO and stroke volume were noted ($P>0,2$). Blood gases, pH, lactates and pyruvates remained unchanged. SP increased by 15% but was not significant ($P>0.05$). An increase of dP/dt max by 36% ($P < 0.01$), and of contractility index by 40% ($P < 0.001$) was noted 15-30 min. after start of dcAMP. In one study, intravenous propranolol (1 mg/kg) reduced contractility index by 36% but failed to block the positive inotropic effect of dcAMP. A direct effect of cyclic AMP on myocardial contractility has thus been demonstrated in the intact subject.

THE MAXIMUM STEADY STATE WORK RATE: A SAFE LEVEL OF ACTIVITY FOR PROLONGED EXERTION IN CHILDREN. Gerd J. Cropp. Dept. Ped., Univ. Colo. Med. Ctr., Denver, Colorado.

Despite increasing interest in exercise tolerance of subjects with cardiopulmonary disease, it remains difficult to identify patients who do not perform normally. Present tests usually assess the work subjects can do when nearly or totally exhausted but they do not indicate how much work can be done safely for long periods of time. We developed a test which identifies the highest work rate which can be done before subjects enter a non-steady state. $\dot{V}O_2$, $\dot{V}E_{BPTS}$ and mixed expiratory O_2 concentration were measured on a bicycle ergometer in 8 healthy subjects at rest and an initial work rate of 0.2-0.5 W/kg. The load was increased every 4 min by the initial amount until exhaustion was approached. Work rates below 1.0 W/kg were always performed in a steady state. Maximum steady state work rates ranged between 43 and 66% of maximum work capacity and were associated with heart rates between 112 and 160 bpm, a $\dot{V}O_2$ of 20-28 ml/kg, maximum O_2 extraction from the inhaled air and usually optimum mechanical efficiency and O_2 utilization. When work exceeded the maximum steady state work rate, subjects began to hyperventilate, to extract O_2 from the inspired air less efficiently, and often to increase their heart rates excessively with further increases in work rate. When we have established the lower limits of maximum steady state work rates for normal children of different ages and activity, we can identify those patients who are restricted in their ability to exercise because of disease or voluntary inactivity. Only when appropriate training programs fail to improve exercise tolerance in patients who are considered capable of normal activity, can their low exercise tolerance be considered a result of their disease.

SILENT AORTIC INSUFFICIENCY (A.I.) IN VENTRICULAR SEPTAL DEFECT (IVSD). Ivan Dimich, Leonard Steinfeld, Moshe Steier (Intr. by Horace L. Hodes) The Mount Sinai School of Medicine, Department of Pediatrics, N.Y.,N.Y.

Insufficiency of the aortic valve has been reported in 7% of ventricular septal defects. Such insufficiency appears to be more common with subpulmonic defects (SPVSD) than with one involving subcristal region membranous types (SCVSD). Most commonly, the right coronary cusp prolapses into the defect and becomes insufficient. Surgical closure of the IVSD, if done early, has been shown to preserve the integrity of the aortic valve.

In the attempt to detect the early stage of the aortic valve herniation, 7 patients with SPVSD and 35 with membranous type (SCVSD) between the ages of 5 and 12 years were studied. At the time of this study there was no diastolic murmur or any other clinical evidence of A.I. in any of these cases. The clinical diagnosis of SPVSD and SCVSD was confirmed in each case by left ventriculography. Supravalvular aortography was done in all patients and demonstrated a moderate amount of aortic regurgitation in 3 patients with SPVSD and in 2 with SCVSD. Most striking feature in the aortograms, in addition to A.I., was marked dilatation of the right coronary sinus of Valsalva. A.I. was further confirmed in 3 patients who had undergone surgery. Two unoperated patients developed a blowing diastolic murmur during the follow-up period, 2 to 4 years after cardiac catheterization. The data suggest that ventricular septal defects can coexist with an early stage of aortic insufficiency when the murmur of A.I. is not audible. In view of the unpredictability regarding aortic insufficiency, selective aortography should be done in all patients with VSD undergoing cardiac catheterization.

CYCLIC AMP AND MYOCARDIAL CONTRACTILITY IN THE HUMAN HEART
Anthony F. Cutilletta, René A. Arcilla and Robert L. Replogle, Univ. of Chicago, Dept. of Pediatrics, Chicago, Illinois

Previous works on isolated papillary muscles have demonstrated good correlation between cyclic AMP (cAMP) levels and myocardial contractility. However, these studies have not been done on intact human hearts. Left ventricular (LV) function studies were done on 10 children before and after ischemic arrest during open-heart surgery; in 4 of these LV biopsies for cAMP levels were obtained. In 7 additional subjects, only LV biopsies were taken. Analysis for cAMP was by the method of Gilman. Myocardiac contractility was measured with the aid of a microtransducer catheter, RC differentiator and an X-Y recorder for vector loop display of LV pressure versus dP/dt. Contractility index (CoI) was expressed by the isovolumic maximal $\frac{dP}{dt}$ relation in sec^{-1}. Other parameters included dP/dt max, P LV pressure, cardiac output (aortic flow probe) and stroke power. Function studies and biopsies were done before bypass (control), 5-15 min after, and 30-45 min after, the end of ischemic arrest. Control values for cAMP, CoI and dP/dt max were: 2.0 pmoles/mg wet weight ± 1.2, 61.4 sec^{-1} ± 15.9, 1700 mm Hg/sec ± 245, respectively. Changes in dP/dt max, CoI and cAMP ranged from -20% to +52%, -43% to +136%, and -67% to +235%, respectively. There was no correlation between these changes and duration of ischemic arrest, bypass time or time of study after ischemic arrest. Good correlation was noted between changes in cAMP and CoI ($r=0.86$), and less so between cAMP and dP/dt max ($r=0.76$). In one study, the improvement in CoI following calcium was not accompanied by similar effect of cAMP. This study has demonstrated that changes in myocardial contractility of the intact human heart, as evaluated by CoI, correlate well with myocardial tissue cAMP levels.

ASEPTIC VALVULAR THROMBOSIS OF THE NEONATAL HEART. Blaise E. Favara and Ralph A. Franciosi. (Introduced by Wm. E. Hathaway) Children's Hospital, Denver.

Sixteen cases of neonatal aseptic valvular thrombosis (vegetative endocarditis) have been studied. This 3 year experience represents an incidence of 6% on our neonatal autopsy service. Lesions occurred on both atrioventricular valves in 7 cases, on the mitral valve only in 4 and on the tricuspid valve only in 5. In one case a lesion of the right atrial endocardium was found and in another the right ventricle was involved as well as atrioventricular valve.

Associated conditions included low birth weight in 7 cases, hyaline membrane disease in 13, erythroblastosis fetalis in one, pulmonary hemorrhage in one, aspiration of amniotic fluid in one, and there were 3 infants of diabetic mothers. The mean age at time of death was 3 days. There were two cases less than 7 hours of age at death.

Microscopy, histochemistry and electron microscopy revealed that the sterile lesions were predominantly platelet masses adherent to a valve lacking endothelium at the point of attachment. Underlying fibroblasts were large. "Healing" lesions in one case showed re-endothelization and incorporation of the hyaline material into valve mesenchyme.

The valvular lesions were associated with widespread thrombosis of medium and small arteries and veins of lung, liver, kidney and brain in all cases. Complications of this thrombo-embolic process included renal infarction in 2 cases, cardiac papillary muscle infarction in one case and cutaneous gangrene in one case. Capillary fibrin thrombi were not observed; however, laboratory evidence of consumption coagulopathy as manifest by thrombocytopenia, "burr" erythrocytes, prolonged prothrombin, partial thromboplastin and thrombin time were observed in the eight cases in which these studies were performed.

Aseptic valvular thrombosis represents another manifestation of hypercoagulability in the severely ill newborn infant and may occur as early as 3 hours of age.

ROENTGENOGRAPHIC SIGNS OF CONGENITAL ASPLENIA: AN EVALUATION BASED ON 32 NECROPSIED CASES. Robert M. Freedom and Kenneth E. Fellows, Jr. Children's Hospital Med. Ctr. Boston, Mass. (Intr. by Alexander S. Nadas).

The asplenia syndrome includes those patients with congenital asplenia, visceral heterotaxy, complex congenital heart disease, and abnormalities of bronchopulmonary lobation. Because earlier recognition of this syndrome might facilitate an increased salvage of these often critically ill infants, a retrospective examination of 32 necropsied cases of asplenia, the single largest group studied at one institution, was undertaken to evaluate the usefulness of the three extra-cardiac roentgenographic or angiographic signs thought to be highly characteristic of this syndrome. 1. Abnormal hepatic symmetry: 16 patients had either normal or inverse normal livers, both roentgenographically and at necropsy, while the remainder tended towards abnormal hepatic symmetry. 2. Bilateral eparterial bronchi: this was found in 30 of 32 patients at necropsy, but roentgenographically this pattern could be ascertained only in approximately one third of the patients. 3. Anomalous location of the abdominal aorta and inferior vena cava - both on the same side of the spine: this abnormal juxtaposition was noted in 14 of 19 catheterized patients and at post mortem in 21 of 32.

NON-INVASIVE TECHNIQUE FOR EVALUATION OF CARDIAC FUNCTION IN INFANTS AND CHILDREN. A. Hernandez, R. B. Klint, G. A. Okamoto and D. Goldring. (Intr. by D. Goldring). Washington University Medical School, Department of Pediatrics, St. Louis Children's Hospital, St. Louis, Missouri.

There has been re-awakened interest in the use of systolic time intervals (STI), i.e., the ratios of the pre-ejection period (PEP) and the left ventricular ejection time (LVET) in the assessment of cardiac performance. The carotid pulse wave as picked up by a sensitive contact sensor is a vital trace for the measurement of the STI and technically difficult to obtain in infants but easily obtained by the Doppler ultrasound technique. The validity of using the Doppler technique in place of the above was tested in 5 dogs in whom 30 determinations of the STI (PEP, LVET) by the two methods were compared and when related to the heart rate (HR) their respective slopes were positively correlated. Measurements of STI were then performed on 77 normal infants from 2 days to 1 year of age; 39 were males and 38 were females. The carotid pulse was recorded with the aid of the ultrasound Doppler technique. The electrocardiogram and phonocardiogram were recorded in the usual manner. The PEP and LVET showed an inverse linear relationship to HR. The regression equations derived from these data were as follows: PEP = 159.1 - 0.422 HR; LVET = 247 - 0.527 HR; the ratio of PEP to LVET ranged from 0.35 to 0.76; and was not affected by HR. This method has potential value as an easy, uniquely suitable, practical, atraumatic means of serially following cardiac performance in infants and children under cardiovascular stress.

CHANGES IN THE CIRCULATION OF THE PULP OF THE FINGER IN CHILDREN WITH RECURRENT ABDOMINAL PAIN. Ian S. E. Gibbons, Deborah A. Barto, Victor C. Rivera, Giulio J. Barbero. Dept. of Ped., Hahnemann Med. Col. and Hosp., Philadelphia.

Two groups of children were investigated to compare finger pulp circulations (as an index of autonomic function), in response to stress induced by the cold pressor test. There were 14 patients aged 5-17 years, and 20 controls aged 6-18 years. A photoelectric hemodensitometer was applied on the thumb to measure the peripheral circulatory responses to 30 second immersion of the opposite hand in cold water ($5^{o} \pm 2^{o}C$). The degree of change was expressed as a percentage of the baseline measurement with the patient at rest. Means were calculated for each group. Maximum reduction in flow was similar in both groups, viz. controls 66% and children with recurrent abdominal pain (RAP) 67%. There was no significant difference in the rate of achieving maximum reduction. Similarly the initial time of recovery to baseline was the same, 88 and 89 seconds respectively. There were highly significant differences in augmented flow in the finger after initial recovery; controls 11% and children with RAP 42%.

These findings reflect instability in the control of the peripheral arteriolar circulation and are consistent with previous studies showing unstable pupil reactions in response to stress. This affords further evidence that autonomic nervous function is disturbed in children with RAP.

EFFECT OF GLUCAGON ON INFANTS AND CHILDREN WITH HEART BLOCK by Roger A. Hurwitz (Intr. by Robert L. Baehner) from Dept. of Ped., Indiana Univ. Med. Sch.

The cardiovascular effects of glucagon were studied in 13 infants and children with advanced atrio-ventricular block (AVB). Eight patients had congenital AVB, 4 had surgically acquired AVB, and one infant had severe metabolic derangement which probably caused his AVB. In 11 patients AVB was complete. Glucagon was administered parenterally, usually as a bolus of 0.05 mg/kg. In the 12 patients receiving glucagon intravenously, ventricular rate rose in all; the group mean rose from a resting rate of 63 to 71 beats/minute at maximal effect ($p < 0.001$). Cardiac output rose in the 4 patients in whom measurement was performed. On set of action was almost immediate, with peak effect commonly before 10 minutes. The duration of response following single injections of glucagon was relatively brief; positive effects were seldom seen beyond 20 minutes. There were similar responses between infants and older children, and between those with congenital AVB and acquired AVB. With the exception of one case in which there was a late drop in cardiac output at the time of extreme nausea, adverse side effects were not encountered. *Glucagon neither caused blood pressure to drop nor did it produce additional* arrhythmias. Though hyperglycemia was noted, it was mild. Thus, glucagon may be useful for situations necessitating relatively short-term therapy for symptomatic AVB.

AGE-RELATED CHANGES IN NORMAL INFANTS DURING THE FIRST YEAR OF LIFE: A DOCUMENTATION AND A COMPARISON OF THE FRANK VECTORCARDIOGRAM AND STANDARD ELECTROCARDIOGRAM. Barbara Guller, William H. Weidman, James W. DuShane, Peter C. O'Brien, and Ralph E. Smith, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

In 67 newborns up to 4 days of age, a Frank vectorcardiogram (VCG) and a standard electrocardiogram (ECG) were recorded simultaneously with the Mayo Clinic computer system. Each infant was restudied 1 to 4 times during the first year of life (143 follow-up observations), allowing a longitudinal analysis of the data with normal age limits and trend predictions. The VCG demonstrated readily apparent changes in loop rotation in the horizontal plane or an increase in the area of horizontal leftward forces between observations in 90%, whereas in the ECG expected changes of a decrease in *the size of the R wave and R/S ratio in lead V1 and an increase in R-wave* size and R/S ratio in lead V6 occurred in 54% and 74%, respectively. A computer program for detecting abnormal VCGs in infants must include the age variables of direction and magnitude of timed and maximal vectors.

THE EFFECT OF LEFT VENTRICULAR DIMENSIONS ON CORONARY HEMODYNAMICS IN THE DOG Mouazza M. Jarmakani Duke Univ. Med. Ctr., Durham, N.C.

In order to evaluate the effects of increasing left ventricular (LV) size on coronary hemodynamics, phasic coronary blood flow was measured in open chest dog preparations during changes in LV volume induced by inflating LV balloon. Statham electromagnetic flow probes were implanted on the ascending aorta (Ao) and left circumflex coronary artery (LCCA) in 5 adult mongrel dogs weighing 25-35 kg. Pressures were measured in the aorta (AP) and LV (LVP) through suitable catheters. A balloon was passed into the LV via the apex and inflated with saline at 10 cc increments. Aortic and coronary vein blood samples were obtained for oxygen saturation.

Maximal LV balloon size (LVBS) ranged from 60 to 80 cc. Stroke volume, AoP, LVP, and heart rate did not change significantly with balloon size < 50 cc. Total coronary blood flow (CBF) increased in all experiments to an average of 166% of control at LV balloon size of 50 cc, and decreased for LVBS > 50 cc. Myocardial oxygen uptake increased to 180% of control at LVBS of 50 cc. Systolic CBF was retrograde at LV balloon size > 30 cc. Hyperemic coronary flow was abolished at LVBS > 40 cc.

These data suggest that the increased LV wall tension caused by increased LV radius is a major determinant of coronary flow. Intramyocardial pressure also may play a significant role in regulating coronary blood flow.

INDIRECT SYSTOLIC TIME INTERVALS IN PEDIATRIC PATIENTS WITH CONGENITAL HEART DISEASE

Aaron R. Levin, Philip R. Liebson, and Bernard Diamant
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Indirect systolic time intervals, using simultaneous recording of the phonocardiogram, electrocardiogram, and carotid pulse tracing were evaluated for correlations with angiographically determined left ventricular stroke volume (SV), end-diastolic volume (EDV), and ejection fraction (EF) in 26 pediatric patients undergoing cardiac catheterization. Patients, aged 1 to 12, were grouped according to two functional classes. Group I (17 patients) consisted of those without shunting of blood from the left ventricle (atrial septal defect, patent ductus arteriosus, mild aortic stenosis). Group II (nine patients) had either ventricular septal defects or mitral regurgitation, allowing shunting of blood during left ventricular systole. Significant correlations ($p < .01$) between indirect systolic indices and calculated left ventricular volume data were found in Group I: Indirect left ventricular ejection time (LVET) was directly correlated with EDV ($r = 0.78$) and SV ($r = 0.76$). Pre-ejection period/LVET ratio correlated inversely with EF ($r = -0.64$) and SV ($r = -0.63$). No correlations were found between angiographically determined volumes and indirect systolic indices in Group II. LVET tended to be shorter in this group for a specific EDV and SV. These findings suggest that, in pediatric patients with congenital abnormalities which do not involve left ventricular shunting away from the aortic valve, indirect systolic intervals may be used to estimate left ventricular performance.

LDH AND HBD IN INFLAMMATORY HEART DISEASE IN CHILDREN.

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Lactate dehydrogenase (LDH) has been used as a measurement of myocardial muscle damage in adults with myocardial infarction. Alpha hydroxybutyrate dehydrogenase (HBD), thought to be similar to if not identical with the fast-moving fraction of LDH, appears more specific as an indicator of heart muscle damage. Serial measurements of serum levels of these enzymes were carried out in children with acute rheumatic fever and viral myocarditis.

Normal values appeared somewhat higher than accepted adult levels. Children without evidence of disease showed LDH levels varying from 434 to 689 spectrophotometric units, mean 546, HBD from 500 to 1000, mean 788. Nine children with 10 episodes of acute rheumatic carditis showed maximal LDH levels of 672-1386, mean 824. No consistent pattern could be shown, mean values often still exceeding original ones after six weeks of treatment with aspirin or prednisone. Occasionally a marked transitory increase in LDH and/or HBD occurred during withdrawal of steroid therapy without apparent relationship to clinical condition. A single child with acute rheumatic arthritis without carditis showed consistently normal enzyme levels.

The LDH/HBD ratio, proposed as a refined index of myocardial damage in adults, was not useful in assessment of activity. HBD levels paralleled those of LDH at a higher level and were useful in relating LDH elevation to the fast moving (cardiac) fraction.

Five children with viral myocarditis showed high initial levels (720-1120, mean 900), rapid decline (350-685, mean 510 in 1 week), low levels on steroid therapy, marked rebound during withdrawal (peak 1400) and rapid fall to normal over the next 2-3 weeks.

THE IMPORTANCE OF EJECTION FRACTIONS IN ANOMALOUS LEFT CORONARY ARTERY

James A. Menke, Reda M. Shaher, Grace S. Wolff (Introduced by Paul Patterson) Albany Medical College, Albany Medical Center Hospital, Division of Pediatric Cardiology, Department of Pediatrics, Albany, New York

The indications for surgery in anomalous coronary artery arising from the pulmonary artery are not readily agreed upon. It was the purpose of this study to investigate a parameter which would assist in the selection of surgical candidates. Consequently, ejection fractions were determined in 10 patients with this anomaly. It was found that all patients with ejection fractions above 0.55 survived while those with ejection fractions below 0.36 died. It is proposed that determination of ejection fractions offers a helpful guideline to management of patients with anomalous coronary.

CLINICAL COMPETENCE OF CHILD HEALTH ASSOCIATES: III. PHYSICAL ASSESSMENT OF THE CARDIOVASCULAR SYSTEM.

John B. Moon, John E. Ott, Pavel Machotka. (Intr. by Henry K. Silver) Univ. of Colorado Med. Ctr., Colorado Gen. Hosp., Dept. of Ped., Denver.

The present study was performed as part of an ongoing program to evaluate the clinical competence of a new allied health professional, the child health associate (CHA). Physical examinations of the cardiovascular system performed by second year CHAs were compared to those performed by fourth year medical students (MS), pediatric interns (PI), and pediatric residents (PR).

Scoring was done by two observers stationed behind a one-way mirror during the subjects' examinations of a 6 year old male with a known ventricular septal defect (VSD). Each subject was given one point of credit for properly performing any of 20 observable tasks (such as taking blood pressure, timing the pulse, percussing the chest, palpating femoral pulses, etc.).

The mean number of scoreable tasks actually performed by each group was CHAs 12.4, MSs 14.3, PIs 14.0, and PRs 13.8. The differences between the CHA's mean score and those of the others could be accounted for by chance alone more often than once in ten.

The specific organic defect was diagnosed by 6/9 CHAs, 4/7 MSs, 4/4 PIs, and 4/6 PRs. All subjects who misdiagnosed the lesion listed VSD in their differential diagnosis.

These data are consistent with the (null) hypothesis that CHAs with 17 months of formal medical training perform a physical examination of the cardiovascular system as thoroughly as MSs, PIs, and PRs with 34, 46, and 70 months, respectively, of formal medical training.

ASSESSMENT OF THE ADEQUACY OF PULMONARY ARTERY BANDING BY THE PHONOCARDIOGRAM.

Zoltan G. Mesko, Kalim-Ud-Din Aziz, and R. Curtis Ellison. (Intr. by Donald C. Fyler). Harvard Medical School, The Children's Hospital Medical Center, Department of Cardiology, Boston, Massachusetts.

Phonocardiograms (PCG's) were analysed from 17 patients (pts.) who had previously undergone pulmonary artery banding for ventricular septal defect with large left to right shunt and pulmonary artery hypertension. It was sought to determine if the PCG could be utilized to assess whether or not the pulmonary artery constriction was adequate in reducing the pulmonary artery pressure distal to the band (to less than 50 mmHg systolic). The PCG's were obtained at the time of follow-up cardiac catheterization.

In 11 pts., the second heart sound (S_2) was found to be widely split (greater than 45 msec) during expiration; only minimal, if any, respiratory variation was noted, and the pulmonic component (P_2) was diminished in relationship to the aortic component in 10 of the 11. All of these patients were found to have adequate constriction of the pulmonary artery, and the band was proximally located in relationship to the pulmonic valve.

In 6 pts., S_2 was narrowly split (less than 40 msec) with an increased intensity P_2. Four of these patients were found to have adequate pulmonary artery constriction, but the band was located distally from the pulmonic valve (greater than 2.1 cm), producing a valve-band "chamber" with a high diastolic pressure. The other 2 patients were found to have inadequate banding of the pulmonary artery with persisting pulmonary artery hypertension distal to the band. These 2 patients also had high diastolic pressures which caused an early and loud P_2.

Thus the PCG can be of assistance in assessing the adequacy of pulmonary artery banding. A widely split S_2 with a low intensity P_2 would indicate an adequate and proximally located band; a narrowly split S_2 with an increased P_2 would indicate either that the band was inadequately constricting the pulmonary artery or that the band was adequate but located distally.

AN ENVIRONMENTAL TRIGGER TO CARDIAC INSTABILITY IN THE NEONATE,

Paul H. Perlstein*, Neil K. Edwards*, Harry C. Atherton*, and James M. Sutherland, Univ. of Cincinnati College of Medicine, Department of Pediatrics, Cincinnati, Ohio.

Unstable heart rates in newborn premature infants inversely reflect cyclic changes in incubator air temperature. This dynamic relationship appeared in a comparison of heart rates in 5 non-apneic infants between 1500-2000 gms housed in standard skin servo controlled incubators, with the heart rates in 5 matched infants housed in computer controlled incubators. The 24-hour mean 15-minute change in air temperature in the standard system was 1.74+SE.03° C (range 0 to 3.6° C) which is significantly higher than the 0.29+.09° C (range 0 to 2.5° C) change in temperature measured in the computerized system ($p<.001$). The mean 15-minute variation magnitude in pulse rate was determined by analysis of the 240 hours of recorded data generated during the monitoring of the 10 infants. The results for each group are tabulated below with significance levels for differences.

Control Mode	N	Mean 24-hour pulse BPM	SE	Mean 15-min.Δ pulse BPM	SE
Standard servo	5	139.4	1.2	13.5	.66
Computer	5	132.2	0.7	7.6	.38
Significance (p)		<.001		<.001	

Moreover, rises in heart rate correlate with falls in air temperature while heart rate falls coincide with increasing air temperatures ($p<.001$). In fact, closer analysis of individual patient records suggests that this statistical relationship understates the influence of changing incubator temperature as a trigger to recurrent bradycardia in the neonate.

THE HEMODYNAMIC EFFECTS OF NONIONIC POLYOL SURFACTANT (PLURONIC F68). Amnon Rosenthal and S. Bert Litwin. The Children's Hospital Medical Center and Harvard Medical School, Boston, Massachusetts.

Pluronic has been used in experimental and clinical extracorporeal circulation studies to reduce blood hemolysis and viscosity and to improve flow in the microcirculation. The hemodynamic effects of intravenous Pluronic (single dose: 25, 50 and 100mg/kg of 10% solution) were studied by right and left heart catheterization in 16 closed chested anesthetized dogs. The animals were hypertransfused with packed red cells 24 hours prior to the study. In the control group (N=5) mean hematocrit (Hct.) decreased from 60.7% to 59.8%. Changes in cardiac output (CO), peripheral vascular resistance (PVR), and viscosity (measured at shear rates of 2.3sec^{-1} to 115sec^{-1}) averaged zero, 2% and 1% respectively. Administration of Pluronic was associated with an average increase in CO of 21% (range:2-31%)($p < 0.02$), a 16% (range:1-27%) decrease in PVR ($p < 0.02$) and a 15% (range:1-32%) decrease in blood viscosity ($p < 0.02$). Average Hct. decreased from 55.4% to 54.8%. The increase in CO was proportional to administered dose and occurred 20-40 minutes after infusion with a gradual return to control level. There were no significant changes in arterial blood pH, pO_2, pCO_2, VO_2 and heart rate. Right atrial, pulmonary, aortic, and left ventricular end-diastolic pressures did not change after infusion of Pluronic F68. We conclude that Pluronic increases CO and lowers PVR. These changes are likely to be due to a reduction in blood viscosity and surface tension.

VARIATIONS IN Vmax WITH SPECIFIC CARDIAC MALFORMATIONS. Burton L. Perry, Joan M. Sigmann, & Aaron M. Stern. University of Michigan Medical School (Intr. by William J. Oliver).

A measure of myocardial performance (Vmax) has been determined in 40 children with varying types of heart disease in an effort to establish a distribution of values and possible significant variations. Vmax is a measure of the rate of fiber shortening derived during isovolumetric ventricular systole and extrapolated to zero developed pressure.

Pressures were measured via a fluid filled catheter-manometer system during intracardiac catheterization. The first derivative was determined with a RC differentiation circuit. The pressure and derivative were converted into actual values and Vmax calculated for each pressure at 4 millisecond intervals. The regression plot of Vmax vs. pressure was performed using a statistical program with an IBM 360 computer. Vmax at zero load was then examined for frequency distribution.

While the numbers are small, several trends seem to be clear. Volume overloading of either ventricle is associated with an increase in Vmax, apparently independent of the calculated volume of shunting or regurgitation. Vmax is also increased for mixed pressure and volume overloading in the right ventricle. In the myocardiopathies there appears to be a distinction between the dyskinetic and hypertrophic groups, the latter with and without obstruction. These findings suggest that a ventricle compensates for an increased volume load by increasing the rate of contraction of the fibers as would be expected from the Frank - Starling law.

THE PATTERN OF STREPTOCOCCAL ANTIBODY TITERS IN RHEUMATIC AND CONGENITAL DISEASE OF THE MITRAL VALVE - Stanford T. Shulman, Benjamin Victorica, Ira Gessner, and Elia M. Ayoub, Dept. of Peds, Univ. of Fla., Gainesville, Fla.

The etiology of mitral insufficiency (MI) in patients without documented acute rheumatic fever (ARF) is frequently obscure. Previous studies demonstrated that patients with rheumatic valvar heart disease had elevated antibody to the streptococcal group A carbohydrate (A-antibody) but normal antistreptolysin O (ASO) and anti-desoxyribonuclease B (anti-DNAse B) titers, several years after their last ARF attack. The possible use of these antibody tests in the differentiation of rheumatic from non-rheumatic mitral disease was explored. The pattern of antibody response was determined prospectively in 23 children (ages 4-15 yr, mean=10.4) with ARF and MI. In 12 patients the ASO/anti-DNAse B did not decline to normal levels during the observation period, whereas in the other 11 patients these antibodies declined to normal levels 6-24 months after the acute attack. In 9 of these 11 (81%), the A-antibody remained significantly elevated. Antibody titers were also assayed on sera from 11 patients (ages 4-10 yr, mean=6.3) with congenital MI of the endocardial cushion type, proved by angiocardiography. All 9 patients with normal ASO and anti-DNAse B titers had normal A-antibody levels. These data suggest that the finding of elevated A-antibody in the presence of normal ASO and anti-DNAse B titers in patients with MI is associated with a rheumatic etiology. A third category of patients studied consisted of 25 children (ages 4-15 yr, mean=10.9) presenting with MI without documented ARF. Five patients had elevated ASO/anti-DNAse B titers and A-antibody levels, reflecting recent streptococcal infection. Of the remaining 20 patients, 7 had elevated A-antibody levels, with normal ASO and anti-DNAse B, while 13 had normal levels of all three antibodies. Of interest is that four patients with "balloon" mitral valves fell into the latter category. Based on the streptococcal antibody studies, it may be concluded that about two-thirds of all our patients presenting with MI without documented ARF have disease which is probably of non-rheumatic etiology.

LARYNGEAL WEB AND INTERVENTRICULAR SEPTAL DEFECT; FIRST REPORTED CASES. W. T. Shearer and D. Goldring. (Intr. by D. Goldring). Washington University Medical School, Department of Pediatrics, St. Louis Children's Hospital, St. Louis, Missouri.

Three patients with the combination of an anterior laryngeal web (demonstrated by direct laryngoscopy) and an interventricular septal defect (IVSD) are presented to call attention to a previously unreported combination of congenital defects. The patients were followed since infancy. Case #1, 9 months old, had repeated hospitalizations because of numerous episodes of choking, aspiration, cyanosis and congestive heart failure. Pulmonary artery banding was considered but maintenance of an adequate airway with a laryngeal web which occluded 75% of the air space seemed an insurmountable problem. Lysis of the web was necessary and successfully done and allowed the baby to be maintained without cardiac surgery. Case #2, 8 years old, and Case #3, 6 years old, had hoarse, weak voices but no respiratory difficulties and both had successful repair of their IVSD. Each defect, independently, may cause sufficient cardiorespiratory distress to be life threatening. Also, this combination of defects may mutually compound the severity of the clinical picture so that assignment of priority to the therapy of malformations may be difficult (Case #1). These patients may help focus attention upon this combination of defects so that the true incidence of these malformations may be learned and the spectrum of severity of these abnormalities better delineated.

USE OF ARTIFICIAL PLACENTA IN THE INVESTIGATION OF CARDIOVASCULAR SYSTEM OF THE FETAL LAMB. Bijan Siassi, Houchang Modanlou, Raymond K.Y. Li, Carlos E. Blanco and Paul Y.K. Wu. (Intr. by Paul F. Wehrle). Dept. of Pediatrics, Los Angeles County-USC Medical Center, Los Angeles, California.

In order to investigate the effect of a single biological factor on the cardiovascular system of the fetal lamb, we have assembled an extracorporeal system replacing the ventilatory function of the placenta while leaving the fetus in a stable physiological condition and completely accessible for study. The extracorporeal circuit is made up of a roller pump with fine head adjustment and rate control, 1/2 M^2 Lande-Edwards membrane oxygenator, silicone rubber tubing-reservoir and a cannulated type electromagnetic flow-probe. The total priming volume of the system is between 130-150 ml. A specially designed flow-sensing device controls the extracorporeal volume within $\pm$ 4ml. The reservoir, roller pump and membrane oxygenator are warmed by a servo-controlled radiant heater. The lambs are delivered by C-section and connected to the extracorporeal system through the umbilical vessels without the loss of fetal state.

Twenty fetal lambs have been studied using this system. Their gestational age varied 115 to 130 days, weight 2.87 $\pm$ 1.1 Kg, duration of perfusion 4.4 $\pm$ 3.3 hr., umbilical flow (extracorporeal) 120 $\pm$ 40 ml/Kg/min, oxygen consumption 4.9 $\pm$ 1.9 ml/Kg/min, heart rate 169 $\pm$ 47/min, umbilical arterial pH 7.32 $\pm$ 0.15, umbilical venous pH 7.39 $\pm$ 0.19 and mean umbilical arterial pressure 48.3 $\pm$ 11.1 mmHg. Umbilical arterial PO_2 and PCO_2 could be varied at will by ventilating the oxygenator with appropriate mixture of oxygen, nitrogen and carbon dioxide. This study indicates the feasibility and potential usefulness of this system in the study of cardiovascular status of isolated fetal lambs.

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THE ECG IN RELATION TO RHEUMATIC AND NONRHEUMATIC LATE SYSTOLIC MURMURS AND/OR CLICKS.
Leonard Steinfeld, Ivan Dimich, Moshe Steier (Intr. by Horace L. Hodes) The Mount Sinai School of Medicine, Department of Pediatrics, N.Y., N.Y.

In a 15 year period, from 1956 to 1971, 185 cases of acute rheumatic fever with associated mitral insufficiency were encountered. In each case, mitral insufficiency was the only valvular lesion and was evidenced by the typical pansystolic or near pansystolic apical murmur. 34 patients from this group developed a mid-late systolic murmur (LSM) and/or a nonejection click (NEC) during a period of observation ranging from one month to 8 years. In 3 of the 34 patients, because of uncertain diagnosis, a left ventricular angiocardiogram was performed which clearly demonstrated in each a billowing mitral valve. None of the 34 patients, some observed more than 10 years, showed T-wave abnormalities on serial electrocardiograms. Another group of 12 patients, each with an apical LSM and/or NEC, was selected for special studies because the etiology of the mitral lesion was felt to be nonrheumatic. Two unrelated families were the source of 6 of the 12 patients. In 5 of the 12, abnormal T-waves were readily identified on the first electrocardiogram recorded. In the remaining 7 patients, the ECG when first seen was completely normal. In 2 patients, serial ECGs at yearly intervals uncovered spontaneous transient T-wave abnormalities. In 4 of 5 patients with initially normal T-waves, provocation with either exercise or positional changes succeeded in inducing T-wave abnormalities. The labile T-waves characteristic of this group were not noted in the rheumatic patients. The data indicate that so long as T-waves are normal and stable in a patient with LSM and/or a NEC it is reasonable to assume a rheumatic etiology. Under the circumstances a recommendation for antistreptococcal prophylaxis is warranted. On the other hand, abnormal T-waves, either spontaneous or induced, in association with a LSM murmur suggest a nonrheumatic etiology.

ALTERATIONS IN 2, 3 DIPHOSPHOGLYCERATE (DPG) AND P_{50} FOLLOWING MUSTARD PROCEDURE FOR TRANSPOSITION OF THE GREAT ARTERIES. Cecille O. Sunderland, Dharam S. Dhindsa, James Metcalfe, Lawrence Bonchek, Martin H. Lees, Jack Rosenberg. Univ. of Oregon Med. Sch., Dept. of Ped., Med., Surgery. Portland, Oregon.

Elevation of P50 and DPG in response to the hypoxemia of right to left shunting is an important adaptation to cyanotic congenital heart disease. P_{50}, hct, and DPG were measured before surgery and following surgery on days 3, 10-30, 48-60, in 5 children (ages 13-31 months) who successfully underwent the Mustard procedure.

All patients had elevated hct, DPG and P_{50} before surgery. Three patients who were given ACD blood in the postoperative period had normal DPG and P_{50} at 3 days. Of these, 2 had developed abnormally high levels by 20-30 days, and one remained in the high normal range. Two patients who received no blood after surgery continued to have elevated DPG and P_{50} at 10-30 days, but had normal values at 55 days. These findings were not related to pulmonary complications, or hct. In spite of total surgical palliation, these children failed to achieve normal levels of DPG and P_{50} for a prolonged period following surgery and those who received ACD blood showed evidence of a continued stimulus for DPG production.

These findings suggest that in spite of the near normal cardiovascular function, there is a continued need for the increased oxygen delivery afforded by elevated P_{50}. This may be due to intrapulmonary right-to-left shunts, partial coronary venous return to the systemic circuit and other unknown factors. The administration of bank ACD blood in the postoperative period probably imposes a physiologic disadvantage and would urge the use of fresh blood and where possible, the use of agents such as fresh frozen plasma where volume replacement alone is sufficient. (Supported in part by USPHS, NIH Grants HE 05499, HE 06042 and the Oregon Heart Assn.)

POSTOPERATIVE HEMORRHAGE IN PATIENTS FOLLOWING THE MUSTARD PROCEDURE. Anne L. Wedemeyer and Jessica H. Lewis, (Intr. by Richard H. Michaels), Univ. of Pittsburgh Sch. of Med., Children's Hosp. of Pittsburgh, Depts. of Ped. and Med., Pittsburgh.

In a retrospective study of 27 patients with transposition of the great arteries (TGA) undergoing the Mustard procedure, 12 had excessive bleeding (>5ml/kg/hr). Abnormal clotting studies, believed to be secondary to hypoxia of the liver, and marked polycythemia (Hct >65%) were present in 9 of the 12 patients. Four expired from bleeding; autopsy findings included gastrointestinal and pulmonary hemorrhages and emboli.

The prospective part of the study included 10 markedly polycythemic patients with TGA who were thought to be high risk for bleeding on the basis of thrombocytopenia in 7 and abnormal thrombin time associated with low levels of factors II, VII, IX and X in 6 patients. Multiple phlebotomies (100 ml/M^2/day) were performed preoperatively to simultaneously lower the hematocrit and elevate depressed coagulation factors. None had excessive bleeding postoperatively. Average blood loss after operation was 4.3 compared to 8.3 ml/kg/hr in the untreated group with hematocrits exceeding 65%.

SURGICALLY INDUCED RIGHT BUNDLE BRANCH BLOCK WITH LEFT ANTERIOR HEMIBLOCK: AN OMINOUS SIGN IN POSTOPERATIVE TETRALOGY OF FALLOT. Grace S. Wolff, Thomas W. Rowland, and R. Curtis Ellison. (Intr. by Alexander S. Nadas). Harvard Medical School, The Children's Hospital Medical Center, Department of Cardiology, Boston, Massachusetts, and Albany Medical College, Albany Medical Center Hospital, Department of Pediatric Cardiology, Albany, New York.

A review of the electrocardiograms of 291 patients who survived more than one month after complete repair of Tetralogy of Fallot disclosed that 24 (8.2%) developed a pattern of right bundle branch block and left anterior hemiblock (RBBB-LAH) following surgery. When the course of these 24 patients was compared with a control group of 100 additional patients who did not develop this pattern following surgery, a significant increase in morbidity and mortality was noted.

Complete heart block developed at some time in the follow-up period in 41.7% of the RBBB-LAH group and in 4% of the control group. The incidence of serious ventricular arrhythmias was 16.7% for the RBBB-LAH group and 1% for the control group. Sudden death occurred in 12.5% of the patients with RBBB-LAH and in 2% of the controls. At the time of this review (one to twelve years following surgery) overall late mortality was 25% for the RBBB-LAH group and 2% for the controls.

The study indicates that serious complications are much more frequent in Tetralogy of Fallot patients who acquire the RBBB-LAH pattern after surgical repair. Prophylactic or therapeutic pacing may be indicated in many of these patients.

ENDOCRINOLOGY

First Session

HUMAN PROLACTIN (HPr) RESPONSES TO THYROTROPIN RELEASING HORMONE (TRH) IN NORMAL CHILDREN AND HYPOPITUITARY PATIENTS **Thomas P. Foley, Jr., Laurence Jacobs, William Hoffman, William Daughaday and Robert M. Blizzard. Johns Hopkins Univ. Dept. of Ped. Baltimore, and Washington Univ. Dept. of Med. St. Louis.**

We have recently reported that TRH releases thyrotropin (TSH) in vivo in normal children, 13 of 13 patients with growth hormone (GH) deficiency without TSH deficiency, 10 of 13 with GH and TSH deficiency and 1 of 5 with GH and TSH deficiency postoperatively for craniopharyngiomas. In addition, TRH has been reported to elevate HPr levels in adults. The current study examines the HPr release secondary to TRH in these patients and compares HPr release with TSH release. All patients received 7 ug/kg dose of TRH IV over 30-60 seconds. The following results were obtained using radioimmunoassays for TSH and HPr:

PATIENTS	TEST TIME:	-20	0	+15	+30	+45	+60	+90	+120	PEAK
Normals no. 20	MEAN TSH	2.4	2.0	19.7	21.5	17.7	14.6	6.3	3.7	21.7
	± SEM	0.4	0.3	2.0	2.0	1.7	1.2	1.0	0.5	3.1
	MEAN HPr	7.1	6.9	33.0	29.8	24.1	18.8	7.6	8.0	39.5
	± SEM	1.2	1.2	5.0	4.0	4.0	3.5	1.8	1.8	5.0
GH deficient TSH normal no. 11	MEAN TSH	2.3	1.8	15.2	20.6	16.0	13.1	8.3	6.3	21.0
	± SEM	0.3	0.2	1.8	3.0	1.9	2.1	1.8	1.4	3.4
	MEAN HPr	3.9	3.3	12.0	7.8	10.0	4.4	3.0	7.5	13.9
	± SEM	0.7	0.8	1.9	2.0	2.8	1.0	0.5	3.1	2.8
GH and TSH deficient no. 11	MEAN TSH	2.5	2.5	17.5	24.8	25.8	25.5	22.5	19.8	29.2
	± SEM	0.3	0.4	3.5	5.0	5.0	5.0	5.0	4.0	4.3
	MEAN HPr	20.8	23.2	50.2	51.1	52.7	42.0	44.5	43.0	65.8
	± SEM	5.0	5.0	9.0	8.1	8.2	10.0	12.0	10.0	10.0

All 3 patients in whom TSH did not rise after TRH had a HPr rise. Baseline HPr and post-TRH HPr levels were elevated in patients with GH + TSH deficiency compared to normals and GH deficiency with normal TSH. These elevated HPr levels returned toward normal after thyroid replacement therapy.
SUMMARY: 1) TRH causes TSH and HPr release from the pituitary in normal and most hypopituitary patients. 2) Elevated HPr levels may be related to thyroid and/or prolactin inhibiting factor deficiencies.

PROLACTIN AND TSH RESPONSES TO THYROTROPIN RELEASING HORMONE AND CHLORPROMAZINE IN HYPOPITUITARY DWARFS: AN ATTEMPT TO ASSESS HYPOTHALAMIC FUNCTION. Louis E. Underwood, Raymond L. Hintz, David R. Clemmons, Sandra J. Voina, Roger W. Turkington, and Judson J. Van Wyk, Univ. of North Carolina Sch. of Med., Dept. of Ped., Chapel Hill; and Univ. of Wisconsin, Dept. of Med., Madison.

Thyrotropin releasing hormone (TRH) stimulates the pituitary directly to release TSH and prolactin (PL), whereas chlorpromazine (CPZ) is presumed to stimulate PL release by lowering hypothalamic prolactin inhibitory factor (PIF). We have attempted to independently test hypothalamic and pituitary function in 11 hypopituitary dwarfs and a group of normal sibling controls by measuring their plasma TSH and PL responses to the administration of TRH (0.5 mg, IV) and CPZ (0.5 mg/kg, IM). Following each injection, PL levels were measured on serially collected plasma samples by a sensitive in vitro bioassay. TSH levels were measured by a radioimmunoassay. Growth hormone (GH) responses to appropriate challenges were absent or abnormally low in the dwarfed group and were normal in the control group. Results: Virtually all the subjects in both groups responded to TRH with increases in plasma TSH and PL. PL responses were likewise seen in all the hypopituitary patients after CPZ. Marked differences in the prolactin responses to the two stimuli were observed in individual subjects in both groups, and there were also marked differences in the magnitude of the responses between subjects. None of the response patterns observed in hypopituitary patients, however, were distinctive from those in normal individuals. Conclusion: The normal release of PL following stimuli operative at the pituitary and the hypothalamic level does not negate the possibility that defective GH secretion in these patients might be due to hypothalamic dysfunction. It does, however, emphasize the need for specific tests utilizing GH releasing factor before the lesion in GH deficient patients can be localized.

FAMILIAL CONGENITAL GLUCOCORTICOID INSUFFICIENCY-ACTH UNRESPONSIVENESS? Thomas Moshang, Jr., Robert L. Rosenfield, Alfred M. Bongiovanni, John S. Parks and James A. Amrhein. The University of Pa. Sch. of Med. The Children's Hosp. of Philadelphia.

The syndrome of familial congenital glucocorticoid insufficiency is biochemically characterized by low basal excretion of urinary 17OH steroids, no increase in 17OH steroids with ACTH administration, but a normal increase in aldosterone excretion in response to sodium restriction. A deficiency of the ACTH receptor system has been proposed as an explanation for the pathophysiology of this syndrome (Migeon et al, Ped.Res. 2:501,1968). Five siblings, 3 males and 2 females, with this syndrome were studied. All excreted low levels of 17OH steroids and did not increase with ACTH. Urinary aldosterone excretion increased with sodium restriction. One male sibling was infused with 80 U. of ACTH and urinary aldosterone excretion increased from 4 µg/24 hrs. to 10 µg/24 hrs. One female sibling, at age 2 years, excreted 0.5 mg. 17OH steroids/24 hrs. and increased her urinary excretion of 17OH steroids (2.4 mg/24 hrs.) in response to ACTH. She subsequently developed hyperpigmentation at age 3½ years. When retested at this age the biochemical characteristics of this syndrome were demonstrated. Her aldosterone excretion during a 4 hr. infusion of ACTH is being determined. The progressive development of this syndrome in this sibling with normal ACTH responsiveness at an earlier age suggests that the pathophysiology might be better explained by a familial degenerative process involving the structural components of the zona fasciculata and reticularis rather than a deficiency in the ACTH receptor system. Furthermore, it has been well documented that aldosterone excretion transiently increases in response to ACTH. The normal aldosterone response to ACTH is more in keeping with the former hypothesis. Otherwise, we must postulate two ACTH receptor systems.

UNCONJUGATED ESTROGENS IN THE PERINATAL PERIOD. Kitti Angsusingha, Dora Stinson, Alec Allen, Julane Hotchkiss, and Frederic Kenny, University of Pittsburgh School of Medicine, Depts. of Ped. and Physiol.,Pittsburgh, Pa.

Serum concentrations of unconjugated estrone(E1), estradiol(E2), and estriol(E3) were compared in maternal antecubital vein; the umbilical artery and vein at birth; and in babies during the first 3 days of life. The individual estrogens were isolated by Sephadex LH-20 chromatography of ether extracts of serum, and quantitated by radioimmunoassay. In ten normal vaginal deliveries the mean values in picograms/ml were:

Mat'l Antecubital Vein		Umbil. Vein	Umbil. Artery	Baby 24 h	48 h	72 h
E1	13,610	25,980	14,600	120	70	40
E2	21,780	9,130	6,060	65	45	35
E3	33,020	289,250	159,880	3,415	320	140

In paired specimens, E1 and E3 were higher in umbil. vein than umbil. artery or maternal antecubital vein. However, E2 was higher in mat'l antecubital vein than umbil. artery or vein and no consistent umbil. A-V difference was detected. Significant amounts of the three estrogens were present for 72 hrs in infants, permitting determination of t 1/2. There was no difference between levels in male vs female infants. In a male with familial congenital absence of adrenals (3 affected male siblings died before 50 hours of age and no adrenal tissue was detected at autopsy), low levels of the three estrogens were found in maternal and umbilical vessels. The data suggest that (1) despite the extensive capacity of the fetus to conjugate estrogen produced by the feto-placental unit, large amounts of the principal estrogens escape conjugation; (2) paired umbil. V-A differences suggest that the term fetus consistently metabolizes E1 and E3 to a greater extent than E2; (3) the mother maintains a higher level of E2 than the feto-placental unit, perhaps because of her relatively higher sex steroid binding plasma protein, and by her conversion of E1 to E2; (4) in the baby lacking adrenals, failure to provide estrogen precursors was reflected in both maternal and fetal levels of the three principal estrogens.

THE LITTLEST GIANT: HYPOTHALAMIC-PITUITARY RELATIONSHIPS IN A 4 YEAR OLD ACROMEGALIC. Harvey Guyda, Jules Hardy and Eleanor Collé, McGill Univ.-Montreal Children's Hosp. Research Inst. and Hôpital Notre Dame, Montreal.

A 4 year old white female child with height age of 8 years, bone age of 5 years, and a growth velocity of > 10 cm/year has been studied. Sellar enlargement as well as clinical and x-ray evidence of acromegalic changes were present. Initial levels of growth hormone (HGH) were > 300 ng/ml and of prolactin (HPr) > 200 ng/ml. HGH rose following oral glucose. During a 24 hour period spontaneous variation of HGH between 200 and 400 ng/ml occurred but no pattern was discernable. A normal diurnal variation in total blood corticoids (TBC) was present, however, and metyrapone tests were normal. There was no change in HGH or HPr in response to the acute administration of chlorpromazine, 10 mgm, or medroxyprogesterone, 10 mgm. Chronic administration of these drugs in combination for a 2 month period suppressed the diurnal variation of TBC but had no effects on the levels of HGH and HPr or on growth velocity. However L-DOPA (250 mgm po) caused a decrease in HGH and HPr levels (< 100 ng/ml) both before and after the unsuccessful attempt at therapy with chlorpromazine and provera. Thyrotropin releasing hormone (TRH) caused extreme elevation of both HGH (1700 ng/ml) and HPr (780 ng/ml) 15 minutes after i-v injection, but no increase of TSH. Following 10 months of observation an eosinophilic adenoma was removed transphenoidally. On incubation, the tissue released both HPr and HGH in amounts greater than that released by normal adult glands under similar in vitro conditions. Post-operatively a lowering but not a normalization of HGH (50 ng/ml) and HPr (100 ng/ml) levels occurred. L-DOPA again caused a decrease in both HGH and HPr levels post-operatively.

The tumor tissue in this patient appeared to be responsive to hypothalamic stimulation. Responses to L-DOPA, TRH and glucose were excessive and for HGH paradoxical. A paradoxical response of HGH to glucose is also seen in the immediate post-natal period, a time when high levels of both HGH and HPr are normally present.

EVIDENCE FOR THE EPISODIC SECRETION OF LH AND DECREASING SENSITIVITY OF THE HYPOTHALAMIC-PITUITARY "GONADOSTAT" IN ADOLESCENT PATIENTS WITH GONADAL DYSGENESIS. R.P.Kelch, F.A.Conte, S.L.Kaplan, M.M.Grumbach, Dept. Ped., Univ. Calif-San Francisco; San Francisco, California

In studies on plasma gonadotropins in 45 patients with the syndrome of gonadal dysgenesis, we observed significant variations in the concentrations of plasma LH in serial samples. Further, the unrestrained hypothalamic pituitary "gonadostat" of these patients seemed less sensitive to the negative feedback effect of exogenous estrogens. To examine these observations further, plasma gonadotropins were determined every 15 minutes for 3-5 hrs in 6 patients with gonadal dysgenesis (11-10/12-20-1/12 yr old). All of the subjects were sexually immature and were studied before they were treated with exogenous estrogens. Six of 6 had elevated plasma FSH values and 5/6 had elevated LH values. Daily plasma and urinary gonadotropins were determined in 5 of these patients who were given 50 μg/day (25 μg (0) q 12°) of ethinyl estradiol (EE) for 5 da. LH (LER960) and FSH (LER869) concentrations in plasma and kaolin-acetone urinary concentrates (2nd IRP) were measured by radioimmunoassay. Episodic increases in plasma LH were found in all subjects except the patient who had consistently low LH values (<1 ng/ml) during the test period. The ratio of highest/lowest LH values ranged from 1.31-1.83, $\bar{x}$ = 1.59. Fourteen LH peaks were noted during a total of 21 hours of monitoring. The concentrations of plasma FSH showed only minor fluctuations (highest/lowest:1.26-1.32). EE caused statistically significant suppression of plasma and urinary gonadotropins in all 6 patients. However, the response was age-dependent: the values in the 2 youngest patients (11-10/12 and 13-2/12 yrs) fell to within the normal range while the values in the 3 older patients (16-2/12, 17-10/12, 20-1/12 yrs) were higher in the control period and remained elevated after 5 days of EE. We conclude the following: 1)LH is secreted episodically in agonadal patients; and 2) maturation, or the decrease in sensitivity of the hypothalamic-pituitary "gonadostat" at the onset of puberty, is not dependent on the presence of a functionng gonad.

HIGHLY SPECIFIC TESTICULAR ISOZYME OF CYCLIC NUCLEOTIDE PHOSPHODIESTERASE ASSOCIATED WITH SEXUAL MATURATION. Robert O. Christiansen and Marcia Desautel, Department of Pediatrics, Stanford University Medical School and Stanford Medical Center, Stanford, California.

Adenosine-3',5'monophosphate (cyclic-3',5'AMP) is known to be the intracellular mediator of the action of several hormones. Both ICSH and FSH have been shown to increase testicular cyclic-3',5'AMP concentration. Cyclic-3',5'AMP has been shown to stimulate the formation of testosterone from cholesterol. The effective concentration of cyclic-3',5'AMP is determined both by its rate of synthesis catalyzed by hormone sensative adenyl cyclase and its rate of degradation effected by cyclic nucleotide phosphodiesterase. Seven separate isozymes of cyclic nucleotide phosphodiesterase (labelled a to g) are present in tissues of rat and rabbit. The adult rat testis contains the c and f components; the f component is only found in the testis. In the 20 day old rat only the c component is present. The f component begins to appear at 40 days of age and reaches adult levels by 50 days of age. Histological sections show spermatids present at 30 days and mature spermatozoa at 50-60 days of age. Total cyclic nucleotide phosphodiesterase activity increases 5 fold from day 20 to day 50. This increase in cyclic nucleotide phosphodiesterase activity is paralleled by an identical increase in testicular adenyl cyclase activity over the same time period. Microdissection of mature rat testis shows the f isozyme to be located in the seminiferous tubules. Subcellular fractionation shows the f isozyme to be associated with the nuclear fraction. Kinetic analysis indicates the c isozyme has a Km of 6.5 x 10^{-5}M for cyclic-3',5'AMP and a Km of 6.8 x 10^{-6}M for cyclic-3',5'GMP. The f component has a Km for cyclic-3',5'AMP of 2.5 x 10^{-6}M, some 24-fold lower. The highly specific isozyme of cyclic nucleotide phosphodiesterase associated with sexual maturation is mainly a cyclic-3',5'AMP phosphodiesterase.

SERUM PROLACTIN (HPr) IN INFANCY AND CHILDHOOD. Harvey J. Guyda* and Henry G. Friesen*, McGill Univ. - Montreal Children's Hosp. Research Inst. and Royal Victoria Hosp., Montreal. (Intr. by Eleanor Collé).

Human prolactin has recently been isolated and characterized as a pituitary hormone distinct from HGH in man. The development of a specific and sensitive radioimmunoassay for serum prolactin (PNAS, 68:1902, 1971) has permitted the first study of pituitary prolactin (HPr) secretion in childhood. Markedly increased HPr levels, similar to maternal levels at term, were observed in cord blood (246 ± 88 ng/ml, N = 31) (means ± S.D.) with no A-V difference. Serum HPr in full term neonates declined rapidly from 278 ± 118 ng/ml (N = 18) on day 1 to 80 ± 37 ng/ml (N = 13) on day 7, with a further decline to < 20 ng/ml by 6 weeks. Premature infants had similar HPr levels on day 7 (92 ± 20 ng/ml, N = 15) but elevated HPr values persisted from 2 to 6 weeks of age (95 ± 20 ng/ml, N = 24). Low levels of serum HPr were maintained during the first year of life (10.6 ± 6.0 ng/ml, N = 36) and subsequent childhood (10.7 ± 2.9 ng/ml, N = 30). There were no sex differences in serum HPr in the prepubertal child. After puberty, mean serum HPr levels for adolescent and adult males (4.0 ± 1.7 ng/ml, N = 25) were lower ($p < .02$) than mean HPr levels in normal adult females (8.8 ± 8.9 ng/ml, N = 100) but the latter group showed greater variability that was not cyclic in nature. Preliminary studies indicate that known provocative stimuli for HGH secretion (insulin hypoglycemia, arginine and glucagon) have no consistent effect on serum HPr secretion, whereas chlorpromazine and TRH (Thyrotropin Releasing Hormone) increased and L-DOPA decreased serum HPr responses similar to those seen in adult subjects. These studies demonstrate increased secretion of pituitary prolactin in the neonate, similar to the increase seen for HGH, and provide normal data for interpretation of disturbances in hypothalamic-pituitary regulation of prolactin secretion in children. Greatly elevated HPr levels in amniotic fluid (1000-6000 ng/ml) support the thesis that prolactin may have an important function during intrauterine life.

GROWTH HORMONE AND MITOCHONDRIAL PROTEIN SYNTHESIS EFFECT OF CORTISOL AND ESTRADIOL. Raj K. Sharma, Vaddanahally T. Maddaiah, Platon J. Collipp, Shang Y. Chen, and Joseph Thomas. Nassau County Medical Center, East Meadow, New York.

To understand the antagonistic effect of cortisone and estradiol on linear growth promoting effect of growth hormone, the effect of estradiol and cortisol on the stimulatory effect of growth hormone on liver mitochondria and microsome protein synthesis of hypophysectomized rats was studied, by measuring radioactive leucine incorporation in vivo and in vitro. In vivo estradiol did not affect mitochondrial and microsomal protein synthesis, but when injected together it blocked the stimulatory effect of growth hormone on mitochondrial and microsomal amino acid incorporation. Cortisol had no effect on mitochondrial protein synthesis but increased microsomal incorporation. When injected together, cortisol blocked the effect of growth hormone on mitochondrial protein synthesis. Stimulatory effects of the two hormones on microsomal incorporation were not additive of the stimulatory effects observed when administered separately, as listed below:

Treatment	Number of Rats	Weight Gain	L-[4,5-^{3}H] Leucine Incorporation (cpm/mg Protein)	
			Mitochondrial	Microsomal
Saline	9	0.2 ± .5	1263 ± 166	2886 ± 199
HGH	9	15.6 ± 0.7	2326 ± 397	3932 ± 206
Estradiol	4	2.1 ± 1.2	1501 ± 301	2761 ± 196
Estradiol + HGH	5	4.9 ± 1.3	1447 ± 235	2471 ± 238
Cortisol	6	6.4 ± 1.9	1422 ± 317	4450 ± 335
Cortisol + HGH	5	10.6 ± 0.2	1641 ± 376	4109 ± 372

Similar results were obtained when in vitro effect of these hormones was studied. These results suggest the probable mechanism by which cortisol and estradiol antagonize the growth promoting effect of growth hormone.

A NEW SYNDROME OF PERIPHERAL AND PITUITARY RESISTANCE TO THYROID HORMONE. Hans H. Bode, M. Danon, F. Maloof, J.D. Crawford, B. Weintraub, Harvard Med. Sch., Mass. Gen. Hosp., Shriners Burns Institute, Boston.

Refetoff postulated selective tissue resistance to thyroxin to account for the elevated PBIs in 3 clinically euthyroid sibs with deaf-mutism, stippled epiphyses and goitre. The chemical values were unaltered by high doses of T_3 or PTU (JCEM 27:279, 1967; Endocr. Soc. Abst. #111; Nicoloff, ibid., Abstr. #177, 1971). An 8-year-old boy referred for evaluation of mild mental retardation and hyperactivity was found to have a small goitre. There was no parental consanguinity and 6 sibs showed no thyroid abnormalities. Hearing, epiphyseal structures, TBG and TBPA were normal. He had no signs of thyroid dysfunction but was chemically hyperthyroid (T_4 19.5 mcg%, free T_4 4.0 ng%). TSH averaged 5.5 uU/ml, higher than is usually seen in thyrotoxicosis (<.50 uU/ml). Methimazole, 50 mg daily, depressed thyroxin synthesis (T_4 10.3,free T_4 2.1) and caused a further rise in TSH to 10 uU/ml. After discontinuation of treatment, TSH declined to 4.1 uU/ml and chemical hyperthyroidism returned (T_4 21.0, free T_4 4.2, total T_3 475 ng%, RAI uptake 67%) but clinically and by serial studies of BMR and insensible water loss, the patient remained euthyroid. TSH releasing hormone (TRH), 200 mcg IV (which is ineffective in hyperthyroid or T_4 treated patients), caused a steady rise in T_4 to 28 mcg%, free T_4 to 5.7 and T_3 to 730 ng% while TSH rose to 28 uU/ml, indicating pituitary resistance to his own T_4 and T_3. Serum dilution confirmed that TSH was also immunologically normal. Neither propranolol 60 mg, chlorpromazine 30 mg, nor prednisone 15 mg daily influenced thyroid indices; the thyroid response to TRH during steroid treatment, however, was suppressed. T_3 (12.5 mcg tid) suppressed TSH to 0.50 uU/ml, T_4 to 13.5 mcg%, free T_4 to 2.6 ng% in 7 days while BMR remained constant. Phenotypically and by his response to antithyroids, T_3 and TRH, this patient differs from the previous reported cases and may represent a new syndrome of either partial L-T_4 resistance, impaired conversion of T_4 to T_3 or elaboration of a non-calorigenic hormone which reacts chemically like T_4 and T_3, possibly the D-isomer.

ENDOCRINOLOGY

Second Session

INTERRELATIONSHIP OF MAGNESIUM METABOLISM AND PARATHYROID FUNCTION IN MAN. Constantine S. Anast, James M. Mohs, Sheldon L. Kaplan and Thomas W. Burns, Departments of Pediatrics and Medicine, University of Missouri School of Medicine.

Hypocalcemia, which responds rapidly to the administration of magnesium salts, is a frequent and puzzling complication of magnesium deficiency in man. The present study was carried out in an effort to elucidate the underlying pathophysiologic mechanism responsible for hypocalcemia in a mentally retarded adolescent girl with chronic hypomagnesemia. The hypomagnesemia in this patient appeared to be secondary to an isolated defect in the intestinal transport of magnesium. In addition to a low serum Mg level of 0.5 mg/100 ml (normal 1.6-2.8 mg/100 ml) the red blood cell and muscle Mg levels were depressed. End organ responsiveness to parathyroid extract was demonstrated as indicated by a rise in serum Ca and urinary cyclic AMP and a fall in serum $PO_4^=$ and TPR. Sequential measurements were made of serum immunoreactive parathyroid hormone (IPTH), total Ca, ionized Ca, Mg and $PO_4^=$ levels as well as renal $PO_4^=$ clearances before and after the intramuscular administration of $MgSO_4$ (100 mg of Mg q 8 hours). It is of particular interest that in the presence of hypocalcemia and hypomagnesemia serum baseline levels of IPTH were non-detectable to low. After 24 hours of Mg therapy the serum Mg increased to within normal range, the serum total and ionized Ca rose but were still below normal, the renal $PO_4^=$ clearance increased and there was a striking increase in serum IPTH to twice the upper limit of normal. Twenty-four hours later the serum Ca increased to normal and the serum IPTH decreased to the upper normal range where it remained during the remainder of Mg therapy. The results of this study indicate that 1) the synthesis and/or secretion of parathyroid hormone may be impaired in the magnesium deficient state in man and 2) magnesium administration rapidly restores the ability of the parathyroid to respond appropriately to the level of ionized calcium in blood.

PROPANOLOL ENHANCEMENT OF IMMUNOREACTIVE GROWTH HORMONE (IRGH) RESPONSE TO GLUCAGON IN CHILDREN. Utai Ruangwit*, Anita Cavallo*, Joseph N. Fisher* and John F. Crigler, Jr., Harvard Medical School, The Children's Hospital Medical Center, Department of Pediatrics, Boston, Massachusetts.

It is well established that intramuscular injection of glucagon (0.03 mg/kg, maximum 1 mg) induces an increase of plasma levels of IRGH in most normal subjects. When given orally 2 hours before glucagon, propanolol (0.75 mg/kg, maximum 40 mg) enhanced the IRGH response to glucagon in 8 control subjects: 7 pre-pubescent children, ages 5-16 years, and 1 adolescent girl, age 18, with primary amenorrhea. It did not change the IRGH response in 3 patients with hypopituitarism (ages 8, 7 and 8 years). No significant side effects were observed. Increment (Δ) IRGH (maximum minus fasting baseline IRGH) responses were compared in each category.

SUBJECTS (No.)	TEST	Δ IRGH (ng/ml) mean	(range)
Control group (8)	Glucagon	8.2	(4.3-17.5)
Hypopituitarism (3)	Glucagon	0.4	(0.1-1)
Control group (8)	Propanolol-glucagon	16.2	(4.5-23.5)
Hypopituitarism (3)	Propanolol-glucagon	0.4	(0.1-1)

From these data we conclude that beta-adrenergic blockade with propanolol promotes a greater IRGH response to glucagon in susceptible pediatric patients and is to be preferred to glucagon alone as a provocative test.

L-DOPA STIMULATION OF GROWTH HORMONE (GH) RELEASE IN CHILDREN AND ITS SIGNIFICANCE B.A. Porter*, R.L. Rosenfield, and A.M. Lawrence*. Univ. of Chicago Pritzker Sch. of Med., Depts. of Ped. and Med., Chicago, Ill.

Evaluation of an "l-dopa test" was initiated when it was shown that l-dopa, a precursor of intracerebral norepinephrine (NE), stimulates GH release in Parkinson's disease. The most reliable means by which to diagnose GH deficiency has been by inducing hypoglycemia (ITT); this effect of ITT may be NE-mediated. The release of GH in response to l-dopa administration has been studied in order to 1) compare GH secretion in children following l-dopa and insulin and 2) investigate the possibility that l-dopa might act at a higher center than the pituitary. Serum GH levels were measured after a l-dopa test dose of 0.5 gm/1.73 m^2; testing was performed after 2 days acclimation to low-dose l-dopa. L-dopa and insulin effects were examined in each of 12 control children (8 with short stature of non-endocrine etiology and 4 with various endocrine disturbances). Peak serum GH titers ensuing from hypoglycemia were ≥ 6.0 ng/ml, those from l-dopa were ≥ 9.2 ng/ml. As noted in insulin testing, l-dopa did not acutely stimulate further GH discharge when the control GH concentration was elevated. No change in blood sugar, TSH, LH, FSH, or cortisol occurred. Side effects were minimal. Six hyposomatotropic children (no response to both hypoglycemia and arginine) were also studied. Two of this group seem to have intact pituitary tissue after partial resection and irradiation therapy of suprasellar tumors: one grew at a normal rate and is thought to be functionally stalk-sectioned; another has TRH deficiency (hypothyroid with normal TSH increase after TRH). None of these hyposomatotropic children produced GH following l-dopa, even in two pretreated with propanolol.

All children who secrete GH in response to hypoglycemia have thus far been shown to do so in response to l-dopa. By virtue of its safety and reliability, the l-dopa test appears to be the preferable means of determining GH reserve. Furthermore, these data are compatible with the evidence in animals which indicates that an l-dopa-derived neurotransmitter may act at or above the median eminence to induce GH-RF release.

TRIIODOTHYRONINE KINETICS IN MATERNAL AND THYROIDECTOMIZED FETAL SHEEP. A. Erenberg, K. Omori, W. Oh, R.W. Lam & D.A. Fisher, Harbor Gen. Hosp. & UCLA Sch. of Med., Dept. of Peds., Torrance,Cal.

We previously have described thyroxine (T4) and triiodothyronine (T3) kinetics in the normal ovine fetus and have reported studies of T4 metabolism in the thyroidectomized fetus. The present study assesses the effect of fetal (F) thyroidectomy (Tx) on T3 metabolism. F sheep were Tx at 90 to 125 days gestation. Following placement of exteriorized catheters, tracer doses of T3-I-125 and T3-I-131 were injected into the fetus and mother, respectively, 4 to 37 days post Tx. Serial blood samples were drawn for 24 hours during maternal (M) perchlorate administration. Alkali-washed butanol extracts of serum were prepared for dual isotope counting. From this data, the M and F volumes of T3 distribution (VD), mean fractional T3 clearance rates (K), and half times of T3 turnover (t 1/2) were estimated. The M values, 26.7 liters, 2.52 K and 6.7 hours respectively, were similar to M non-Tx animals. The F VD, 7.5 liters was similar to F non-Tx values, but t 1/2 (10 hours) was significantly longer and K (1.68) significantly less than non-Tx values (5.5 hours and 3.18 K, resp.). F serum T3 values were not measureable (<30 ng%), while M values were constant throughout the study period. Mean M and F T3 turnover were 1.27 μg/kg/day and <1.75 μg/k/d (normal = 1.43 + <1.45) resp. Placental transfer of T3 occurred in both directions, with <1 μg/day being transferred from M→F. The F to M gradient of TSH (300-1000 μU/ml to 10 μU/ml), the M to F gradient of T4 (8.9 μg% to 1.2 μg%) and M to F gradient of T3 (95 ng% to <30 ng%) confirm the autonomy of the F pituitary-thyroid system. Net placental transfer of T4 (<1 μg/d) and of T3 (<1 μg/d) in the M to F direction are inadequate for F needs, and confirm the relative impermeability of the ovine placenta to the thyronines.

THE ROLE OF TRIIODOTHYRONINE IN THYROID DISORDERS OF THE NEONATAL PERIOD, CHILDHOOD AND ADOLESCENCE. Theodore W. AvRuskin, Shi Ching Tang, Louis Shenkman, Terunori Mitsuma and Charles S. Hollander. (Intr. by Joseph Dancis), Depts. of Ped. The Brookdale Hosp. Med. Ctr. and Depts. of Ped. and Med., NYU School of Med., New York, N.Y.

Recent observations suggest that triiodothyronine(T3) contributed a major portion of the calorigenic potency of the thyroid hormones and plays a significant role in the pathogenesis of clinical disorders of thyroid function in the adult. Whereas serum thyroxine(T4), T4 turnover rate, iodide kinetics, andthyroidal iodine uptake are largely independent of age from the 3rd to the 6th decade of life, an age dependence has been observed for these parameters in childhood. Therefore serum T3 was determined by a newly developed radioimmunoassay technique on unextracted serum in 7 neonates and in 72 nl children: 5 from 1-2 yrs, 21 from 3-4 yrs, 15 from 5-7 yrs, 10 from 8-10 yrs and 21 from 11-18 yrs. Mean serum T3 for the entire group of 79 subjects was 134.3±22ng/100ml (±S.D) and ranged from 92ng/100ml to 170ng/100ml. These values did not vary from those found in adults and there were no differences in T3 levels among the 6 sub-groups. In 2 patients with untreated hypothyroidism T3 was 72 and 80ng/100ml. Eight untreated thyrotoxic pts mean T3 was 468ng/100ml and ranged from 210 to 1200ng/100ml. There was no overlap with the nl gp. With the achievement of euthyroidism after the initiation of therapy T3 levels fell to nl in the 2 in whom it was measured (112,144ng/100ml) T3 concentrations were also normal in 3 patients with nontoxic nodular goiter (132,140 and 140ng/100ml). A 13 yr old girl with all the clinical characteristics of Graves Disease including an elevated and non-suppressible thyroidal uptake of radioiodine was found to have a nl free and total T4 but an elevated free T3 (3.0ng/100 ml, nl .23-.45ng/100ml) and total T3 (1200ng/100ml) thereby fulfilling the criteria for T3 toxicosis. In conclusion: 1) In childhood as in the adult, T3 plays a major role in the pathogenesis of clinical disorders of the thyroid. 2) A case of T3 toxicosis in the pediatric age group has been identified for the first time.

RETENTION OF BIOLOGIC AND IMMUNOLOGIC ACTIVITY OF HGH AFTER REDUCTION AND ALKYLATION. M.H.Connors, A.Vinik, S.L.Kaplan and M.M. Grumbach.Dept.Ped., Univ.Calif-San Francisco; San Francisco, Cal.

The synthesis of human growth hormone (HGH) would be simplified if disulfide bridges, unnecessary for tertiary structure, were not required for biological and immunological activity. This study demonstrates retention of lipolytic, nitrogen-retaining, calciuric, insulinotropic and immunologic functions of reduced tetra-S-carbamidomethyl HGH (RCAM-HGH). HGH was reduced with dithiothreitol and alkylated with iodoacetamide to yield RCAM-HGH (Li). Total reduction was confirmed by quantitative yield of 4 residues of S-carboxymethylcysteine per mole RCAM-HGH. After 8 days on a diet of known composition, 2 boys received 5 mg RCAM-HGH daily for 5-6 days. Five to 7 days later, 5 mg HGH was given daily for 4 days. RCAM-HGH administration caused an average daily decrease in urinary nitrogen of 39% and increased urinary calcium to 153% of control value. Four hours after IM RCAM-HGH plasma free fatty acids rose 165% above basal concentration. Intravenous glucose disposal on the 4th day of RCAM-HGH administration was unchanged (Kg value 1.55). Fasting insulin (IRI) increased from 6 to 21 μU/ml and area of IRI response rose to 250% above control value. Despite qualitative similarity in biological activity of RCAM-HGH and HGH, immunologically, RCAM-HGH showed 66%, 25% and 5% of the activity of native HGH in hybrid (^{131}I-HGH and HCS antiserum), homologous (^{131}I-HGH and HGH antiserum) and hormone-specific (^{131}I-HGH and monospecific HGH antibody) assays.

PLASMA PROLACTIN LEVELS IN JUVENILE HYPOTHYROIDISM AND PRECOCIOUS PUBERTY. Gertrude Costin, Maurice D. Kogut, Ann K. Kershnar, and Roger W. Turkington. Dept. Ped., Childrens Hospital, USC School of Medicine, Los Angeles, Calif. and Dept. Medicine, University of Wisconsin, Madison, Wisconsin.

The association of precocious puberty and hypothyroidism is uncommon and its pathogenesis not clear. The results of studies in two 8-year-old girls with myxedema and precocious puberty suggest a disturbance of the hypothalamic pituitary regulatory mechanism. Patient I.M. had breast development for 14 months and menstruation for 6 months prior to study. She was short (ht age 5½ yrs), obese (wt age 12 yrs) with developed breasts from which collostrum was expressed. Bilateral ovarian masses were present. Bone age was 4½ years and sella turcica was normal. Serum T_4 was 0.3 μg/100 ml and antithyroid antibodies were present. Plasma LH was 25 mIU/ml, FSH 13 mIU/ml, TSH 1000 μu/ml (normal 2-10) and prolactin 900 ng/ml (normal <2). Urinary estrogens were 61 μg in 24 hours. Menstruation ceased 1 month and lactation 6 months after thyroid extract was begun. Following 6 months of treatment, she grew 8 cm and lost 6.5 kg; serum T_4 was 6.1 μg/ml, LH 2.5 mIU/ml, FSH 4.3 mIU/ml and prolactin 70 ng/ml. Patient J.B., with Down's syndrome, had a 2 year history of hypothyroidism and monthly vaginal bleeding for 3 months. She was short (ht age 4½ yrs) and obese, (wt age 8½ yrs). Both nipples were enlarged with pigmented areolae. Sella turcica was enlarged and bone age was 6 10/12 years. Serum T_4 was 0.6 μg/100 ml and antithyroid antibodies were present. Plasma LH was 18 mIU/ml, FSH 13 mIU/ml and prolactin 144 ng/ml. Urinary estrogens were 98 μg and gonadotropins, 6-16 MUU/24 hours. Following 6 months of treatment, she grew 6 cm and lost 5.5 kg.

It is speculated that thyroid releasing factor (TRF) was increased because of decreased amounts of T_4. Elevated plasma LH and FSH may be the result of cross-reactivity with TSH or non-specific stimulation of gonadotropins at the pituitary or hypothalamic site. Elevated plasma prolactin probably resulted from TRF stimulation of the pituitary or, less likely, the result of interference with normal tonic suppression of prolactin secretion.

CYCLIC AMP PRODUCTION IN THE RAT FETUS AND NEWBORN: EFFECTS OF GLUCAGON AND PARATHORMONE. Solomon A. Kaplan, Kenneth H. Thaver, Barbara ". Lipne, and S-L. Raymond Wong, Dept. Ped., U.C.L.A., Sch. of Med., Los Angeles.

Development of adenylate cyclase activity during fetal growth is necessary for action of hormones whose effects in target organs are mediated through cyclic AMP. The following studies were carried out to determine when adenylate cyclase activity develops in rat fetal and neonatal tissues and when it becomes responsive to hormonal stimulation. Cyclic AMP was measured by the method of Krishna et al. (J. Pharm. Exper. Theran., 163: 379, 1968) and adenylate cyclase activity units are expressed as moles cyclic AMP produced per mg. protein by tissue homogenates. Until the last day of gestation basal liver enzyme activity was low, averaging 2.71 x 10^{-6} units from the 14th to the 21st day. In the presence of 2 x 10^{-6} M glucagon, activity was increased to an average of 5.34 x 10^{-6} units. Within 24 hours of birth, basal levels in the liver increased to as much as 1.83 x 10^{-5} units and, in the presence of glucagon this level increased further, three to five times. In striking contrast, adenylate cyclase activity equivalent to that of the adult was present in the kidney at least from the 16th day of gestation and little change occurred at birth. The average basal level was 1.02 x 10^{-5} units and in the presence of 10^{-6} M parathormone, was increased to 2.49 x 10^{-5} units. These experiments suggest that availability of hepatic glucose to the newborn may depend on the capacity of the liver to activate adenylate cyclase activity immediately after removal of the maternal supply of glucose at the time of birth. On the other hand the kidneys have developed an active adenylate cyclase sensitive system which is responsive to parathormone at an early stage of development. This finding is consistent with evidence developing from fetal renal function studies that parathormone is active at an early stage in fetal development.

ENHANCED GROWTH RESPONSES IN HYPOPITUITARY DWARFS TREATED WITH GROWTH HORMONE-ANDROGEN COMBINATION VERSUS GROWTH HORMONE ALONE. Margaret H. MacGillivray, Marvin Kolotkin, Thomas Aceto, Jr. and Richard W. Munschauer, Sch. of Med., SUNY at Buffalo, Children's Hosp., Dept. of Ped. and Radiology.

Prolonged treatment of hypopituitary dwarfs with growth hormone (GH) is associated with declining rates of growth with each additional year of therapy. This necessitates prolongation of the treatment period and the use of a larger total amount of GH. The purposes of this study were to determine: 1. whether hypopituitary dwarfs grow faster when treated with a combination of GH plus androgen than when treated with GH alone; 2. whether the GH-androgen combined therapy is associated with marked acceleration in bone maturation; 3. whether the time required to achieve "catch-up" growth may be shortened by the GH-androgen combination thereby reducing both treatment time and total dose requirement of GH.

Twelve hypopituitary patients (2 organic, 10 idiopathic) were treated with GH for 12 consecutive months (0.1 u/kg 3 x weekly in 11 patients, 0.05 u/kg in 1 patient). From the 7th to 12th months inclusive of GH therapy, halotestin, 2.5 mg/m^2/day per os was added to the regimen. Bone maturation was estimated from wrist films taken at 0, 6 and 12 months. From the 13th through 18th months, no therapy was used, and bone maturation was evaluated at the 18th month. Results:

	Growth cm/yr		Weight kg/yr		Δ Bone Age in Months		
	GH	GH + androgen	GH	GH + androgen	GH	GH + androgen	post treatment
mean	9.4	13.4	3.4	13.0	11.5	11.0	11.0
S.D.	2.3	3.0	2.4	7.0	4.5	5.7	5.6

Conclusions: Hypopituitary dwarfs treated with GH plus androgen exhibit greater rates of linear growth and weight gain than with GH alone. Skeletal maturation did not differ significantly in the 2 treatment periods. The increased height ages observed in the combined treatment group compensate for the increased bone maturation. GH and androgen appear to work synergistically in hypopituitary dwarfs.

DIFFERENTIAL EFFECTS OF STARVATION UPON THE SECRETION OF LUTEINIZING(LH)AND FOLLICLE STIMULATING(FSH)HORMONES IN INTACT AND CASTRATED ADULT MALE RATS. Allen W.Root and R.David Russ, Temple University School of Medicine, Albert Einstein Medical Center, Division of Pediatrics, Philadelphia, Pa.

The effects of total starvation for 168 hours upon serum and pituitary levels of LH and FSH, determined by radioimmunoassay, were evaluated in intact and gonadectomized 250-350 g male rats. (A) Castration of ad lib fed animals was followed by elevation of serum LH and FSH concentrations one week after operation and by significant increases in both serum and pituitary LH and FSH values two weeks after surgery. (B) Starvation depressed serum FSH concentrations in intact animals (FSH: fed- 126.0 ± 14.6 (SEM) mμg/ml, starved- 33.3 ± 13.7 mμg/ml, $p<0.01$); serum LH and pituitary LH and FSH values fluctuated erratically in these animals. (C) Starvation depressed serum LH concentrations in orchiectomized rats if initiated concomitantly with surgery (LH: fed- 385.0 ± 12.8 mμg/ml, starved- 75.0 ± 17.1 mμg/ml, $p<0.01$), while serum FSH levels were similar in fed- and starved-castrated animals; pituitary LH and FSH concentrations were significantly higher in starved-castrated than in fed-castrated animals. (D) Starvation failed to depress LH levels in orchiectomized rats if initiated one week after castration; under these conditions serum FSH levels were significantly higher in starved-castrated than in fed-castrated animals.

It is concluded that 1)starvation partially suppresses FSH secretion in intact adult male rats; 2)starvation partially suppresses LH release in orchiectomized animals, if initiated at the time of surgery

ENDOCRINOLOGY

Read by Title

AGE RELATED CHANGES IN SERUM CALCIUM AND PARATHYROID HORMONE. Sara B. Arnaud, Gunnar B. Stickler, Claude D. Arnaud and Ralph S. Goldsmith. Mayo Clinic and Foundation, Rochester, Minnesota.

In normal adults there is a negative relationship between total serum calcium (TCa) and serum parathyroid hormone (IPTH) as measured by sensitive radioimmunoassay. We studied these indices of calcium homeostasis in 110 midwestern children without evidence of skeletal disease aged 6 months to 20 years and found age-dependent changes. Mean serum calcium gradually decreased from 10.2 mgm/100 ml at 1.5 years to a mean of 9.6 mgm/100 ml at the 16th year. The range of normal values was narrow except under 4 years and at adolescence, where there were increases in TCa. The overall pattern of serum calcium as a function of age resembled growth velocity curves. Mean serum IPTH decreased from 1.5 years to 12 years and increased again at adolescence. Divergence of mean values for serum TCa and serum IPTH after the 6th year suggested a negative correlation which did not prove to be statistically significant on analysis of individual samples. There was, however, a highly significant negative regression between ionized calcium and serum IPTH in all of the subjects in whom ionized calcium determinations were made (n = 50).

Our data underline the importance of recognizing normal variations in serum calcium and IPTH which occur during skeletal maturation and, also, indicate that the negative relationship between ionized calcium and parathyroid hormone is present within the physiologic range of TCa in children.

DOSE DEPENDENT CONVERSION OF CORTISONE TO CORTISOL IN MAN

William H. Barr, Thomas Aceto, Jr., and John Rider
State University of New York at Buffalo, Departments of Pharmaceutics and Pediatrics

Because cortisone (E) is commonly prescribed, but metabolically inactive, we have quantitated the relative amount of hydrocortisone (F) available in the systemic circulation following the oral administration of 5 or 50 mgs of E containing 1 to 6 μC ^{14}C-E. Twenty-five studies were done on 7 healthy children and adults and 7 children with well-controlled adrenogenital syndrome (AGS). Plasma concentrations of F were determined by liquid scintillation counting following TLC separation using silica gel HF-254 and a solvent system of methylene chloride-ethanol (90-10). The relative fraction of F which reaches the systemic circulation was determined from the area under the plasma concentration-time curve (AUC) normalized for differences in the radioactive dose and surface area of the subject. The normalized AUC values (in units of Percent Radioactive Dose, Liter^{-1}, Min.) for the 5 and 50 mg dose were 283 (SD ± 104.7, 13 subjects) and 157.8 (SD ± 80.6, 12 subjects) respectively, indicating almost a 50% difference in conversion efficiencies at the two doses.

Conclusion: Conversion of E to F is dose dependent at the 5 to 50 mg dosage range in both normal subjects and in patients with well-controlled adrenogenital syndrome apparently due to saturable enzymes in the gut and liver. For those patients in whom a precise amount of hydrocortisone is needed, we recommend that cortisone not be prescribed.

(Supported in part by a grant from Syntex Research Corporation)

DEFERMENT OF PUBERTY IN "LATE" TREATED CONGENITAL ADRENAL HYPERPLASIA. A.M.Bongiovanni, T.Moshang and J.S.Parks. Child. Hosp. of Phila., Sch. of Med., Univ. of Penna., Philadelphia,Pa.

Five subjects with congenital adrenal hyperplasia due to 21-hydroxylase deficiency who were first diagnosed between the ages of 3 and 7 years all had markedly advanced bone ages.There were 4 males and 1 female. These subjects were followed carefully following the institution of treatment into adolescence. Despite the marked advancement of bone age in these five subjects it was noted that the bone age came to a virtual standstill for a number of years,the rate of growth was restored to a more normal pattern but was in no instance arrested and gonadal development did not occur precociously but was deferred until a more normal age despite the skeletal advancement at the initiation of treatment. The single female who was recognized at age 3½ years had a bone age of 10 years. The skeletal age remained relatively constant until approximately 11 years of age linear growth was parallel to normal channels and menarche occurred shortly after the 13th birthday.These observations are contrasted with a single male who at 6 years had a bone age of 14 years and following treatment underwent rapid gonadal development accompanied by diminution in the rate of linear growth with eventual compromised stature.These observations suggest that in certain cases of congenital adrenal hyperplasia with late diagnosis and treatment, despite advanced skeletal maturation there may be certain obscure controls which defer the onset of puberty.

DEXTRAN COATED CHARCOAL (DCC) SEPARATION TECHNIQUE: A SURFACE ABSORPTION, NOT A MOLECULAR SIEVING, PHENOMENON. Michel A. Binoux and William D. Odell, UCLA Sch. of Med., Harbor Gen. Hosp. Dept. of Med., Torrance, California

It is reported that free is separated from bound hormone by DCC by a molecular sieving action of Dextran permitting small molecules access to charcoal but preventing access of larger molecules. We have systematically investigated this concept. ^{125}I human TSH (HTSH*) was incubated with excess anti HTSH, (> 90% was bound). Solutions of either HTSH* or Ab·HTSH* were incubated with varying concentrations of untreated charcoal or charcoal coated with varying Dextrans. Using untreated charcoal, a concentration of charcoal existed which bound no HTSH*; increasing concentrations bound more HTSH* until 100% was bound. Ab·HTSH* was also bound; a parallel, but right shifted, dose response curve between 0 and 100% existed. D-10 or D-50 or D-150 DCC also bound both HTSH* and Ab·HTSH* and a series of parallel dose response curves also existed. Addition of serum or plasma shifted all curves further right, and also separated a curve for Ab·HTSH* from HTSH* further. In no instance did Dextran coating prevent binding of large molecules. Optimal assay conditions for HTSH, existed with untreated charcoal. We conclude: (1) charcoal separation is a surface absorption phenomena and Dextran coating does not produce a molecular sieve separation,(2) serum produces similar but greater, effects than Dextran coating, (3) knowledge of the complete dose response curves of labeled hormone versus charcoal dose and Ab-hormone versus charcoal dose permits selection of optimal concentration of charcoal for assay purpose.

EVIDENCE FOR A POLYCLONIC ORIGIN OF THE STEROIDS IN A CASE OF ADRENOCORTICAL CARCINOMA IN A GIRL. Jose Cara, Kingsbrook Jewish Medical Center, SUNY Downstate Medical Center, Brooklyn, N. Y.

A 12 year old girl with slight hirsutism, arterial hypertension and episodes of hypoglycemia presented the following 24-hour urinary steroid pattern: total 17-Ks. 31.0 mg.; "beta" fraction 18.0 mg.; 17-OH-corticoids 43 mg.; tetrahydro "S" 7.2 mg.; pregnanetriol 2.4 mg.; DHA 3.3 mg.; ANDRO 0.4 mg.; ETIO 3.3 mg.; 11-O-ETIO 0.7 mg.; 11-OH-ETIO 0.6 mg.; pregnenediol (3β, 20α) 13.4 mg.; pregnenetriol (3β, 17α, 20α) 25.5 mg.; pregnenetriol (3β, 16α, 20α) 9.5 mg.; and 16α-OH-pregnenolone 8.7 mg. The delta 5, 3 beta-hydroxysteroids were further identified by I.R. spectrography. This urinary steroid pattern points to a relative deficiency of 3 beta-hydroxysteroid dehydrogenase, 11β-hydroxylase and to an active 16α-hydroxylating system. After removal of a 700 gm. adrenocortical carcinoma of the right adrenal the urinary steroid pattern returned to normal. Five months after surgery the patient developed metastasis with hirsutism, cushingoid features and marked arterial hypertension, but no hypoglycemia. The urine revealed a large amount of 17-hydroxycorticoids reaching values of 80 mg./24 h. and more, 15 to 20 mg./24 h. of THS, and 18 mg./24 h. of 17Ks. However 3-beta-hydroxysteroids were either absent or present in slight amount. The changes in the clinical picture and in the urinary steroid pattern before surgery and after the development of metastasis point to a difference in the enzymatic endowment of the cells of the original tumor and the cells of the metastatic tumors. We postulate the existence of more than one clone of cells in the original tumor and the possibility that one or more of these clones may be responsible for the development of the metastasis.

URINARY CYCLIC AMP SECRETION, PLASMA CALCITONIN (CT) AND PARATHYROID HORMONE (PTH) IN PSEUDOHYPOPARATHYROIDISM (PHP). Hans H. Bode, T. Murray, L.J.Deftos, John D. Crawford,Harvard Med. Sch., Massachusetts Gen. Hosp., Shriners Burns Institute, Boston.

Albright (Endocr.,30:922,1942) described hyperplastic parathyroid glands in PHP suggesting increased hormone secretion; Frantz (PNAS,56:1138,1966) found the thyroid content of CT increased and Chase (JCI, 47:18,1968) noticed decreased urinary cyclic AMP excretion in response to PTH. Seven patients with PHP, 4 having the characteristic phenotypical appearance and 1 with pseudo-PHP were studied. All patients had measurable PTH levels and except for the patient with pseudo-PHP, failed to show PTH induced increases in tubular phosphate reabsorption. Urinary cyclic AMP excretion did not rise significantly after PTH infusion (200 U/m^2) in 5 patients; the patient with pseudo-PHP responded normally and the 2 patients lacking the PHP phenotype showed peaks in cyclic AMP excretion of 31 and 47 nmoles/min (controls > 60 nmoles/min). CT, which was undetectable (< 100 pg/ml) in normocalcemic patients even during induced hypercalcemia, rose in the hypocalcemic patients from < 100 pg/ml to 750-7720 pg/ml during calcium infusion (5-10 mg/kg/hr); simultaneously PTH fell from a mean of 852 pg/ml to a mean of 220 pg/ml. During EDTA infusion, PTH rose to a maximum of 2300 pg/ml in 1 of the patients as his serum calcium declined to 6.0 mg%. The 2 phenotypically normal patients did not have elevated plasma PTH levels while hypocalcemic (calcium - 6.7-7.8 mg/ml).

The varying response in urinary cyclic AMP to PTH stimulation suggests more than 1 mechanism for the end organ resistance to PTH in PHP. The high CT levels elicited in chronically hypocalcemic patients during calcium infusion may be due to increased stores of CT in the thyroid gland of these patients which can be released by appropriate stimuli. These results also confirm that PHP is not due to PTH deficiency.

CHANGES IN CALCIUM AND PHOSPHORUS METABOLISM AFTER GROWTH HORMONE ADMINISTRATION IN DWARFISM. Salvador Castells, Bhujanga Rao and Chun Lu. Department of Pediatrics, Downstate Medical Center, Brooklyn, New York

It has been shown in animals that administration of bovine GH has marked effect in Ca and P metabolism by increasing bone formation. In humans although it is well known that normocalcemic hypercalciuria occurs at the initiation of HGH therapy, the effect of HGH in Ca and P metabolism has not been that well studied. Two dwarfs with isolated HGH deficiency and two with normal or elevated plasma GH levels were placed on controlled N, Ca and P intakes with metabolic balance measurements. After two weeks of control, 5mg of HGH were given daily for 6 days. HGH produced marked increase in N balance only in the two HGH deficient dwarfs. In these two children urinary Ca (mg/day) during the control period averaged 68 and 72 and increased to 112 and 92 respectively. Fecal Ca (mg/day) strikingly decreased from 339 and 420 to 209 and 268 respectively. As a result positive Ca balance (mg/day) markedly increased from 331 and 278 to 409 and 389 respectively. In the two patients with subresponsiveness to HGH, hypercalciuria also occurred as shown by an increase in urinary Ca (mg/day) from 35 and 20 to 77 and 69 respectively. Fecal Ca (mg/day) before therapy was 578 and 509 and after therapy 535 and 578 respectively. As a result Ca balance (mg/day) slight increase in one patient (from 169 to 181) and decrease in the other (from 233 to 117). The pattern of changes of P balance in the two groups followed that of Ca. Blood levels of Ca and P were maintained constant during the study. Thus, HGH increased the intestinal absorption and the retention of Ca and P by the skeleton only in HGH deficiency. The presence of hypercalciuria in both types of dwarfs may indicate that this effect of HGH is independent of that on Ca and P metabolism.

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TOTAL BODY POTASSIUM, HEIGHT, AND WEIGHT CHANGES IN RESPONSE TO HUMAN GROWTH HORMONE. Platon J. Collipp, Raj K. Sharma, Vincent R. Curti, Stanton H. Cohn, Vaddanahally T. Maddaiah and Joseph T. Thomas. Nassau County Medical Center, East Meadow, N.Y. and Brookhaven National Laboratories, Upton, N.Y.

12 children received human growth hormone 2 u 3x/wk (NPA A-11) for 7 months, stopped for 4 months and then started again for 8 months. Total body potassium was determined at 2 month intervals using a whole body counter calibrated against a phantom containing known amounts of potassium. The changes in height, weight and potassium were:

	7 mos. HGH	Control 4 mos.	8 mos. HGH
Height (inches/month ± SD)	0.17± .08	0.07*± .02	0.17± .05
Weight (pounds/month ± SD)	0.28± .27	0.60*±0.40	0.27±0.16
Potassium (grams/month ± SD)	0.57± .35	0.41**±.50	0.50± .26

*p < 0.05 **p < 0.10

There was a 10% change in total body potassium during treatment and a 2.6% change in height, suggesting that potassium measurements might be a more sensitive indicator of growth hormone responsiveness than height measurements. 40 duplicate potassium measurements were obtained prior to treatment to evaluate precision of the method. The mean potassium was 37.2 grams ± 2.8 (S.D.).

BENIGN PHEOCHROMOCYTOMA IN ASSOCIATION WITH ELEVATED HOMOVANILLIC ACID EXCRETION. Stanley E. Gitlow, Laura M. Bertani, Steven M. Greenwood, Biao Lan Wong, and Stanley W. Dziedzic. (Intr. by Donald Gribetz). The Mount Sinai School of Medicine of the City University of New York, Dept. of Med., New York.

In adults, benign pheochromocytoma is characterized by moderate elevations in the excretion of the norepinephrine and epinephrine metabolites, vanillylmandelic acid (VMA) and total metanephrines (TM), whereas the dopamine product, homovanillic acid (HVA), is excreted in normal quantities. Less than one-half of those adults with malignant pheochromocytoma excrete elevated quantities of HVA. In children, elevated HVA and markedly elevated VMA most often characterize the malignant neural crest lesion, neuroblastoma, but may rarely be found in association with the benign tumor, ganglioneuroma. Nine children varying from 5 to 15 years of age presented with evidence of neural crest lesions. Their VMA, TM, and HVA excretions were determined prior to and following resection of one or more well-encapsulated, grossly and histologically benign pheochromocytomas. One-third of these subjects presented with elevated HVA and markedly increased VMA and TM excretion, biochemical evidence opposed to the presence of a benign pheochromocytoma. No significant difference in age, sex, clinical presentation, course, or postoperative biochemical evaluation could be detected between this group and the six remaining subjects. It is apparent that HVA excretion, indicative of a malignant pheochromocytoma in the adult fails to carry this serious prognostic import in childhood. Moreover, the pattern in childhood of elevated HVA and markedly increased VMA and TM excretions, usually associated with neuroblastoma, fails to rule out the diagnostic possibility of benign pheochromocytoma.

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VARIATIONS IN PLASMA LH AND FSH WITH AGE IN 35 PATIENTS WITH XO GONADAL DYSGENESIS. F.A. Conte, M.M. Grumbach, and S.L. Kaplan. Department of Pediatrics, University of California San Francisco, San Francisco, California.

Plasma FSH and LH were determined in 35 patients from ages 2 months to 17 years with the syndrome of gonadal dysgenesis. Six patients under 2 years of age had a marked discrepancy between plasma FSH and LH, as reflected by a plasma FSH/LH ratio of 18. Plasma FSH was significantly elevated (26 ng/ml ± 4.4 SEM - LER 869), but LH values (1.4 ng/ml ± 0.3 - LER 960) were not significantly different from the normal for this age. Five patients, 7-10 years of age, had a mean plasma FSH value of 3.4 ng/ml ± 0.8, which is significantly lower ($p < .01$) than the levels found from 0-2 years. Plasma LH was 1.8 ng/ml ± 0.5 with a FSH/LH ratio of 1.9. In 1 patient studied serially from 9 to 13 years, a marked rise in FSH and LH did not occur until 12-8/12 years. Twenty-four patients over 10 years of age had a mean plasma FSH value of 61 ng/ml ± 0.84, a mean LH of 7 ng/ml ± 0.9, and a FSH/LH ratio of 8.5. The data suggest that a sensitive negative feedback mechanism is operative in prepubertal children and that absence of gonadal function can be documented as early as 2 months of age in the syndrome of gonadal dysgenesis by detecting an elevation of plasma FSH but not necessarily LH. The lower FSH values found in the 7-10 year old patients, when compared with the infants and older patients, suggests either an inhibitory effect by non-gonadal steroids or a change in the set-point of the hypothalamic "gonadostat". The pattern of change in plasma FSH values with age in patients with gonadal dysgenesis is similar to that in normal female children, but the magnitude of the change and the plasma concentration are greater. These observations support the notion of sex-specific differentiation of the hypothalamic "gonadostat" in man.

GROWTH HORMONE-INDUCED SOMATOMEDIN-LIKE ACTIVITY FROM LIVER. Raymond L. Hintz, David R. Clemmons, and Judson J. Van Wyk, Univ. of North Carolina Sch. of Med., Dept. of Ped., Chapel Hill.

Somatomedin (SM) is the designation recently applied to the growth hormone dependent sulfation factor (SF) in plasma, a neutral peptide of ~7,000 MW. Although growth hormone (GH) action on skeletal tissue and possibly on other target organs is mediated by this peptide, the site of origin and mechanism of production of SM are poorly understood. McConaghey and Sledge (Nature 225:1249, 1970) have reported that growth hormone, when perfused through rat liver, stimulates SF-like activity. Hall and Uthne (Acta Med. Scand. 190: 137, 1971) found that GH stimulates SM production during incubation with liver microsomes. In the present study an *in vitro* superfusion technique was used to examine the time course of this stimulation in rat liver slices and to determine whether the SM-like activity induced was similar to the activity circulating in plasma. Perfusion with TC 199 was carried out at the rate of 1 ml/min through a 1.5 ml chamber containing 700 mg of liver slices cut at 0.5-1 mm. Activity in the superfusate was assayed in costal cartilage segments from hypox rats by the technique of Van den Brande *et al.* (Acta Endocr. 66:65, 1971). Within 10 minutes following the addition of human GH into the system (100 µg/ml) there was a two-fold increase in SM-like activity in the superfusate. A second exposure to GH after 50 minutes produced a further increase within 5 minutes. Chromatography on Sephadex G-75 resolved the biological activity into a major peak in the 6,000-12,000 MW range (similar to plasma) and a smaller peak in the MW <2,000 range. Since none of these preparations gave a dose response curve parallel to that of plasma SM, further purification is being carried out to determine whether plasma SM and liver SM are identical. Studies are also being carried out with selective inhibitors of protein and RNA synthesis to determine whether hepatic SM arises from degradation of a pro-hormone or requires *de novo* protein synthesis.

GROWTH HORMONE AND CORTISOL SECRETION RATES IN HYPERTHYROIDISM. Jordan W. Finkelstein, Robert M. Boyar, David K. Fukushima, Howard P. Roffwarg, Elliot D. Weitzman, T. F. Gallagher and Leon Hellman, Montefiore Hospital and Medical Center, Albert Einstein College of Medicine, Institute for Steroid Research and Departments of Pediatrics, Oncology, Neurology and Psychiatry, Bronx, New York. (Intr. by Laurence Finberg)

Growth hormone (GH) and Cortisol (F) secretion rates (SR) were calculated by a previously described method in 3 hyperthyroid girls, ages 14-17, from plasma concentrations of GH and F measured at 20-minute intervals for 24 hours. Polygraphic monitoring of sleep stages was carried out. In the hyperthyroid state GH-SR were 380, 400, and 80 µg/day (normal 680 µg/day) and increased to 570, 650 and 180 µg/day respectively following tapazole treatment. In the first two patients who became euthyroid and whose GH-SR returned to normal, F-SR fell from 59 and 38 mg/day to 20 and 17 mg/day respectively during treatment (normal 15-20 mg/day). In the third patient who was still somewhat hyperthyroid, GH-SR rose the least and remained in the subnormal range while the F-SR rose from 25 to 42 mg/day. GH and F were secreted episodically as previously described. All patients had normal sleep patterns during both studies, indicating that alterations in sleep were not the cause of the changes in GH-SR. These data indicate that hyperthyroidism can be associated with a reduction in GH-SR (not related to sleep) and an increase in F-SR, both of which returned to normal in the two patients who became euthyroid during treatment. The elevation of F-SR in the third patient with only partial remission of hyperthyroidism requires further study.

CONSTITUTIONAL DELAY AND ANDROGEN TREATMENT. J.G. Kaplan, T. Moshang, Jr., R. Bernstein, J. Parks and A.M. Bongiovanni. Univ. of Pennsylvania Sch. of Med. The Children's Hosp. of Philadelphia.

Forty male children with "constitutional delay in growth and/or development" qualified for retrospective study of the effects of androgens on final adult stature. 21 patients served as untreated controls. All groups had comparable bone ages (all greater than 10 years) with retardation (average 2.2 years). 19 were treated. The latter consisted of 13 methyl-testosterone (MT), 4 fluoxymesterone (F) and 2 testosterone enanthate (TE) recipients. (Average duration 5.3 months). Final heights were obtained 18 or more months after treatment. Predicted mature height (P.M.H.) was overestimated in the controls by 1.3 inches. It was less so in the treated group, averaging 0.2 inches. Matched bone age groups (bone ages 12-13.25 years) revealed average loss of P.M.H. of 1.8 inches in controls and 0.7 inches in the MT group. Statistically significant average gains in P.M.H. of 1.3 inches for the H-group and 1.4 inches for the TE group, were realized. The treated children were "boosted" an average of 1.1, 3.1 and 3.2 inches, MT, F and TE respectively, over controls.

Although the trend suggests improvement with treatment, there is nonetheless occasional loss of P.M.H. Factors influencing the decision are several and will be discussed.

EFFECT OF THYROTROPIN RELEASING FACTOR (TRF) ON RELEASE OF HUMAN PITUITARY PROLACTIN. S.L.Kaplan, M.M.Grumbach, and H.G.Friesen*. Dept. Ped., Univ.Calif-San Francisco; San Francisco, Ca and *McGill Univ., Montreal, Canada.

Two observations suggest that TRF may induce not only release of TSH but of prolactin as well: 1) the occurrence of galactorrhea in females with juvenile or adult forms of primary hypothyroidism; 2) the recent demonstration that TRF provokes the release of prolactin in cultivated mouse pituitary tumor cells (Tashjian et al,1971). To assess the effects of TRF on the secretion of immunoreactive prolactin, 3 groups of patients were studied: 11 with multiple idiopathic pituitary hormone deficiencies, including TSH deficiency, 13 with isolated growth deficiency, and 13 short normal children.

A rise in plasma TSH and plasma prolactin was demonstrable in all patients (13) with isolated GH deficiency (peak plasma concentration of TSH of 21.3 μU/ml and of prolactin 22.5 ng/ml) and in all 13 normal short children (peak plasma TSH of 19.5 μU/ml and peak plasma prolactin of 26.5 ng/ml). Ten of 11 patients with idiopathic multiple pituitary hormone deficiencies including TSH deficiency (mean T^4 0.8 μg/100 ml) had a response that was comparable to that of normal short children with a peak plasma TSH of 29.3 μU/ml and a peak plasma prolactin of 22.3 ng/ml. No plasma TSH or plasma prolactin rise was seen following TSH in 1 child post-hypophysectomy. These results 1) indicate that prolactin secretion is induced by TRF and 2) further support our suggestion that the primary defect in many patients with idiopathic hypopituitary dwarfism is a deficiency of hypophysiotropic hormones.

SUPPRESSION OF URINARY AND PLASMA GONADOTROPINS BY EXOGENOUS ESTROGENS IN PREPUBERTAL AND PUBERTAL CHILDREN. R.P. Kelch, S.L. Kaplan and M.M. Grumbach. Dept. Pediatrics, Univ. Calif. San Francisco, San Francisco, California.

In a recent report from this laboratory, clomiphene citrate, an "anti-estrogen" with mild estrogenic properties, was shown to inhibit rather than stimulate gonadotropin excretion in prepubertal and early pubertal children (Science 166:1912, 1969). These and other data suggested that the sensitivity of the hypothalamus-pituitary "gonadostat" decreases at the onset of puberty. To test this hypothesis further, the daily excretion of urinary gonadotropins was determined in 21 children (5 "short normals" and 16 with isolated HGH deficiency) who were given ethinyl estradiol (EE) (2-15 $\mu g/m^2$/day) for 4-7 days. In addition, plasma and urinary gonadotropins and plasma estrogens were serially determined in 2 prepubertal females (with isolated HGH deficiency) given 2 injections (24 hours apart) of estradiol benzoate, 10 μg/kg. FSH and LH concentrations in plasma and kaolin-acetone urinary concentrates, and plasma 17β-estradiol (E_2) and estrone (E_1) were measured by radioimmunoassays. Two to 3 $\mu g/m^2$/day of EE significantly suppressed urinary FSH (and LH when detected in the control period) in 3 out of 6 prepubertal children, while all doses > 5 $\mu g/m^2$/day suppressed urinary gonadotropins to undetectable levels (< 0.1 IU/day) in 9 prepubertal subjects. Five to 10 $\mu g/m^2$/day of EE produced statistically significant suppression of urinary FSH in early to mid-pubertal subjects, but failed to suppress to undetectable levels. Two subjects in late puberty (stage 4) showed no response to 7 and 8.3 $\mu g/m^2$/day. In both subjects treated with estradiol benzoate, plasma FSH promptly decreased 12 hours after the first injection. Urinary FSH was suppressed to < 0.1 IU/day on day 2 and urinary and plasma gonadotropins remained suppressed for the duration of the study (3 days). Plasma E_2 and E_1 values rose from < 10 pg/ml to peak values of 150 and 250 pg/ml (E_2), and 50 and 100 pg/ml (E_1) at 36 hours. We conclude that the hypothalamic-pituitary-gonadal axis is operative in the prepubertal child and that decreased sensitivity of the "gonadostat" appears to be the initiating factor governing the onset of puberty in man.

FAILURE TO SUPPRESS PLASMA TESTOSTERONE AND GONADOTROPINS WITH NEW ORAL PROGESTINS IN PRECOCIOUS PUBERTY. Stephanie Landey and Maria I. New, Cornell Univ. Med. Col., The New York Hospital, Dept. of Pediatrics, New York.

Two new progestational agents were evaluated in the treatment of idiopathic sexual precocity in a 3 9/12 year old male. The effects of Depo-Provera and the new progestational agents, mergestrol acetate and Danazol on plasma androgens and gonadotropins were compared. Although the boy presented at the age of 2 11/12 yrs with adult male plasma testosterone and gonadotropin levels, and a bone age of 6 yrs, treatment with progestational agents was refused by the parents until 3 9/12 yrs, at which age genitalia and pubic hair had progressed to Tanner stage IV and bone age was 13 yrs. Plasma levels of androstenedione and DHEA were prepubertal, suggesting puberty had occurred in the absence of adrenarche. A progestational agent, 17α-acetoxy-6-methyl-pregna-4,6-diene-3,20-dione,(mergestrol acetate) was given for 11 mos, 2.5 mg p o daily. Initially the plasma testosterone fell from 0.8 μg% to 0.5 μg% and plasma gonadotropins similarly decreased, but despite continued treatment plasma testosterone and gonadotropins rose to pretreatment levels. Bone age and pubertal status remained unchanged. The linear growth rate was 1 cm/mo. During the next five months the patient was treated with a new synthetic analogue of ethinyl testosterone, 17α-pregn-4-en-20-yno-(2,3-d) isoxazol-17-ol (Danazol) 400 mg daily. Plasma testosterone was partially suppressed to 0.32 μg% for four months and then returned to previous high levels despite continued treatment. No significant suppression of gonadotropins was observed during this period. Growth rate, bone age and pubertal status remained unchanged. Medroxyprogesterone acetate (Depo-Provera), known to suppress plasma testosterone and gonadotropins in precocious puberty, was then given, 200 mg IM, at 3 wk intervals. After 6 wks a reduction in plasma testosterone, greater than that achieved with the previously used drugs was obtained. It appears that Depo-Provera was the most effective agent tested in lowering plasma testosterone in male sexual precocity.

MATERNAL AND PLACENTAL CHORIONIC SOMATOMAMMOTROPIN LEVELS IN RELATION TO PRENATAL AND POST-NATAL GROWTH. Duncan R. MacMillan* and Robert G. Howard* Univ. of Louisville Sch. of Med. Dept. of Ped., Louisville, Ky. (Introduced by Jacqueline Noonan.)

Chorionic somatomammotropin (HCS) concentrations were determined in maternal serum and placental tissue obtained at time of delivery in 43 women whose offspring have been subsequently studied for 2 to 4 years. Assays were performed by duplicate parallel-line radio-immunoassay technique using HCS-I-131.

Twenty-two infants considered small for gestational age (SGA) showed a mean maternal HCS level of 3.4 ug/ml compared to a mean of 5.2 ug/ml for twenty-one infants considered appropriately grown for gestational age (AGA). (Level of significance 0.1) At the time of most recent reexamination, 18 of the children were considered to be short (HA/CA < 0.8) while 25 were considered to have normal stature. The short children had a mean maternal HCS level at birth of 3.6 ug/ml and the normally grown group a mean of 4.8 ug/ml. The eleven SGA infants who were still short at time of reexamination had a mean maternal HCS level of 2.4 ug/ml compared to a mean maternal level for the 32 other infants of 5.0 ug/ml (significant at 0.05 level).

Placental HCS levels were similar in all groupings.

No. Cases	Status at Birth	Status at 2-4 yrs.	Maternal HCS	Placental HCS
11	SGA	Short	2.4 ug/ml	29.8 mg/gm dry wt
11	SGA	Normal	4.5 ug/ml	29.7 mg/gm dry wt
7	AGA	Short	5.4 ug/ml	33.0 mg/gm dry wt
14	AGA	Normal	5.1 ug/ml	27.0 mg/gm dry wt

These findings suggest that maternal chorionic somatomammotropin levels, but not placental concentrations of the hormone, may be of prognostic value with regard to future growth in apparent intratuterine growth retardation.

STUDIES ON THE TRYPTOPHANYL FLUORESCENCE (TF) OF HUMAN AND BOVINE GROWTH HORMONES (HGH, BGH). Vaddanahally T. Maddaiah, Platon J. Collipp, Shang Y. Chen, Raj K. Sharma, and Joseph Thomas. Nassau County Medical Center, East Meadow, New York.

Although HGH and BGH have 61% of their amino acid residues identical and in the same sequence, BGH is not biologically active in humans. Fluorescence, being a sensitive probe for several aspects of protein tertiary structure, appeared ideal to investigate differences in tertiary structure around the single tryptophanyl (T) residues of the two hormones. Emission maximum of HGH (excited at 280 nm) was at 348 nm whereas that of BGH has been reported to be at 315 nm. Rates of TF increase with ethanol (up to 30% by volume) of N-acetyl-tryptophanamide, HGH and BGH were 0.080, 0.077 and 0.043 respectively. Further, KI at low concentrations (0-0.2 M) quenches TF of only HGH in aqueous solution. At low concentrations of KI quenching appears to be due to binding near the T residue of HGH. In guanidine solution KI quenches TF of both hormones. Due to radiationless energy transfer TF of HGH was quenched by about 35% in the pH region of tyrosyl ionization (pH 9-11) in aqueous solution but not in guanidine solution. TF of BGH has been reported to increase in the above pH range. These results suggest that the single T residue of HGH is accessible to solvent molecules, or "exposed" and may be situated close (~13.4 Å) to tyrosyl residue(s). On the other hand, the T of BGH may be situated in the interior of the hydrophobic region of the molecule. Thus, there appears to be some differences in tertiary structure which may account for the different biological specificities of the two hormones.

NEW ENDOCRINE DATA IN DEXAMETHASONE SUPPRESSIBLE HYPERALDOSTERONISM, Maria I. New, Elliot J. Siegal, and Ralph E. Peterson, Cornell Univ.Med.Col, New York.

New endocrine data in an 18 year old boy (EM) with dexamethasone suppresible hyperaldosteronism clearly excludes the previously proposed impairment of 17α hydroxylase activity as a cause of the hypertension. Secretion rates of cortisol(F), corticosterone(B), desoxycortisol(S) and desoxycorticosterone(DOC) were compared to those in a male pseudohermaphrodite(ES) with 17α hydroxylase defect as follows:

Secretion rate $mg/m^2/24h$	age(yrs)	F	B	S	DOC	aldo
Dexamethasone suppressible(EM)	12	3.95	0.735	0.19	0.022	0.216
	13	6.3	3.18	0.45	0.039	-
17hydroxylase deficient(ES)	24	1.3	16.0	0.023	0.35	0.035
mean of normals		7.5	2.2	0.26	0.055	0.13

The normal secretion rate of B and DOC in EM as compared to the markedly elevated values in ES rule out 17α hydroxylase deficiency as a cause of hypertension in EM. This is further supported by the normal values for secretion of S and F in EM, while the values in ES are very low. Aldosterone secretion in the patient with 17α hydroxylase deficiency(ES) was very low while aldosterone secretion was elevated in EM. Indeed, the only hormonal abnormality which persisted over 6 yrs of followup is hyperaldosteronism. At age 12 the patient(EM) was first placed on low dosage glucocorticoid therapy with excellent control of blood pressure and suppression of aldosterone secretion. At age 18 after 10 mos off therapy he again had hypertension, mild hypokalemic alkalosis, low plasma renin activity and hyperaldosteronism unaltered by sodium restriction or elevated sodium intake. Dexamethasone (1mg/24h) caused a decrease in aldosterone excretion to normal and an increase in renin activity. The patient again became normotensive within 72 hours of treatment. The prompt and complete response to medical therapy in this patient emphasizes the importance of a trial of glucocorticoid suppression in the hypertensive child with chemical evidence of hyperaldosteronism.

THE EFFECT OF PROPRANOLOL AND GLUCAGON ON GROWTH HORMONE RELEASE IN NORMAL AND HYPOPITUITARY CHILDREN. John S. Parks, James A. Amrhein, Thomas Moshang, Jr., and Alfred M. Bongiovanni. Univ. of Pennsylvania Sch. of Med., The Children's Hospital of Philadelphia.

Both propranolol and glucagon produce sustained elevations of serum growth hormone (GH) in normal children. GH responses to propranolol, 40 mg. p.o., followed in 120 minutes by glucagon, 0.5 mg. I.M., were determined in 33 children with short stature and retarded bone age.

Eight hypopituitary children who had failed to respond to other stimuli also failed to respond to propranolol and glucagon (peak GH < 5 ng/ml). The other 25 showed varying GH responses to propranolol. GH levels prior to glucagon were < 5 ng/ml in Group I; 5 to 10 ng/ml in Group II; and > 10 ng/ml (> 2 s.d. above mean basal value of 4.2 ng/ml) in Group III.

Group	Number	Mean GH value (ng/ml) Propranolol	Glucagon	Rise	Mean Age (years)
I	8	2.78	11.33	8.55	10.25
II	7	6.30	**22.98	*16.68	10.14
III	10	22.57	***38.91	16.34	* 6.10

p for comparison with preceding group: *,<.02; **,<.005; ***,<.001

The effects of propranolol and glucagon are additive. Mean GH rose 16.5 ng/ml following glucagon in Groups II and III. The increment is similar to that seen with glucagon alone, but peak values are higher than we have found with any other stimuli. Group I (propranolol non-responders) showed a lesser rise. Mean age in Group III was less than in I and II. Blood glucose did not differ in the 3 groups. GH deficiency had previously been diagnosed and treated in 2 members of Group I.

Propranolol and glucagon is a safe, convenient and effective test for GH deficiency. Children who show a response to propranolol and glucagon but not to other stimuli may also show accelerated growth during long-term treatment with β-adrenergic blocking agents.

PLASMA ANDROSTENEDIOL IN NORMAL AND ABNORMAL DEVELOPMENT

R.L. Rosenfield, A.I. Barmach de Niepomniszcze* and Patricia Otto*. Univ. of Chicago Pritzker Sch. of Med., Dept. of Ped., Chicago, Ill.

Plasma androstenediol (androst-5-ene-3β,17β-diol) has been measured in infants and children for the first time so as to gain insight into the role of this steroid in growth and development. This compound is a modestly androgenic intermediate in the formation of testosterone from dehydroepiandrosterone, the most abundant 17-ketosteroid. Androstenediol levels were recently demonstrated to be elevated in some adult women with male-pattern hirsutism in whom plasma testosterone levels were normal. This finding suggested that androstenediol might be of significance under certain circumstances and led to the present studies.

C-19 steroids were analyzed by competitive protein binding methods in 5 ml plasma. Plasma androstenediol levels in children, women, and men averaged 27 ± 8, 68 ± 25, and 124 ± 45 (SD) ng%, respectively. In order to further investigate the possibility that androstenediol plays a role in sexual development, girls with precocious adrenarche were examined. Though dehydroepiandrosterone sulfate is elevated in such children, the basis of the premature development of pubic hair is unknown since testosterone and androstenedione are not clearly increased. Plasma androstenediol was high (50-54 ng%) in three of six. Androstenediol was also found to be elevated (73 ng%) in a child with a virilizing adrenal tumor. Precursors of androstenediol are known to play an important part in feto-placental hormone metabolism. It is, therefore, noteworthy that androstenediol levels in two pools of umbilical cord plasma (48-55 ng%) exceded those in children and pregnant mothers (32-40 ng%).

These data indicate that androstenediol production parallels that of other androgens: moderately high in the newborn (and fetus?), low during childhood, rising coincident with sexual maturation. Androgen action appears to result from the net effect of several steroids. Elevated androstenediol may be clinically important when levels of more potent androgens are relatively low, as in the fetus or adrenarchal child.

DIAGNOSIS AND NATURAL HISTORY OF THYROIDITIS IN CHILDREN. Marvin L. Rallison, Brown M. Dobyns, F. Raymond Keating, Joseph E. Rall, and Frank H. Tyler (Intr. by M. Eugene Lahey). Univ. of Utah Med. Ctr., Salt Lake City and Cleveland, Rochester (Minn.), and Bethesda.

In a 6 year study of thyroid abnormalities in 5,000 children, ages 11 to 18, 62 cases of thyroiditis were identified with prevalence peaks at 11.5 and 15 years of age. The incidence of 13 cases of thyroiditis per 1,000 children was surprisingly high in this young, healthy population. We identified no correlation between thyroiditis and exposure to radiation, iodide ingestion or viral illnesses.

Thyroiditis was suggested by an enlarged, firm, pebbly gland, lymph nodes, evidence suggesting hyper- or hypothyroidism, widely split PBI-T4I and by elevation of anti-thyroglobulin antibodies. TSH was elevated in 6 of 16 subjects, including 2 with hypothyroidism. Immediate discharge of over 10% of accumulated radioiodine after administration of perchlorate occurred in 4 of 20 tested. A split of greater than 2 mcg/100 ml in PBI-T4I was seen in 20% of the 62 cases. Tanned red cell hemagglutination antibodies in titers over 1:16 were found in 72% of the 62 subjects; median titer was 1:128, the highest 1:4096. Elevated titers, as well as other laboratory confirmation, were absent from 4 of 9 biopsy confirmed cases of thyroiditis.

Treatment with thyroxine was prescribed for those with hypothyroidism or serious involvement. A distinct tendency for recovery from childhood thyroiditis was observed with both regression of goiter size and decrease in antibody titer with or without treatment. Over half of the 62 subjects were normal by the end of the observation period. Mild hypothyroidism was found in 5 patients; no additional cases appeared during the period of observation.

ESTROGEN TREATMENT OF TALL GIRLS

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Of 38 tall girls (above the 97th percentile for height) who reached mature height, 21 were treated with estrogen during growth and 17 were untreated. Bone age was determined according to Greulich and Pyle standards, and the Bayley and Pineau tables were used to estimate mature height.

The 17 untreated girls when first seen had a mean age of 12.1 years, mean bone age of 12.7 years, and a mean predicted mature height of 175.9 cm. Upon cessation of growth, their mean actual mature height was 175.7 cm., 0.2 cm. shorter than predicted. Mature heights were randomly distributed around the mean: 8 girls were taller than predicted, and 9 shorter. The 21 treated girls were given conjugated estrogens (Premarin®) 10 mg. daily, cyclically (3 weeks on, one week off therapy); mean duration of treatment was 24.8 months. At the start of treatment their mean age was 12.1 years, mean bone age 12.0 years, mean predicted mature height 182.8 cm. When growth ceased, the mean actual mature height of the treated group was 178.9 cm., 3.9 cm. less than predicted; 20 girls were shorter than predicted, and 1 slightly taller (2.0 cm.). The difference between the predicted and actual height disparities in the treated and untreated groups is significant ($p < .001$). Spontaneous menses resumed promptly after discontinuation of estrogen; one girl subsequently became pregnant.

The findings in the untreated group indicate that height can be accurately predicted for tall girls. Treatment with estrogens under the conditions described leads to a modest decrease (about 4 cm.) in estimated mature height, without evidence of interference with subsequent ovarian function.

Contrary to expectation, correlation was poor between bone age at onset of treatment and degree of disparity from predicted mature height in those given estrogen. For those starting at bone age <12 years, mature height was 4.0 cm. less than predicted; for those 12-13 years mature height was 4.3 cm., and for those 13+ years it was 2.5 cm. less than predicted.

STIMULATION OF GROWTH HORMONE(GH)SECRETION BY L-DIHYDROXYPHENYL-ALANINE(L-DOPA)IN CHILDREN, ADOLESCENTS AND ADULTS. Allen W.Root and R.David Russ, Temple University School of Medicine, Albert Einstein Medical Center, Division of Pediatrics,Philadelphia, Pa.

The effect of the oral administration of L-DOPA (0.5 g) upon serum GH concentrations, determined by radioimmunoassay, was evaluated in 22 children and adolescents (17 males, 5 females; 6-20 yrs) with growth disturbances of non-pituitary origin, 4 patients (16-18 yrs) with hypopituitarism (3 idiopathic, 1 craniopharyngioma),2 normal adult males (22,36 yrs), and 4 subjects (65-76 yrs) with Parkinson's disease. In 22 patients with non-pituitary causes of growth retardation GH levels increased from the basal value of 1.2 ± 0.3 (SEM) mμg/ml to a maximum of 8.9 ± 1.5 mμg/ml 60 minutes after L-DOPA ingestion. The mean peak GH concentration recorded in these subjects was 11.2 ± 1.4 mμg/ml; the mean GH increment was 10.1 ± 1.4 mμg/ml. The mean peak GH level noted after an arginine-insulin tolerance test (N=19/22) was 13.4 ± 1.3 mμg/ml; the mean GH increment was 11.9 ± 1.2 mμg/ml. Serum GH concentrations did not increase in patients with hypopituitarism following arginine, hypoglycemia or L-DOPA. Serum GH values increased in both adult males and in 1/4 patients with Parkinson's disease after L-DOPA ingestion. Blood glucose concentrations increased erratically while serum insulin (N=5) levels did not change following the administration of L-DOPA. Nausea (N=7/32) and vomiting (N=3/32) occurred after L-DOPA ingestion, but no relationship between these symptoms and the peak GH level recorded was discerned. It is concluded that L-DOPA effectively stimulates GH secretion in young subjects.

PARATHYROID FUNCTION IN PATIENTS WITH CYSTIC FIBROSIS (CF). Artemis P. Simopoulos, Lynn M. Taussig, F. Murad, C. D. Arnaud, Paul A. di Sant'Agnese, John Kattwinkel, and Frederic C. Bartter, NIH, Bethesda, Md.; Univ. of Virginia, Charlottesville; Mayo Clinic, Rochester, Minn.

Five patients with CF underwent calcium infusion tests for parathyroid function: the results were consistent with a state of hyperparathyroidism, as previously reported. In two of these patients parathyroid hormone determinations revealed high normal values which failed to decrease at the end of the calcium infusion despite an increase of serum calcium from 9.4 and 9.6 mg% to 11.2 and 12.4 mg% respectively.

To further delineate the abnormality, the responsiveness of bone and kidney to parathyroid extract (PTE) and the rate of calcium absorption were studied in the five patients. PTE in graded doses of 400 and 600 units for three days each was given intramuscularly while the patients were receiving a diet of 400 mg calcium and 800 mg phosphorus which was low in collagen. Serum calcium increased, serum phosphorus decreased, urinary calcium and hydroxyproline increased, urinary phosphorus increased. In all patients urinary cyclic adenosine monophosphate was elevated during the control period, in three patients it increased even further with PTE and returned to control values after PTE was discontinued.

Gastrointestinal absorption of calcium was studied by the measurement of forearm radioactivity in a large-volume liquid scintillation counter following separate oral and intravenous doses of $^{47}CaCl_2$: it was within the normal range for all subjects despite the presence of malabsorption.

The data indicate that the response to PTE administration in patients with CF does not differ from that of normal subjects, indicating a normal end organ responsiveness. However, the secretion of parathyroid hormone does not suppress normally and is independent of the control of serum calcium.

A NEW CONCEPT IN ADRENOCORTICAL REGULATION. W. Roy Slaunwhite, Jr., Thomas Aceto, Jr., Margaret H. MacGillivray, Cheryl R. Seifert and Susan P. Keenan. School of Medicine, State University of New York at Buffalo, Children's Hospital of Buffalo, Departments of Pediatrics and Biochemistry, Buffalo.

Eight children, 5-16 years of age, in good health were studied in the hospital for 25 hours. Blood was obtained through an indwelling needle every 30 minutes while the subject pursued normal activities. Notes of sleeping, eating, drinking and emotional status were made. Plasma cortisol was determined by a protein binding method. All the subjects secreted cortisol episodically having 5-9 episodes daily. The maximal plasma concentration of cortisol attained during each secretory episode varied greatly in each subject. The highest peak in each subject was rather uniform: 180-250 ng/ml. All subjects but one, who was anxious and emotional, exhibited prolonged hypocortisolemia (< 20 ng/ml) during the late afternoon and evening. Even though there was great variability in sleep patterns, the major secretion of cortisol appeared from 3 hours before waking to 1-2 hours after waking. Nocturnal adrenocortical activity prior to this time was variable, being shown by one subject while awake and not shown by two who were asleep. The major exception was the 5 year-old girl who exhibited important secretory episodes 4 and 5.5 hours before final awakening. There was no discernable relationship between ingestion of meals or snacks and the concentration of plasma cortisol. Thus, these data suggest that our old concept of negative feedback needs refurbishing. While high concentrations of plasma cortisol may suppress hypothalamic CRF, low concentrations do not appear to release the suppression. Some CNS activity, such as anxiety, may be required for reactivation of the hypothalamus.

PLASMA TESTOSTERONE VALUES IN CONGENITAL VIRILIZING ADRENAL HYPERPLASIA (CVAH) Irene L. Solomon, Edgar J. Schoen, Larry Donelan, and David Brandt-Erichsen Kaiser Foundation Hospital, Kaiser-Permanente Medical Center, Department of Pediatrics, Oakland, California

Because it is difficult to obtain reliable 24-hour urine samples for measurement of urinary 17-ketosteroids (17-ks) and pregnantriol, we studied plasma testosterone (T) levels as a means of assessing CVAH control by corticosteroid and compared T levels with urinary 17-ks. Normal values for T measured in our laboratory by a competitive binding method are: prepubertal children <40 mμg/100 ml., adult females 37-100 mμg/100 ml., adult males >400 mμg/100 ml. T was measured on 26 occasions in 9 patients with CVAH. Results in 5 patients are illustrated in the table.

	Untreated CVAH			Steroid-suppressed CVAH		
Sex	Age yr.	17-ks mg./24 hr.	T mμg/100 ml.	Age yr.	17-ks mg./24 hr.	T mμg/100 ml.
M	5	9.7	324	6	3	0
F	4.9	7.5	92	8.5	2	0
*F	7.6	2	83	5.6-8	2	15
*F	19.6	24	129	16.8-19	2.5	20
†M	20.9	—	493	27	7	42

*Corticosteroid therapy interrupted 2-4 weeks for testing purposes.
†Has had bilateral gonadectomy.

In all untreated patients, T was elevated for age and degree of sexual maturation. In the same patients treated with corticosteroids, T values were in the normal prepubertal range. Elevated T values in inadequately treated CVAH varied widely, tending to reflect the severity of CVAH. T values indicate satisfactorily the adequacy of corticosteroid suppression of CVAH, and may even indicate CVAH control more sensitively than urinary 17-ks.

REDUCED METABOLIC CLEARANCE OF GROWTH HORMONE IN JUVENILE DIABETES MELLITUS. M.A. Sperling, F. Wollesen, & D.A. Fisher, UCLA Sch. of Med., Harbor Gen. Hosp., Dept. of Peds., Torrance, Calif.

Previous studies in patients with juvenile diabetes mellitus have reported significantly elevated levels of plasma growth hormone (HGH) over the course of a normal day and in response to exercise or glucagon. To further evaluate the potential role of HGH in the diabetic state, the metabolic clearance rate (MCR) of HGH was determined in 6 insulin dependent diabetic patients and in 3 normal volunteers. Equilibrium MCR was measured by giving a primary dose of 131-I-HGH followed by constant infusion. HGH radioactivity was assessed by double antibody precipitation of both serum and infusate samples. A statistically significant reduction of mean HGH MCR was found in the diabetic group ($p < 0.05$). This was true when results were recorded absolutely or relative to surface area.

	MCR in Liters/Day Mean ± SEM	MCR in Liters/M^2/Day Mean ± SEM
Diabetes Mellitus	91.3 ± 16.4	58.7 ± 8.7
Normal	338.7 ±102.2	198.7 ±65.7

The reduced HGH MCR in the diabetic patients could not be correlated with insulin requirements or the quality of diabetic control. Thus, the elevated plasma growth hormone levels observed in diabetes may reflect reduced MCR. To what extent this reduction in HGH MCR contributes to the perpetuation of the diabetic state remains to be ascertained.

PATHOGENESIS OF HYPOCALCEMIA IN PRIMARY HYPOMAGNESEMIA. Se Mo Suh, Armen H. Tashjian, Jr., David K. Parkinson and Donald Fraser. Univ. of Toronto, Dept. of Paed., The Hosp. for Sick Children, Res. Inst., Toronto, Canada, and Harvard Med. Sch., Dept. of Pharm., Boston.

Hypocalcemia is a frequent feature of hypomagnesemia in man and several other species. To elucidate the cause of this hypocalcemia, we studied a child with primary hypomagnesemia and secondary hypocalcemia during magnesium supplementation when he was normomagnesemic and normocalcemic, and after magnesium restriction for 16 days when he became hypomagnesemic (0.5 mEq/l) and hypocalcemic (3.4 mEq/l), and had positive Chvostek's and Trousseau's signs.

Whether in the normomagnesemic or hypomagnesemic state, intravenous bovine parathyroid extract (PTE) 8 u/kg caused prompt transient increases in urinary phosphate excretion, renal phosphate clearance and c-AMP excretion. These responses were similar in magnitude to those observed in a small series of hypoparathyroid patients. When he was hypomagnesemic and hypocalcemic, intramuscular PTE, 8 u/kg 8 hourly for 4 doses, caused prompt hypercalcemia. Serum concentrations of parathyroid hormone were normal (< 0.6 ng/ml) in both phases of the study. Calcitonin was uniformly unmeasurable in serum.

We conclude that, in hypomagnesemia, (1) the end-organs - both skeleton and renal tubules - are responsive to PTE, (2) excess calcitonin is not the cause of hypocalcemia, (3) serum PTH does not become elevated inspite of severe hypocalcemia. The findings support our thesis that magnesium depletion causes impaired synthesis or secretion of parathyroid hormone.

CONGENITAL JUXTAGLOMERULAR HYPERPLASIA MANIFESTED BY ELEVATION OF SODIUM, CHLORIDE AND RENIN WITH NORMAL POTASSIUM AND BLOOD PRESSURE. Hulda J. Wohltmann, Phyllis M. Hartroft and Wladimir Wertelecki. Med. Univ. of South Carolina, Dept. of Ped., Charleston, South Carolina and Washington Univ. Sch. of Med., Dept. of Path., St. Louis, Missouri (Intr. by Jean H. Thurston).

A 3 months old caucasian male with a normal prenatal and birth history was studied because of fever, irritability, vomiting, flushing and sweating episodes beginning at 2 weeks of age. Examination revealed normal growth parameters, and no evidence of dehydration and was normal except for a high-pitched cry and poor head control. Flush blood pressures were normal. Serum Na ranged from 150-168, Cl 111-130, K 4.6-5.6 and Mg was 2.7 mEq/l. Mean 24 hr. urine volume was 535 cc. Aldosterone excretion was 8 μg per 5.9 kg. per 24 hours. Plasma volume was normal and plasma renin was 10-30 times higher than normal by radioimmunoassay and bioassay.

At 3½ months of age, pitressin-resistant polyuria developed. A renal biopsy showed extreme hyperplasia and hypergranulation of juxtaglomerular(JG) cells. The macula densa appeared normal. Response of B.P. to an infusion of angiotensin was blunted. Plasma epinephrine and norepinephrine were slightly elevated (4 μg, 1.55 μg/l plasma).

Treatment with spironolactone (4 mg/kg) produced slight lowering of serum Na and Cl but was complicated by a sharp elevation of K and BUN. Successful treatment was achieved only thru smaller doses of spironolactone (1.5 mg/kg) combined with methyldopa (10 mg/kg). Such combined treatment has maintained the electrolytes in balance and at 21 months of age the patient is well except for polyuria and low growth parameters.

Three chromosomal analyses performed between 3 and 14 months of age revealed the presence of a chromosomal fragment and several chromatid aberrations. A chromosomal analysis at 18 months of age was normal. The chromosomal aberrations may represent cellular damage produced by hypertonicity during early life.

GENETICS

First Session

LESSONS FROM ONE HUNDRED AMNIOCENTESES FOR PRENATAL GENETIC STUDIES, Aubrey Milunsky, Leonard Atkins, John W. Littlefield, Harvard Med. Sch., Children's Service, Mass. Gen. Hosp., W.E. Fernald State Sch., Boston and Waltham, Mass.

Most chromosomal abnormalities and more than forty biochemical disorders can now be diagnosed in utero, in addition to the important fetal sex determination in sex-linked diseases. Our experience with 100 consecutive amniotic fluid samples (94 pregnancies) obtained mainly between 14 to 16 weeks gestation, and submitted for diagnostic studies, has been analyzed. The indications for amniocentesis in 84 cases were for chromosomal analysis (maternal age 40 (14), maternal age 35-39 (24), previous mongolism (20), family history of mongolism (8), translocation carriers (3), miscellaneous (15)), in 3 cases for X-linked diseases and in 7 cases for metabolic disorders. A diagnosis was made from 99% of the amniotic fluid samples received with only one sample lost to contamination. Second amniocenteses were necessary in five patients due to technical problems (2), grossly bloody fluids (2), and transport delay (1). Four affected fetuses were diagnosed prenatally (unbalanced D/G translocation; trisomy 18; Tay-Sachs disease (2)), and the diagnosis confirmed on the abortus (3) or stillbirth (1). Abortion followed amniocentesis in one case, and probably unrelated fetal death occurred in another. No errors have become apparent in the outcome of 62 pregnancies. To accurately determine the risk of amniocentesis in early pregnancy, the reliability of the genetic studies and other important variables, will require a large collaborative study with a matched control group. Such a project has been initiated by the Nat. Inst. Child Health and Human Development.

GM_1 GANGLIOSIDOSIS, TYPE I: IN UTERO DETECTION AND FETAL MANIFESTATIONS. M.M. Kaback, H.R.Sloan, and A.K.Percy, Depts. Ped. and Neuro. Johns Hopkins Hosp., Baltimore, and Molecular Disease Branch, NIHL, NIH, Bethesda, Maryland

GM_1 gangliosidosis-Type I (GG) is a progressive, uniformly fatal, sphingolipidosis of infancy associated with widespread tissue accumulations of GM_1 ganglioside and acid mucopolysaccharides. Total deficiencies of lysosomal β-galactosidase activity (β-gal) and GM_1-^{3}H-gangliosidase activity (GM_1'ase) have been described in this condition.

We have monitored 2 pregnancies in a couple whose first child died of this autosomal recessive disorder. Histochemical staining (BCIG) and enzymatic assays of cultured midtrimester amniotic fluid cells (AFC) showed:

	Control AFC (5)	AFC-1st Preg.	AFC-2nd Preg.
BCIG	++++	++++	0
β-gal*	278.2-757.9	334.3	<25.0
GM_1'ase*	0.27-0.55	0.31	< 0.003

*nano moles product/hr/mg protein

The first pregnancy resulted in a term infant, heterozygous by cord leukocyte analysis, now 18 mos. old and well. The second pregnancy was terminated by hypertonic-saline instillation at 21 weeks. Studies of the GG-fetus compared with both saline and non-saline aborted controls revealed: a 20-100 fold reduction in the specific activities of β-gal and GM_1'ase in brain, liver, and kidney in the GG fetus, lack of BCIG staining in all GG fetal tissues, abnormal PAS and Rinehart staining in GG kidney, liver, and myocardium, and a 3.4 fold increase in GM_1 ganglioside concentration in the GG fetal brain. Lysosomal enzyme levels, histochemical reactions, and sphingolipid concentrations in the saline versus non-saline aborted controls did not differ significantly.

These studies indicate that GG is detectable in utero; that the pathologic process is already evident in early fetal life; and that hysterotomy, which may significantly jeopardize subsequent pregnancies, is not necessary if done only for corroborative studies.

FETAL SEX DETERMINATIONS. Cheryl Adams,* Byron Kilpatrick,* George Kabacy,* Gayle E. Fialko,* and Kenneth W. Dumars,* Univ. of Calif., Irvine, Calif. College of Med., Dept. of Ped., Irvine. (Intr. by Thomas L. Nelson)

Limitations in the intrauterine diagnosis of certain X-linked disorders lends increasing importance to those techniques utilized to aid in the delineation of fetal sex. If one can accurately identify fetal sex in mothers who are heterozygotes for X-linked recessive disorders or pregnancies sired by fathers who have a history of X-linked dominant disorders, the geneticist can more accurately provide counselling regarding management of the pregnancy.

In a group of 51 mothers undergoing transabdominal amniocentesis between 28 and 40 weeks gestation, we had an opportunity to determine fetal sex. Utilizing Y body fluorescence and Barr Body determinations on cells obtained from the amniotic fluid, fetal sex was correctly predicted in 47 of the 49 mothers who have delivered.

In both infants incorrectly identified, a female was predicted (prediction based upon the absence of Y fluorescence and presence of a Barr Body) and ultimately the conceptus was found to be a genotypic and phenotypic male. In one of these infants subsequent karyotyping revealed a small Y with deletion of the normally fluorescent heterochromatic distal segment of the long arm. The second phenotypic male has a normal male karyotype with Y fluorescence.

Absence of the fluorescent heterochromatin on the Y chromosome, which does not produce phenotypic alterations, has been previously described. The variation in heterochromatin content of the Y chromosome and the risk of maternal cell contamination of the amniotic fluid indicates to us that Y body fluorescence and Barr Body determinations used alone are inadequate means of determining fetal sex.

ABH AND LEWIS SUBSTANCES IN AMNIOTIC FLUID BY AMNIOCENTESIS. Minerva B. Arcilla and Phillip Sturgeon. U.C.L.A. Sch. of Med., Dept. of Ped., Los Angeles, California.

Soluble ABH blood group substances are known to be present in the amniotic fluid at the time of delivery and even as early as 9 - 24 weeks of gestation but there are no reports on studies of Lewis substances in amniotic fluid at any stage of pregnancy. We have used semi-quantitative technique to measure ABH, Le^a, Le^b and Le^x substances in amniotic fluid and have correlated these findings with the red cell and salivary ABH and Lewis phenotypes of 8 mother-infant pairs. The amniotic fluids were obtained by transabdominal amniocentesis at various stages of pregnancy (15-40 weeks) and the infants' red cell and salivary phenotypes were determined by serial postpartum studies. The results show that: 1) the Lewis substances Le^a, Le^b and Le^x are present in considerable concentration in the amniotic fluid as early as 15 weeks gestation; 2) the amniotic Lewis substances correspond to the Lewis and secretor phenotype of the fetus. In three cases wherein the mothers were red cell type Le(a-b-x-) Lewis substances appropriate to the fetal Lewis and secretor genotype were present in amniotic fluid. Conversely when the fetus was Lewis negative, no Lewis substance was found although the mother was Lewis positive. 3) The amniotic ABH substance is also related to the ABH and secretor genotype of the fetus.

By amniocentesis, it is therefore possible to determine the Lewis and secretor phenotype of the fetus as early as 15 weeks of gestation. Such knowledge could be useful in prenatal detection of inherited diseases should linkage of these gene loci be found.

DELETION OF SHORT ARM OF CHROMOSOME #9 (46,9p-): A NEW CLINICAL ENTITY. Omar S. Alfi, George N. Donnell, Barbara F. Crandall & Robert L. Podosin. Univ. Southern California Sch. of Medicine, U.C.L.A. Sch. of Medicine, and The Childrens Hosp. of Los Angeles, Los Angeles.

The following report describes two probands, each having a deletion in the short arm of chromosome #9, confirmed by quinacrine fluorescence microscopy, Giemsa-banding, and centromeric staining techniques. Both probands have several features in common, including: Trigonocephaly, broad nasal bridge, everted nares, broad upper lip, moderate micrognathia, narrow high arched palate, low set deformed external ears, short neck, congenital heart disease, hypertonia, and mental retardation. One of the infants had, in addition, omphalocele and diaphragmatic hernia.

Karyotypes of each showed a chromosome #9 with 1/3 of the short arm deleted, and most of the paracentromeric heterochromatic segment of the long arm. The mother and maternal aunt of one of the patients have balanced (9p-, 16q+) translocations.

Dermatoglyphics in both probands showed increased whorls on the fingers.

Three cases in the literature, with short arm deletions or ring formation in a C-group chromosome, thought to be a 9 or 10 chromosome by the standard techniques have many of the above mentioned clinical features. This suggests that the chromosome involved in these reported cases is #9.

The clinical findings described suggest a "9p- syndrome" and utilization of the banding techniques can provide cytogenetic confirmation.

THE SCREENING OF NEWBORN INFANTS FOR Y CHROMOSOMAL ABNORMALITIES--FLUORESCENT STAINING OF UMBILICAL CORD CELLS. Arnold Greensher, David Peakman and Arthur Robinson. Intr. by Henry Silver. Univ. of Colorado Med. Sch., Colorado Gen. Hosp., Dept. of Biophysics and Genetics, Dept. of Pediatrics, Denver, Colorado.

The importance of screening newborn infants for sex chromosomal abnormalities has been amply demonstrated. We now report our experience with the fluorescent staining of the Y body and Barr body in Wharton Jelly cells of the umbilical cord for the detection of abnormalities of the sex chromosomes.

Touch preparations were made from freshly cut umbilical cords and stained with Quinacrine hydrochloride.

To date, blind screening for abnormalities in number of the sex chromosomes has been carried out on 3,472 consecutive births (1,873 male, 1,599 female) and the following abnormalities found: 2 infants with 47,XYY; 3 infants with 47,XXY; 2 infants with 45,X; one 46, XY female infant.

The distinct advantage of this technique is its ability to detect abnormalities of the Y chromosome, as well as some of those of the X chromosome.

Utilization of the combined techniques of fluorescence of the X and Y sex chromatin in Wharton Jelly cells and conventional staining of the Barr body in amniotic membrane now provides us with a complete sex chromatin complement of a newborn. The use of these screening procedures on all new born infants is encouraged as the disorders are common and generally go undetected.

GIEMSA BANDING PATTERN OF HERITABLE 1q+ VARIANT CHROMOSOME CONSISTENT WITH PARTIAL CHROMOSOMAL DUPLICATION. John R. Lobitz*, Barbara K. McCaw*, Frederick Hecht, and Blaine E. Tolby*. University of Oregon Medical School, Portland, Oregon.

A unique class of morphologic variants of chromosome 1 is characterized by increased length of the long arm (1q+) and close apposition of chromatids in the paracentromeric region of that arm. These variants have been found in 1/100 to 1/1000 normal newborns and in children with certain anomalies. Linkage studies have served to assign to chromosome 1 a series of genes including loci for the Duffy blood group, congenital pulverulant cataract, and pancreatic amylase.

We have investigated 3 generations of a family in which 1q+ is segregating.

In the normal chromosome 1, acetic/saline/Giemsa banding studies reveal a dark and a light band in the proximal region of the long arm. In contrast the 1q+ variant shows 2 strikingly similar tandem sequences, consistent with a partial chromosomal duplication, most likely due to unequal crossing-over. Such an event is analogous to what has presumably occurred in the hemoglobin and haptoglobin systems.

RING CHROMOSOME 7 WITH VARIABLE PHENOTYPIC EXPRESSION. Elaine H. Zackai, and W. Roy Breg, Yale Univ. Sch. of Med., Depts. of Ped. and Med., Div. of Med. Genetics, New Haven, Conn., and Southbury Training Sch., Southbury, Conn.

Individuals with the same chromosome deletion, such as 5p-, have been shown to have similar phenotypic abnormalities. Based on previous studies, it has been assumed that individuals with deletions involved in ring formation of a specific chromosome would be phenotypically similar. This assumption is not supported by the present study of two males with apparently identical rings of chromosome 7 and very different phenotypic features.

Patient 1 is severely retarded, has short stature, microcephaly, craniosynostosis, unilateral proptosis, ptosis and microcornea, a small phallus, first degree hypospadius and undescended testes. Patient 2 is of normal intelligence and his only abnormalities are short stature and a small head. The cytogenetic findings in the two cases, however, are similar. Study of lymphocytes at metaphase showed the same proportion of cells with the ring (46,XY,7r) and those without a ring (45,XY,7-) in each case. Quinacrine fluorescence and giemsa banding techniques showed all the bands of chromosome 7 to be present, suggesting little material missing as a result of ring formation. A similar degree of instability of the ring in each case was indicated by the frequency of bridging at anaphase.

These patients raise questions about the phenotypic expression of some ring chromosomes. Our understanding of the effects of ring chromosomes may well be biased by the previously reported cases, which have largely been selected because of multiple malformations and mental retardation. This report suggests caution in predicting the future development of individuals with ring chromosomes detected antenatally or in early infancy.

MULTIPLE ANOMALIES INCLUDING THYMIC APLASIA ASSOCIATED WITH MONOSOMY 22. Ira M. Rosenthal, Maureen Bocian and Eva Krmpotic. Abraham Lincoln School of Medicine of the University of Illinois College of Medicine, Chicago Medical School, Departments of Pediatrics and Pathology, Cook County Hospital and Mount Sinai Hospital, Chicago.

Since the report of Al-Aish et al there have been several reports of children with anomalies and developmental retardation associated with monosomy G. Quinacrine mustard staining with fluorescence microscopy has revealed that these cases have been associated with monosomy for chromosome #21. We report the case of a male infant born at term with multiple anomalies. The infant was proved to have monosomy for chromosome #22 on study by fluorescence microscopy of chromosomes from peripheral lymphocytes and from culture of skin fibroblasts. There was no evidence of mosaicism. Anomalies present in this child included patent ductus arteriosus, and eye anomalies. Multiple severe anomalies of the hands and feet were present including syndactyly of fingers and toes leading to a "lobster claw" appearance. The infant died at 3 months of age. At necropsy an unexpected finding was agenesis of the thymus. This is believed to be the first report of a case of monosomy #22. The possibility of a direct genetic relationship between the chromosomal abnormality and agenesis of the thymus should be considered.

X-LINKED HEART DISEASE? Annemarie Sommer and Jo M. Craenen (Intr. by Stella B. Kontras), Ohio State Univ. Coll. of Med., Children's Hosp., Dept. of Ped., Columbus.

Pedigree analysis of a family revealed that a significant number (18) of male infants had died at ages from a few days to a few months with symptoms of dyspnea and cyanosis and signs of terminal congestive heart failure. Post mortem examination on 3 of the male infants revealed congenital heart disease as the cause of death. All of them had enlarged hearts weighing 55 gm. or more, left and right ventricular hypertrophy and associated moderate endocardial fibroelastosis.

Several unaffected males, as well as several females representing 3 generations were examined; the females all being presumed obligatory carriers of the heart disease in question. Evaluation by a cardiologist, EKG's and fluoroscopic examinations all were within normal limits indicating that we were unable to detect obligatory carrier females by physical examinations.

The pedigree extends over 4 generations. The first generation consisted of a sibship of 8 boys and 10 girls. Six of the boys died in infancy of apparent congestive heart failure and one of prematurity. The single male reaching adulthood is asymptomatic and has had only normal offspring. The 10 females all reached adulthood, but only 4 of them had male offspring dying of apparent heart failure and several of their daughters have had 6 more boys with presumed heart disease.

The outstanding factors in this pedigree are that there has not been any male to male transmission of congenital heart disease and that approximately half of the females of the first generation appeared to have transmitted the disease to approximately 50% of their sons and several of their daughters have had affected sons.

While the exact type of congenital heart disease in this pedigree is unknown, some form of non-constrictive cardiomyopathy inherited as an X-linked recessive disease appears to be the most likely explanation.

GENETICS

Second Session

A PILOT PROGRAM IN THE CONTROL OF GENETIC DISEASE. M.M. Kaback, R.S. Zeiger, H. Gershowitz, The John F. Kennedy Inst., Baltimore, Md. (Intr. by Barton Childs).

A Tay-Sachs disease (TSD) carrier-detection program has been initiated in the Jewish communities of Baltimore and Washington. This effort is designed to identify those couples, of Ashkenazi Jewish ancestry, in which both partners are heterozygous for the TSD gene and thereby are at risk for this recessive disorder in their offspring. Amniocentesis with each pregnancy in these couples could permit the selective birth of only unaffected children and prevent the "mass tragedy" of a TSD child. Moreover, this program could serve as a prototype for evaluation of mechanisms and impact in "delivering specific genetic services" of this kind to defined populations.

The success of voluntary genetic screening may depend critically on the active participation of various sectors of the community in planning, organization, and delivery of the program. Practicing physicians, religious leaders, organization representatives, and other community leaders were involved many months before public pronouncements or screening began. A detailed strategy for public education evolved in this way.

Seven thousand individuals have volunteered for TSD testing to date. This was achieved at 10 community-based screening sessions manned by lay program workers. More than 200 carriers have been defined, and critically, 9 couples have been identified as being at risk for TSD in their offspring. None have previously had a TSD child. The availability of detailed and individualized genetic counseling for carriers, "inconclusives", or other individuals, before and after screening, is essential.

Other important practical, ethical, and social issues are raised by such an "informed-consent", adult-oriented, genetic screening program. The elucidation of these issues and the principles of organization, education, and delivery emerging from this program may have important implications for future, or even current, genetic screening efforts directed at other inherited disorders.

EFFECTIVENESS OF NEONATAL PKU SCREENING. Neil A. Holtzman, Allen G. Meek, E. David Mellits.Johns Hopkins University, School of Medicine, Department of Pediatrics, Baltimore.

Data obtained from 26 State Health Departments and 33 PKU Clinics indicate that problems remain in current screening procedures. 1) Timing. Infants with positive screening tests, in whom a diagnosis of PKU was subsequently made, screened during the first three days had a significantly lower levels than those screened later. Furthermore, 57 of 231 infants whose blood phenylalanine exceeded 20 mg% on follow-up had only minimal elevations on the initial screen ($\leq$ 10 mg%). Although these observations suggest that screening should be delayed, the incidence of false positives rises with age after day 4. Factors responsible for this rise, such as a higher number of low birth weight infants in the late screened group, are being evaluated. 2) Altered sex ratio. In screened infants more males than females were diagnosed as having PKU than would be expected for an autosomal recessive condition (284 males:225 females). This confirms earlier observations and suggests either under diagnosis in females, over diagnosis in males, or both. Of 16 infants with false negative screening tests (who were subsequently proven to have PKU) 10 were females. The equation for the rise of blood phenylalanine as a function of time is being determined separately for male and female phenylketonurics in whom serial determinations were made during the first 8 days of life. 3) Variability of incidence of positive tests between states. Daily incidence figures were obtained from 12 states. In the 9 in whom more screening was performed on the third than any other day of life, the incidence of positives ranged between 5 and 151 per 100,000 screened on this day. All of these states used the Guthrie test; differences in the upper limit of normal did not account for the discrepancy which may be a function of laboratory reliability. In view of these unresolved problems prospective planning for the evaluation of screening for additional inborn errors appears warranted.

SICKLE CELL HEMOGLOBIN PRODUCTION IN AN ABORTED MIDTRIMESTER FETUS. Haig H. Kazazian, Jr., Michael M. Kaback, and William S. Nersesian, Johns Hopkins Univ. Sch. of Med., Dept. of Ped., Baltimore.

The antenatal diagnosis of sickle cell anemia and sickle cell trait has not been accomplished. Recently we have shown that hemoglobin A ($\alpha_2\beta_2^A$) is synthesized in vitro by reticulocytes of the 9-16 week human fetus (Science 174: 698, 1971). Since the β chain genes of hemoglobin A and hemoglobin S ($\alpha_2\beta_2^S$) are allelic, we reasoned that β^S chains would be synthesized in reticulocytes of the midtrimester fetus carrying the β^S chain gene. We obtained blood from a 22 week aborted fetus of a mother with documented sickle trait. The reticulocytes were incubated with ^{35}S-methionine and the hemoglobins were separated in the presence of non-radioactive hemoglobins A and S. ^{35}S-methionine was incorporated into a protein which migrated with hemoglobin S in (1) Biorex column chromatography and (2) cellulose acetate gel electrophoresis. The radioactivity in hemoglobin S was about 2-3% of that of hemoglobin F. Hemoglobin A synthesis, though present, was reduced in these cells to less than 3% of that in hemoglobin F. On the other hand, multiple determinations on 10 previous fetuses of normal mothers had failed to demonstrate the synthesis of hemoglobin S, while hemoglobin A synthesis was 5-15% of the synthesis of hemoglobin F in all cases. These data indicate that hemoglobin S can be detected antenatally in small quantities of blood from fetuses carrying the β^S chain gene.

FAMILY STUDIES OF LACTASE INTOLERANCE IN NIGERIAN ETHNIC GROUPS. O. Ransome-Kuti, Norman Kretchmer, John Johnson*, and John T. Gribble. Dept. of Ped., Lagos Univ. Teaching Hospital, Lagos, Nigeria, and Stanford Univ. Sch. of Med., Stanford.

An intolerance to lactose has been observed in various frequencies in the major ethnic groups of Nigeria. In the Yoruba and Ibo, about 99% of the people (> 3 years of age) are intolerant to the carbohydrate whereas about 50% of Hausa and Hausa-Fulani, and 20% of nomadic Fulani are intolerant. The Nigerian milieu makes a number of studies feasible. There are marriages between Fulani and Hausa and also Yoruba and European although there is predominance of intratribal marriage. Marriages between Fulani and Hausa were initiated about 300 years ago and consequently our results were obtained from a 10-15th generation. All of the offspring studied were intolerant to lactose except where a Fulani-Hausa male married a Fulani female. In three families, consisting of 3 males and 9 females, measurements were made in 16 offspring > 4 years of age (from a total of 25 children). Thirteen of these children were intolerant. Three children from the marriage between a nomadic-Fulani female and a Hausa-Fulani male were tolerant. Studies of members of the Yoruba tribe included 13 families. Ten of the families consisted of Yoruba males, all intolerant, married to 10 European or European-Yoruba females of which only one was intolerant. There were 25 offspring from 9 matings with tolerant non-Yoruba; 18 of the children were tolerant and 7 were intolerant. In the family where the mother was intolerant, all 6 of her children were intolerant. In three other marriages between Yoruba females with European males, there were 9 children of which 3 were tolerant.

Previously, we postulated that lactose tolerance is evidence of a mutation. From these present data, we conclude that tolerance to lactose is transmitted by an incomplete dominant gene(s) with a sex dependency. With continued breeding into an intolerant population, the ability to tolerate lactose disappears.

HYBRIDIZATION: THE RELATIONSHIP OF G_1 AND G_2 STAGES OF THE PARENTAL CELL CYCLE TO CHROMOSOME LOSS. Betty Paul, Karen Gaudio and Ian H. Porter. (Intr. by Herbert S. Strauss) New York State Department of Health Birth Defects Institute, Albany, New York

Cell cycles were determined on five cell lines: hamster-Don (Fl25), mouse (3T3), human fetal (T256), rat kangaroo (PTK_2) and human (Hela). The following combinations were hybridized using the Sendai virus technique: F125-3T3, T256-3T3, and Hela-PTK_2. The chromosomes were periodically analyzed.

In T256-3T3 hybrids, both the G_1 and G_2 stages of the mouse (3T3) are shorter:

	G_1 + Mitosis	G_2
T256	10.5 hrs.	6.5 hrs.
3T3	6.5 hrs.	4.0 hrs.

and the human (T256) chromosomes are always eliminated.

In Hela-PTK_2 hybrids, both G_1 and G_2 stages of the human (Hela) are shorter:

	G_1 + Mitosis	G_2
Hela	7.0 hrs.	5.0 hrs.
PTK_2	15.0 hrs.	7.0 hrs.

and the rat kangaroo (PTK_2) are always eliminated.

In the F125-3T3 hybrids the F125 has the shortest G_1 stage and the 3T3 line has the shortest G_2 stage:

	G_1 + Mitosis	G_2
F125	3.5 hrs.	5.5 hrs.
3T3	6.5 hrs.	4.0 hrs.

Either parent chromosomes are eliminated corresponding to the length of the G_1 and G_2 stages of the cell cycle.

We conclude that the parental chromosomes lost are determined by either the length of G_1 or G_2 stages of the cycles. This information facilitates the selection of hybrid combinations in linkage studies.

RACIAL DIFFERENCE IN RBC GALACTOKINASE ACTIVITY (EVIDENCE FOR A HIGHER FREQUENCY OF THE GALACTOKINASE DEFICIENCY GENE IN BLACKS), Robert Bonow, Thomas A. Tedesco, Karen Miller, William J. Mellman, Johannes Ipsen, Univ. of Pennsylvania Sch. of Med., Depts. of Ped., Med. Genetics, Community Med., Philadelphia

A random study of pregnant women is underway to detect the carrier state of gal-1-P uridyltransferase and galactokinase deficiencies. At this point over 500 women have been studied. RBC transferase assays have revealed distributions similar to those of a previous pilot study with no significant influence on enzyme activity of race, sex, hemoglobin level or gestational age. In striking contrast, galactokinase assays of the same blood samples show a marked influence of race (white females $\bar{x}$=0.318, SE=0.008; black females $\bar{x}$=0.221, SE=0.003; white males $\bar{x}$=0.359, SE=0.019; black males $\bar{x}$=0.228, SE=0.014). This difference cannot be explained in the females by influences of gestational age or hemoglobin concentration.

Statistical analysis of the female galactokinase data indicates that there are possibly three modes in the black distribution, while the white population best fits a single mode. Using the conditional minimum chi square procedure, the black galactokinase distribution can be separated into 3 populations; one with the same mean and SD as the white population (about 10% of the total sample), a major mode with a mean of 0.21, suggesting the existence of a galactokinase protein unique to black individuals, and a mode with a mean of 0.12 (about 5% of the total population).

This statistical analysis, supported by appropriate family studies, indicates the presence of genetic polymorphism in the black race with respect to galactokinase, and suggests that galactokinase deficiency should occur more commonly in black populations than in white ones. The role of intestinal lactase deficiency in protecting galactokinase deficient black individuals from galactose toxicity is also being explored.

SEX DIFFERENCES IN ACTIVITY OF G6PD IN CULTURED FETAL LUNG CELLS DESPITE X-INACTIVATION. Mark W. Steele and Barbara R. Migeon. Depts. of Ped., Univ. of Pittsburgh and Johns Hopkins Univ., Children's Hosp. of Pittsburgh and Johns Hopkins Hosp., Pittsburgh, Pa., and Baltimore, Md.

Recently one of us (MWS) reported that the specific activity of X-linked glucose-6-phosphate dehydrogenase (G6PD S.A.) in sonicates of lung fibroblasts cultured from antenatal females is 46% greater than that of antenatal males. This dosage difference persists until a few weeks postnatally at which time it is nullified by an abrupt rise in G6PD S.A. in the male. There is no difference in G6PD S.A. in cultured lung fibroblasts from antenatal and postnatal females. These findings in cultured lung fibroblasts are in contrast to that in cultured skin fibroblasts where G6PD S.A. is the same for males and females at all developmental ages. To test the hypothesis that the sex difference for G6PD in cultured fetal lung cells results from incomplete X-inactivation in the female, lung and skin (control) fibroblast cultures were established from a 14 week old female fetus heterozygous for the common electrophoretic variants (AB) of G6PD. The karyotype of both cultured skin and lung was normal female with less than one percent tetraploid cells. Although G6PD S.A. assayed from the fetal skin fibroblasts was the same as male controls, G6PD S.A. assayed from the fetal lung fibroblasts was 51% greater than male controls. Single cell clones were obtained from these skin and lung cultures and were assayed qualitatively for G6PD by starch gel electrophoresis. Ninety-eight percent of 44 lung clones and 92% of 24 skin clones showed only a single G6PD band (either A or B) indicating that in both cultured fetal skin and lung only one X chromosome is active. Therefore, the sexual difference in G6PD S.A. in cultured fetal lung cells cannot be attributed to lack of X inactivation in the female but must instead result from unknown regulatory mechanisms which depress the activity of G6PD in the antenatal male.

MUTATION AT THE HL-A LOCUS IN CULTURED HUMAN LYMPHOID CELLS. Donald Pious, Pam Hawley, Gary Forrest. University of Washington School of Medicine, Department of Pediatrics, Seattle, Wash. 98195

No system currently exists for evaluating the effects of drugs, pollutants, household chemicals or other environmental agents as mutagenic agents in man. We have sought to develop a system to detect and quantitate mutagenesis in *cultured human somatic cells. Established human lymphoid cell lines express* the surface antigens specified by the two subloci of the major histocompatibility locus (HL-A). The antigens are expressed codominantly. Cells bearing a given antigen are killed by exposure to monospecific antiserum plus rabbit complement. Using antiserum and complement as a selective system, we have isolated anti-$HL\text{-}A_2$ resistant variant clones from an $HL\text{-}A_2$/ $HL\text{-}A_3$ heterozygous cell line. The variants occur at a frequency of 10^{-5} to 10^{-6}. The resistant phenotype of the variant sublines is stable upon prolonged growth in the absence of exposure to antiserum following isolation, and is specific in that expression of antigens not selected against is unimpaired. Comparison of binding of $HL\text{-}A_2$ antibody by variant and parental cells indicates that the variants bind < 1/1000 the antibody per cell as the parent cells. Chromosomal loss can be ruled out as the mechanism of variation by the fact that the enzyme marker PGM3 which is linked to HL-A, is unchanged in the variants. Our data thus are most compatible with the mutational origin of the variants. Studies of the effects of known mutagens on variant frequency are in progress.

HUMAN FIBROBLASTS IN CULTURE - FURTHER STUDIES OF GLYCOGEN METABOLISM, Salvatore A. DiMauro, William J. Mellman, Lewis P. Rowland, Univ. of Pennsylvania Sch. of Med., Depts. of Neurology, Ped. and Med. Genetics, Philadelphia

Previously we reported that fibroblasts in culture with type II glycogenosis accumulate excessive glycogen, which is utilized when glucose is re*moved from the medium (Ped Res 3: 368, 1969). These studies have been* extended to fibroblasts from patients with glycogenoses III and V. The enzyme defect of type III glycogenosis is expressed in culture, while type V is not.

Normal cells in culture depleted of glycogen by glucose starvation to an average of 15% of the glycogen content in the glucose-fed state were found to completely replete their glycogen within 24 hours in the presence of fresh serum and glucose. When serum is deleted from glucose-containing nutritional medium, the glycogen content of cells was restored to only 38% of maximal repletion. Crystalline insulin (final concentration 5 μg/ml) could substitute for serum in these experiments, such that insulin-containing medium without serum resulted in the complete restoration of glycogen content after a period of glucose starvation.

Phosphorylase activity was measured in these cells under conditions of glucose starvation and maximal glycogen concentration. The 5'-AMP independent (phosphorylase a) form was 10% of the total in the glycogen-depleted cells, and 60% when glycogen was maintained at maximal levels.

These studies suggest that human cells in culture might be used to diagnose genetic aberrations of the regulation of phosphorylase activation.

INDUCTION OF UDP-GLUCURONYL TRANSFERASE ACTIVITY IN GUNN RATS FOLLOWING GRAFTING OF NORMAL LIVER. Anil B. Mukherjee and Joseph Krasner (Intr. by Sumner J. Yaffe). Department of Pediatrics, State University of New York at Buffalo, Children's Hospital of Buffalo, New York.

Gunn rats serve as a unique experimental model for the study of hyperbilirubinemia. A mutant strain of Wistar rats, they are deficient in the enzyme bilirubin UDP-glucuronyl transferase. With normal Wistar rats as donors, approximately 5% of the liver was grafted to the homozygous Gunn rat liver using a uterine punch biopsy forceps. Punch biopsies removed from the recipient animals were replaced by identical sections removed from the livers of the donor rats. The Gunn rats were one to two months of age at the time of grafting. Assay of enzyme activity in punch biopsy specimens obtained from recipient Gunn rats at the time of grafting showed no transferase activity, whereas the donor rats possessed normal enzyme activity (mean value of 2.87 mumoles of bilirubin glucuronide/mg of microsomal protein/30' incubation). Nine to twelve weeks following the graft procedure (when the grafted cells were no longer identifiable histologically) the Gunn rats were sacrificed. Bilirubin UDP-glucuronyl transferase activity was found in the liver microsomes of all twelve recipient animals with activities ranging from 5% to 78% of values found in the normal Wistar rats. The appearance of enzyme activity following grafting may be due to the presence of an agent in the normal liver tissue which allows expression of gene activity by either induction or derepression. Direct genetic transformation could also explain these results.

Supported by USPHS Grant HD 04287 and DHEW Project No. 417.

DETECTION OF HUMAN LIVER GLUCOSE-6-PHOSPHATASE (G) IN SERUM BY IMMUNODIFFUSION. Platon J. Collipp, Shang Y. Chen, Vaddanahally T. Maddaiah, Raj K. Sharma, Iraj Rezvani, and Joseph Thomas. Nassau County Medical Center, East Meadow, New York.

An antiserum was prepared in guinea pigs against partially purified human liver microsomal G. Using double agar diffusion and immunoelectrophoresis, this antiserum was found to produce a single precipitin line with an antigen in normal human serum (in betaglobulins), liver and glycogen storage disease Type III patient's serum and liver. No precipitin reaction occurred with serum or liver from a patient with glycogen storage disease Type I (deficiency of G), which was confirmed by liver biopsy studies.

Enzyme activity*	GSD Type I	GSD Type III	Normal
Glucose-6-phosphatase	0.2	30	40 ± 5
Inorganic pyrophosphatase	0.6	30	40 ± 5
Glycogen	7.8%	8.5%	0 - 4%
Total Lipid	28%	25%	4 - 5%
Phosphorylase	5	30	20 ± 3
Amylo-1,6-glucosidase**	-	0	

*mumoles substrate/mg protein/min.
**courtesy of Dr. B. Brown, St. Louis.

This finding may offer a new method for immunodiagnosis of an inborn error of metabolism which has traditionally required liver biopsy and biochemical procedures.

GENETICS

Read by Title

HYPOCHONDROPLASIA: A RECENTLY APPRECIATED BONE DYSPLASIA ASSOCIATED WITH DWARFISM. Thomas Aceto, Jr., Ehsan Afshani, Margaret H. MacGillivray, Anke A. Ehrhardt, Drina F. Fornasiero and Jerald Kuhn. School of Medicine, State Univ. of New York at Buffalo, Children's Hospital, Departments of Pediatrics and Radiology, Buffalo.

We are reporting clinical, roentgenographic, psychologic and genetic characteristics of 11 patients with hypochondroplasia. Included are: 7 children, 4 adults; 10 caucasians, 1 negro; 6 males, 5 females; two mothers and their three children and 6 isolated cases. Height is -3 to -6 S.D.; weight: -1 to -3 S. D.; span minus height: +1.0 to -11.0 cm. different than expected; U/L: 0.02 to 0.11 greater than expected: head circumference -2 to +2 S.D. On roentgenograms, humeri, radii, femori and tibiae are below the 10th percentile for length (data of Maresh); and broad with flared metaphyses. In addition the deltoid tuberosity of humeri are prominent and distal femoral epiphysis, square shaped. Seven have narrow interpedicular distances in lumbar vertebrae, but only three have lumbar lordosis. Skull X-rays are normal. In the 8 patients tested, the Full Wechsler I.Q. is normal (99.3; S.E. of 2.8). However, the Perceptual factor (method of Cohen) is significantly lower (7.4 ± 0.50) than both the Verbal factor (10.6 ± 0.38) and the Numerical factor (10.8 ± 0.99). The weakness in perceptual functioning is confirmed by the results on the Benton Visual Retention Test.
Conclusions: Hypochondroplasia is a significantly common cause of dwarfism, characterized by symmetrical shortening of the limbs with broad long bones and metaphyseal flaring, slight obesity, relatively large head and often narrowing of the interpedicular distances in the lumbar vertebrae and excellent health. Full I.Q. is normal, but perceptual abilities appear to be impaired. Probably hypochondroplasia arises from a spontaneous mutation and is transmitted as an autosomal dominant.

IDENTIFICATION OF ABNORMALITIES OF CHROMOSOMAL CONSTITUTION BY GIEMSA BANDING. Felix A. Conte, Edith Passage, Donna Daentl, C.J. Epstein, M.M.Grumbach, Dept. Ped., Univ-Calif-San Francisco.

The introduction of quinacrine banding by Cassperson and, more recently, Giemsa banding by Sumner et al, has made possible the rapid and definitive identification of each pair of chromosomes in the normal human complement. We have utilized a slight modification of the Giemsa banding technique to identify and define complex structural chromosome rearrangements which previously had remained cryptic by standard staining techniques and autoradiographic analysis. A variety of patients with chromosome abnormalities involving all groups of chromosomes have been studied. Included in the 18 structural abnormalities detected were the following translocations: (1p-;5p+), (2q+;14q-), (13p+;18p-) and (14q15q). The first two translocations were apparently balanced and were found in mothers of infants who had multiple congenital anomalies and manifested the unbalanced karyotypes (5p+), (2q+), respectively. A (Yq-;7q+) translocation was identified by utilizing quinacrine fluorescence and Giemsa banding, in combination with autoradiographic identification of the translocated long arms of the Y chromosome. Structural abnormalities of the X chromosome, including Xp-, Xqi and Xpi were identified with the Giemsa technique, as were trisomies for chromosomes 13,18 and 21.

The Giemsa banding technique is rapid, inexpensive and more definitive than other recently described staining procedures for the evaluation of human chromosomes.

GENETIC ANALYSIS OF MINIMAL CHANGE NEPHROTIC SYNDROME. Patricia I. Bader, Carl W. Trygstad, John Grove, and Walter Nance. Indiana University Hospitals, Indianapolis, Departments of Pediatrics and Medical Genetics, (Introduced by Ira K. Brandt).

A genetic study of the nephrotic syndrome was conducted using family data from 71 probands who had clinically recognizable idiopathic nephrotic syndrome. Biopsy data was available in 38 cases. Included in this number were 1 pair of monozygotic twins concordant for nephrotic syndrome, 5 sibling pairs, 4 dizygotic discordant twins, 2 first cousins from a consanguinous family, 3 nephrotic patients with close relatives with renal disease, and 2 nephrotic patients from consanguinous families. The ratio of males to females was 9:5. There was no sex related difference in age of onset.

Families with multiple affected children were studied in detail with respect to pedigree information, physical examinations, screening laboratory tests, genotyping, dermatoglyphics, and PTC taster test. Linkage studies were done to test for linkage to ABO, Rh, MN, P_1, P, Kell, Hp, PTC. No conclusive evidence for close linkage to any of these polymorphic loci was found.

Maximum likelihood methods were employed to determine the proportion of high risk cases and the recurrence risk in the families. Appropriate allowance was made for the variable age of onset of the disease. Minimal change nephrotic syndrome does not appear to be a fully penetrant recessive trait, even with allowance for age of onset, but there is an increased risk of recurrence in sibships with an affected member.

THE RELATIONSHIP BETWEEN MONGOLOID BIRTHS AND MATERNAL EXPOSURE TO AUSTRALIA ANTIGEN. Dale E. Dietzman, David L. Madden, John L. Sever, Jerrold J. Lander, and Robert H. Purcell. NIH, Bethesda, Maryland.

Previous epidemiologic studies have shown peaks of births of mongoloid children occurring nine months after peaks of viral hepatitis. Other studies of the relationship of maternal exposure to viral hepatitis around the time of conception to the subsequent delivery of a mongoloid child have been in disagreement. These reports have not distinguished the type of maternal viral hepatitis, whether serum or infectious, and this may account for the discrepancies. In this study we obtained sera during the second trimester of pregnancy from 58 mothers who delivered mongoloid babies, and cord sera from 24 of the mongoloid babies. Similar specimens were obtained from 58 carefully matched control mothers and their normal babies. The sera were tested for Australia antigen (Au antigen), which is associated with serum hepatitis, by gel diffusion and complement-fixation techniques. Antibody to Australia antigen (Au antibody) was detected by the radioimmunoprecipitation test.

Au antigen was not detected in any of the sera of mothers of mongols or the matched control mothers, nor from any of the infants' cord sera. Au antibody was detected in 13.8% (8 of 58) of the sera samples of mothers who gave birth to mongoloid babies. It was detected in 25.8% (14 of 58) of the samples of the matched control mothers who had normal babies. From umbilical cord sera samples, Au antibody was detected in 12.5% (3 of 28) of the mongoloid babies and in 25.0% (7 of 28) of the normal babies. The presence of Au antibody in the cord sera of infants whose mothers had similar antibody indicated placental transfer of the antibody. No infant had Au antibody whose mother did not have such antibody.

This study indicates that maternal exposure to Au antigen at or prior to conception, as reflected by the presence of either Au antigen or Au antibody during pregnancy, is not associated with the subsequent birth of mongoloid babies. As there as yet are no direct tests for infectious hepatitis (IH), we have not excluded a relationship between maternal IH and mongoloid births.

XO/XY/XYY MOSAICISM. John M. Eckerd, C. Charlton Mabry, Abe R. Fosson and John D. Blair, Depts. of Pediatrics and Pathology, University of Kentucky, Lexington.

A newborn infant with ambiguous external genitalia presented the following urogenital findings: enlarged phallus with small chordee and incomplete foreskin, urogenital canal with vagina, and rudimentary uterus; posterior labial fusion permitted a 1 mm external opening ventral to the phallus. No gonads were palpable. No upper renal anomalies were present. 17-ketosteroid and pregnanetriol excretion were normal.

Buccal smear for X heterochromatin was negative. Blood cell karyotype showed XO/XY/XYY mosaicism (31%/5%/64%). Identity of the Y chromosomes was confirmed by quinacrine fluorescence.

Previous reports (5 cases) of XO/XY/XYY mosaicism have shown great variance in phenotype, none having had the same features as our case. Opinion as to proper sex of rearing differed among various specialists. Following our experience with four patients with XO/XY mosaicism who were similar to this patient, we assigned a female sex. This sex assignment was accepted by the parents. The plan of management for this type of chromosome disorder conforms to the general plan of female sex assignment with removal of testicular tissue and subsequent plastic surgery for instances where male genital reconstruction is not feasible.

DETECTION OF 45,X MOSAICISM. Lillian Y. F. Hsu, Josephine Kerr and Kurt Hirschhorn, Mt. Sinai Sch. of Med., Dept. of Ped., N. Y., N. Y.

45,X mosaicism without Y chromosome occurs in at least 1/3 of patients with Turner's syndrome and 45,X mosaicism with Y was found in nearly all patients with "mixed" gonadal dysgenesis. Since diversity of clinical features is known in mosaic individuals, it would be useful if one could use certain clues to select the possible mosaic individuals for cytogenetic studies. Although short stature and sexual infantilism are always used as clues for Turner's syndrome, the latter is useless in preadolescent girls. In 16 patients with 45,X Turner's mosaicism studied (7-XO/XX; 2-XO/XXq-; 2-XO/XXqi; 3-XO/XX/XXX; 1-XO/XXX and 1-XO/XXr), an increased total finger ridge count (TRC) was found in 71.4% (10/14) (TRC>175 in 9 and 157 in 1); short stature in 62.5% (10/16); deceleration of normal linear growth in 2 of 4 preadolescent girls; reduced frequency of Barr body (<20%) of buccal smears in 46.6% (7/15); cubitus valgus in 50% (7/14). In 11 postpubertal patients, 5 had primary amenorrhea, 3 had secondary amenorrhea and 3 had regular menses but repeated miscarriages. Thus, in Barr body positive females, the findings of a high TRC, short stature or deceleration of growth, cubitus valgus and reduced frequency of Barr body may be useful clues for detection of 45,X Turner mosaicism. In postpubertal females without sexual infantilism, attention should also be directed to secondary amenorrhea and repeated miscarriages. In 5 patients with 45,X mosaicism with Y chromosome (3-XO/XY/XYY; 1-XO/XY/XXY and 1-XO/XYY), in addition to abnormal sexual differentiation found in all, high TRC (>195) was found in 2 and *normal (105,151,152) in 3; short stature in 3 and tall stature in 2. Thus,in* patients with abnormal sexual differentiation, finding of a high TRC or short stature may be indicative of 45,X mosaicism.

TREATMENT OF GENETIC T-CELL DISORDERS WITH TRANSFER FACTOR. Armond S. Goldman, Elton Dupree, Randall M. Goldblum and C. Wayne Smith. Shriners Burns Institute and The University of Texas Medical Branch, Department of Pediatrics, Galveston, Texas.

Two girls with genetic defects in thymic-dependent lymphocytes (T-cells) were treated with transfer factor (TF) obtained from dialysates of blood leukocyte extracts. The donors were healthy adult males who displayed strongly positive delayed hypersensitivity (DHS) skin tests to C. albicans and streptokinase-streptodornase (SK-SD) and normal lymphocyte stimulation in vitro with mitogens or antigens.

Although lymphocyte stimulation was not improved after the addition of TF to the cultures, local transfer of DHS to Candida or SK-SD was achieved by a TF dose equivalent to 8×10^6 lymphocytes. Following TF doses of 8×10^7 to 8×10^8 lymphocytes, systemic DHS was induced and the infections subsided in each case. Using the same lot of TF, sensitivity was induced consistently to SK-SD but not to Candida in one case, while sensitivity to Candida but not to SK-SD was induced in the other. Also, TF-induced DHS was temporarily suppressed in one patient during a viral infection.

However, blood lymphocyte counts and in vitro lymphocyte stimulation did not increase and the duration of the TF-induced DHS was brief (4-8 weeks) as compared to normals (1-2 years). These observations suggest that short-lived lymphocytes were sensitized and that long-lived sensitized lymphocytes were not recruited. This is in keeping with our previous findings of a deficiency in T-cells in these individuals.

AN AUTOSOMAL RECESSIVE FORM OF CRANIOFACIAL DYSOSTOSIS (THE CROUZON SYNDROME). Richard C. Juberg and Sue R. Chambers (Intr. by Joseph A. Little) Dept. of Ped., Louisiana State Univ. Sch. of Med. in Shreveport, Shreveport, Louisiana.

Craniofacial dysostosis occurs sporadically and in families; the clearly heritable form heretofore has been autosomal dominant.

We ascertained 2 similarly affected siblings in a sibship of 9. The 10-year-old female had brachycephalus, exophthalmos, external strabismus, unilateral optic atrophy, parrot-beaked nose, maxillary hypoplasia with relative mandibular prognathism and a drooping lower lip; she also had premature closure of the cranial sutures and increased intracranial markings. The 8-year-old male was similarly affected except for less pronounced brachycephalus, normal nasal shape, normal mandibular and lower lip shape; however, he had widening of the pituitary fossa. Both had relatively prominent scaphocephalus.

Neither the negro parents, grandparents, great-grandparents, nor any collateral relatives were similarly affected. The 5 female and 2 male siblings were normal. The parents were not consanguineous. Analysis of 7 blood group systems provided no evidence for exclusion of the legal father.

We concluded that the reasonably typical findings of craniofacial dysostosis in these 2 siblings were probably genetically determined since we had no basis for incriminating environmental factors. Because recurrent mutation at the same locus is highly improbable, and since there is an affected female, autosomal recessive determination is most likely.

XYY GENOTYPE - ASSOCIATION WITH DEVIANCE. Ernest B. Hook. (Intr. by H. Strauss) Birth Defects Inst., N.Y.S. Dept. of Health and Dept. of Peds., Albany Med. Coll., Albany, New York

If settings for deviant individuals are distinguished as mental (for disturbed, retarded etc.), penal (for those requiring security placement), or mental-penal (combined) then the following conclusions emerge from a review of all known studies as of Dec. 31, 1971. 1). The mean and median of prevalence rates of XYYs in the 19 studies not restricted by height in mental-penal settings is 2%. 2). The rate is higher in mental-penal settings specifically for the retarded but to date not over 4%. 3). Rates in exclusively mental or penal settings in contrast are not consistently elevated over the maximum reported newborn rate (0.4%). 4). The prevalence rates of XYYs (and XXYs) in blacks in custody is significantly lower than that in whites, and in fact an association with increased rate of deviance has only been well documented in whites. 5). The few negative studies of mental-penal settings differ from positive studies in a) smaller sample size (on the average) and/or b) racial composition. 6). It is likely most adult XYYs in the population are not in settings for deviant individuals. 7). Neither a) large height, acne or other physical aspects of the phenotype, nor b) association with deleterious environment appears likely to explain the entire association with deviance. 8). Whatever the etiology of deviance it appears more likely to have a threshold than continuous nature. 9). The XXY genotype is also associated with deviance, but to a lesser degree.

SOCIOECONOMIC AND REPRODUCTIVE CHARACTERIZATION OF PARENTS OF PATIENTS WITH G_1-TRISOMY SYNDROME. Richard C. Juberg, C. Robert Goshen and F. Glenn Sholte (Intr. by Joseph A. Little) Dept. of Ped., Louisiana State Univ. Sch. of Med. in Shreveport, and Dept. of Ped., West Virginia Univ. Sch. of Med., Morgantown

This study tested our postulate of the existence of living patterns due to socioeconomic or educational similarities which might lead to the recognition of causative factors in meiotic nondisjunction.

Of 98 patients with G_1-trisomy from one referral hospital and one state institution in W. Va., we obtained data by questionnaire from 80 parents. The 80 couples reported a total of 361 pregnancies giving a mean of 4.5 per couple, though only 32% were presumably through childbearing. Their rate of fetal wastage was 7% leaving a mean of 4.1 livebirths per couple. We confirmed the diagnosis cytogenetically in 35.

The effects of maternal age and birth order were as predicted, and the sex ratio of neither the propositi nor their normal siblings was deviant. Neither maternal nor paternal age differed according to the sex of the propositi. No parents were consanguineous. Frequency of twin pregnancies was greater than expected. Compared with the median school years completed by all residents at about the time the parents were in school, the parents of the propositi had more education. By a similar comparison using the same census data, the parents' per capita income was somewhat less than that of the general population. The frequency of leukemia in the three previous ancestral generations, 3/1120, was not greater than expected; history of malignancy was similar among maternal and paternal ancestors.

We calculated intervals between livebirths determining that 4.18 years preceded the propositi compared with 2.83 years for the normal siblings ($p < .005$); for terminal births the interval preceding the propositi was 5.27 years compared with 2.58 years for the normals ($p < .005$), but for non-terminal births there were no differences.

We concluded that the increased interval before the birth of the propositi may indicate involuntarily delayed fertilization, the cause possibly related to the production of non-haploid gametes.

HETEROZYGOTE DETECTION FOR TAY-SACHS DISEASE (TSD) IN A SAMPLE AMERICAN-JEWISH POPULATION. M.M. Kaback and R.S. Zeiger, J.F.Kennedy Inst., Baltimore, Maryland

Serum hexosaminidase A (Hex A) levels are reduced in obligate carriers of the recessive TSD gene (O'Brien et al, NEJM 283:15, 1970). In order to extend this differential heat inactivation method to mass screening, several modifications were necessary to achieve optimal reaction conditions and for the development of an automated assay method (up to 280 people now can be screened per day). In addition leukocyte (wbc) Hex A studies have provided an accurate and essential "backup system" for use where serum assay does not permit genotype designation: in pregnant females, in individuals whose serum test is in the "inconclusive range" (arbitrarily defined to avoid false negatives), in some females on contraceptive medication, and in couples whose serum analyses indicate risk or possible risk for TSD in their offspring.

After precise statistical data on total Hex and Hex A were developed from sera and wbc from over 40 obligate heterozygotes and a substantial sample of "controls", a pilot program for TSD-heterozygote screening was initiated in the Jewish communities of Baltimore and Washington. In the initial phase, 4550 individuals were screened. Three groups, noncarriers (NC), carriers (C), and inconclusives (INC) were defined by serum screening. INC were retested by wbc Hex A analysis.

	NC	INC	C	TOTAL
Initial results	4140	243	167	4550
Retested inc. (175/243)	138	3	34	175
Final results	4278	3 (68)	201	4550

The measured heterozygote frequency, 0.0448, is substantially higher than that calculated from incidence figures for TSD derived from death records (a method with potential ascertainment error). Screening of appropriate relatives suggests that testing inaccuracy is not significant, although a small number (5) of false positive carriers (by serum only) have occurred. Sample bias or other "skew factors" in this "voluntary" population might account for the apparent high rate of TSD-heterozygosity.

THE ASSOCIATION OF BILATERAL AND UNILATERAL RENAL AGENESIS IN THE SAME FAMILY, Gertrude Kohn and Patricia Borns, Children's Hosp. of Philadelphia, Depts. of Genetics and Radiology

A family came to our attention because of the occurrence of bilateral renal agenesis in second degree cousins. The father of one infant was known to have unilateral renal agenesis. X-ray studies of additional family members have thus far revealed unilateral renal agenesis in this father's sister. Studies of other family members are planned.

It is generally believed that unilateral and bilateral renal agenesis are unassociated, and the reported familial occurrence of either anomaly is rare. Bilateral renal agenesis is common in infants who are stillborn or who die in the neonatal period; unilateral renal agenesis, an asymptomatic anomaly, occurs in 0.1% of autopsies.

The family under study suggests that renal agenesis may not be a sporadic event. Multifactorial inheritance is the most compatible genetic hypothesis that can account for the observed occurrences of both unilateral and bilateral renal agenesis in the same family.

THE RENAL DISEASE OF THORACIC ASPHYXIANT DYSTROPHY. Mildred L. Kistenmacher, Hope H. Punnett, H. Jorge Baluarte, Lourdes Laraya-Cuasay, Bruce Elfenbein, Steven J. Phillips, Alan B. Gruskin, Depts. of Ped., Path., Anat.; Temple Univ. Med. Sch. and St. Christopher's Hosp. for Child., Phila., Pa.

The recently recognized association of renal disease with thoracic asphyxiant dystrophy (TAD) suggests that TAD represents more than one genetic entity. It is not yet clear whether all children surviving respiratory failure in infancy will ultimately develop renal failure. To establish the relationship of kidney disease to this chondrodystrophy we are studying 2 sibships with this syndrome. Three children (ages 16, 13, and 11 years) in one family have short-limb dwarfism, polydactyly, dystrophic nails, pigmentary changes in the retina, long narrow chest, recurrent respiratory infections, reduced renal function, and hypertension. The 16 year old girl is on chronic hemodialysis. Radiographic findings are compatible with TAD. In the 2nd family, the 2 affected children presented with the same clinical and radiographic picture but lacked polydactyly, dystrophic nails and short stature. The older child died at 4½ years with renal failure and severe hypertension; the younger, now 1½ years, already shows mild acidosis and elevated blood pressure. Renal biospy from the 13 year old in the 1st family and the 4½ year old in the 2nd revealed a similar picture: fibrotic glomeruli, interstitual fibrosis and round cell infiltration, and tubular dilation and atrophy. The renal pathology in the 1½ year old suggests early changes, with hyalinization of glomeruli (6/30). Lipid inclusions occurred in chondrocytes of both boys in the 1st family. Single huge (8μ) globules were present in 1, multiple droplets in the other. Further histochemical and fine structure study of the chondrocostal junction, kidney, and cultured fibroblasts, and ophthalmologic ERG are in progress to further delineate this disorder.
(Supported in part by NIH Grants AM 13656 and RR 75).

STUDIES OF LEUKOCYTE ENZYMES IN CHRONIC GRANULOMATOUS DISEASE. Craig B. Liden, Joann G. Bodenbender and Stella B. Kontras, Ohio State Univ. Coll. of Med., Dept. of Ped., Children's Hosp. Res. Fdn., Columbus.

Chronic granulomatous disease (CGD) has been found to show clinical and genetic heterogeneity. Although this X-linked disorder has been studied by various means such as NBT dye tests, bactericidal studies and leukocyte O_2 uptake, the basic biomedical abnormality has yet to be clearly elucidated. The activity of leukocyte glutathione peroxidase was found to be diminished in 2 female patients with CGD by Holmes who suggested that this might distinguish a recessive form of disease of female patients from that of male patients with the X-linked form. This study reports results of assays of glutathione peroxidase and glutathione reductase in leukocytes of controls and patients with CGD. Enzyme assays were done by a modification of the method of Holmes and are reported as nanomoles NADPH oxidized/min/mgm protein. Thirty-eight controls, 7 CGD patients and 18 family members were studied.

	CONTROL ENZYME DATA Glutathione Peroxidase	Glutathione Reductase
Adult F (11)	159 ± 58	68 ± 16
Adult M (12)	140 ± 48	67 ± 22
Children (15)	176 ± 82	63 ± 11
	PATIENTS (CGD) ENZYME DATA	
Male [X-linked] (4)	172 ± 11	83 ± 10
Male [Non X-linked] (2)	117.8	70.3
Female (1)	127.0	139.0

The leukocyte glutathione peroxidase was decreased in 2 males with a non X-linked form of disease, but in the affected female, glutathione reductase was increased. The mothers (carriers) of males with X-linked forms showed increased glutathione peroxidase, 220.4 ± 51. More studies are needed to determine if these enzyme assays can be used to differentiate the genetic modes of transmission of the phenotype of chronic granulomatous disease or to identify heterozygotes.

FAMILIAL PAROXYSMAL POLYSEROSITIS (FPP). A REPORT ON 120 CASES FROM LEBANON. A. K. Khachadurian and H. K. Armenian. American Univ. of Beirut and Northwestern Univ. Med. Sch., Children's Mem. Hosp., Chicago. (Intr. by W. H. Borges)

FPP (Familial Mediterranean Fever, periodic disease) affects primarily people of Mediterranean extraction. 120 cases were seen in Lebanon over a 2-year period and constitute the basis of this report. Diagnostic criteria included (1) a minimum of 4 attacks of unexplained peritonitis or pleuritis and fever sometimes accompanied by arthritis or erythema usually lasting 2-4 days (2) absence of symptoms between attacks. 72% were males. Symptoms started in infancy in 8%, before age 10 in 53%, and before age 20 in 82%. Average duration of symptoms was 16.8 years. Clinical manifestations included peritonitis in 97%, pleuritis in 78%, arthritis in 66%, erythema in 20% and lymphadenitis in 6%. Multiple manifestations were present in 89%. The most frequent symptom in a given patient was fever and abdominal pain. Armenians constituted 53% of the group, Moslem Arabs 34%, Christian Arabs 9%, while they constituted 8%, 45%, 45% of the total Lebanese population respectively. Genetic studies were consistent with an autosomal recessive type of inheritance with incomplete penetrance in females. Among 460 sibs 130 were affected for an expected number of 160; among 204 male sibs 92 were affected for 99 expected. Plasma fibrinogen was highest 48 hours after onset of attacks (515 mg/100 ml ± 119 S.D.) but overlapped with the control values (349 ± 72 $p < .001$). Incidence of amyloidosis was 8% in the total group. Rectal biopsies in 21 consecutive patients aged 40 or above or with duration of illness of more than 20 years were all negative for amyloidosis. Awareness among pediatricians of the existence of FPP will probably lead to increased diagnosis of this entity in the U.S. as experienced by the present authors.

LYSOSOMAL ENZYME VARIATIONS IN CULTURED NORMAL SKIN FIBROBLASTS, Aubrey Milunsky, Christine Spielvogel, Julian N. Kanfer, (Intr. by J.W. Littlefield). Harvard Med. Sch., Eunice K. Shriver Ctr., Mass. Gen. Hosp., Waltham and Boston, Mass.

Homozygous and heterozygous detection in certain lysosomal enzyme deficiency diseases is possible using leukocytes or cultured skin fibroblasts. Wide ranges of activity have been reported for many of the lysosomal enzymes. Multiple biological and biochemical variables in tissue culture may affect the accurate determination of enzyme activities. Concern about these variables prompted this study of the activities of five lysosomal enzymes in cultured fibroblasts derived from the same normal skin biopsy sample grown in quintuplet. The original explant was diced into approximately equal fragments, 4 being placed into each of 5 Falcon dishes and fed twice weekly for 3 weeks. From each of these 5 dishes, and with equal cell innocula, pellets were obtained at each of 3 subcultures for a total of 15 cell pellets. All samples were handled identically including cell harvesting, counting, frequency of feeding, same media, washing and freezing to await assay. The conditions used for the enzymatic assays have previously been determined to be optimal for this laboratory. 4-methylumbelliferyl glycosides or esters were employed as substrates. A wide range of enzyme activities (expressed as mμ moles/mg protein)was observed. β-galactosidase activity ranged from 86-330, β-hexosaminidase from 1828-3132, β-glucosidase from 8-30, β-glucuronidase from 85-210 and arylsulfatase A ranged from 8-42. The total protein content for each of the 15 pellets ranged from 5.6-10.6 milligrams. The 60-500% variation in enzyme activities found in cultured cells obtained from the same skin biopsy cannot satisfactorily be explained. Heterogeneity in cultured fibroblasts from the same biopsy cannot be excluded. These observations introduce a further note of caution into the interpretation of lysosomal enzyme activities in cultured skin fibroblasts used for homozygous and heterozygous detection.

PROPERTIES OF AMNIOTIC FLUID HEXOSAMINIDASES

Jerome V. Murphy (Introduced by F. J. Samaha) Dept. of Neurology, Children's Hospital of Pittsburgh.

Since 1970 Tay-Sachs disease has been prenatally diagnosed by demonstrating the absence of hexosaminidase A in amniotic fluid and cultured and uncultured amniotic fluid cells. In order to use amniotic fluid hexosaminidase diagnostically, it must be shown (1) that the enzyme of this fluid is the same enzyme whose absence is associated with Tay-Sachs disease and (2) that the enzyme is present in significant amounts in normal amniotic fluid.

Incubation of amniotic fluid at 50° C. shows a two step denaturation of hexosaminidase activity very similar to what is seen when serum is identically handled. Hexosaminidase A has a pH peak of 4.4 in a citrate phosphate buffer system, and a 5.2 peak in sodium acetate; this is true whether the source of the enzyme is amniotic fluid, serum or white blood cells. Polyacrylamide gel electrophoresis gave identical migration of hexosaminidases regardless of the source of the enzyme. In 105 normal amniotic fluids the hexosaminidase A was higher than that found in the amniotic fluid of fetuses afflicted with Tay-Sachs disease.

From this data it is evident that the determination of amniotic fluid hexosaminidase A is of value in the prenatal diagnosis of Tay-Sachs disease.

FAMILIAL LEUKOCYTE GLUTATHIONE PEROXIDASE DEFICIENCY: A NEW MOLECULAR DISORDER OF NEUTROPHIL FUNCTION. William D. Rutenberg, Mei C. Yang, E. Brian Doberstyn and Joseph A. Bellanti. Georgetown Univ. Sch. of Med., Dept. of Ped., Washington, D.C.

An 11 year old white female with red hair and fair skin was evaluated because of recurrent skin and respiratory tract infections which began at 6 months of age. Tests of humoral and cell-mediated immunity were found to be normal and subsequent investigations were directed toward evaluation of leukocyte function. The patient's neutrophils had a normal chemotactic activity but revealed diminished quantitative NBT dye reduction and reduced bactericidal capacity; both parents, a maternal grandmother and 2 of 3 male siblings also revealed decreased NBT dye reduction and all family members except the mother and maternal grandmother had impaired bactericidal activity. Analysis of leukocyte enzymes revealed striking decreases in glutathione peroxidase activity throughout the entire kindred (11-43 mμmol/min/mg; normal = 83 mμmol/min/mg). An increased rate of decay of leukocyte glucose-6-phosphate dehydrogenase (G-6-PD) activity was detected in the patient and the 2 male siblings with decreased NBT dye reduction. Moreover, a diminished leukocyte glutathione reductase activity was found in both parents and the 2 affected male siblings, but not in the patient. The pathogenetic defect underlying this form of neutrophil dysfunction appears to be a primary deficiency of leukocyte glutathione peroxidase. These findings suggest an autosomal recessive mode of inheritance and provide further evidence for the heterogeneity of enzymatic defects of the leukocyte which underly the clinical syndrome of chronic granulomatous disease (CGD).

ULTRASTRUCTURAL VARIABILITY IN THE CARTILAGE OF HURLER-HUNTER PATIENTS. Steven J. Phillips, Hope H. Punnett, Mildred L. Kistenmacher. Depts. of Ped. & Anat., Temple Univ. Sch. of Med., St. Christopher's Hosp. for Children, Phila., Pa.

Although Hurler (MPS I) and Hunter (MPS II) syndromes are distinguishable clinically, biochemically and genetically from other mucopolysaccharidoses, great variability may occur in the degree of intellectual impairment, physical and skeletal changes and cardiac involvement within each of these two diseases. Studies of the fine structure and histology of the costochondral junction give further evidence of variability within the two syndromes and fail to distinguish between them.

Rib biopsies from 4 patients, 2 with MPS I and 2 with MPS II, ranging in age from 5 months to 7 years, were examined. Chondrocytes of all 4 contained varying numbers of membrane bound cytoplasmic inclusions as described in MPS I by Rimoin et al (these Abstracts, p. 106, 1971). Cells at the junction in one MPS I patient (age 9 mos.) were normal; inclusions occurred only in cells in the cartilage. This same patient also had dilated rough endoplasmic reticulum containing an amorphous material. This was not seen in any of the other children. The 7 yr. old MPS II patient had very few inclusions in the chondrocytes; the 5 mo. old's cells were filled.

Contrary to Rimoin's observation, abnormalities of matrix were seen in all 4 patients. Varying degrees of fibrous dysplasia, an increase in the density of proteoglycan granules and abnormalities of collagen occurred in all 4. Variability in columnation of chondrocytes was also observed, ranging from exaggerated columns, three times longer than age matched normal controls, to abbreviated, irregular columns or whorls of cells.

There does not appear to be any correlation between severity of symptoms or the age of the patient with the degree of ultrastructural changes observed. (Supported in part by NIH Grants AM 13656 and RR 75).

LSD AS A POSSIBLE MUTAGEN INSTEAD OF A TERATOGEN. Lawrence R. Shapiro and Josephine Kerr, The Mount Sinai Sch. of Med., Dept. of Ped., New York, N.Y. and Letchworth Village, Cytogenetics Lab., Thiells, N.Y. (Intr. by Kurt Hirschhorn)

In 1967, a case of fibular aplasia was reported in a newborn both of whose parents ingested LSD, and it was suggested that LSD might be a teratogen. In 1968, another child was reported with a malformation of one arm and both parents used LSD and smoked cannabis. Subsequent reviews and discussions have disputed the teratogenic or mutagenic effect of LSD.

Two infants have been studied with tibial aplasia and fibular aplasia or hypoplasia whose mothers have denied the use of LSD or other drugs but whose fathers used LSD prior to the time of conception. Chromosome analyses of both infants were normal.

These two additional cases with very similar limb deformities whose fathers used LSD prior to the time of conception would suggest that if LSD is responsible, it is as a mutagen and not a teratogen. The fact that familial tibial aplasia exists as an entity indicates that a gene exists, and the responsible mutation may possibly be induced by LSD.

BRACHYDACTYLY, TYPE E: SHORT DIGITS AND SHORT LIMBS, Vincent M. Riccardi and Lewis B. Holmes, Children's Service, Massachusetts Gen. Hosp., Boston (Introduction by J. W. Littlefield)

Brachydactyly, type E, as a distinct clinical entity is to be differentiated from other disorders with similar brachydactyly, such as pseudohypoparathyroidism and XO Turner's syndrome. We have studied 15 affected individuals in 2 families, spanning 3 and 4 generations. Our findings indicate that this disorder is inherited as an autosomal dominant and includes shortened metacarpals and metatarsals, and short terminal phalanx of the thumb and short-limb dwarfism.

In both families the most marked shortening was of metacarpals and metatarsals 4 and 5, and the distal phalanx of the thumb. In family I, short stature (<10%) was associated with arm-spans 3 to 8 cm. less than standing heights. X-ray grid measurements of the limbs quantitated this shortening. In family II all those studied had normal upper:lower segment ratios, and only 1 short stature (<3%).

In both families the affected individuals had characteristic dermatoglyphic findings which were distinct from those seen in pseudohypoparathyroidism and XO Turner's syndrome. Serum calcium, phosphorous and alkaline phosphatase were normal.

Thus, brachydactyly, type E is a specific autosomal dominant trait characterized by skeletal changes in the absence of either endocrine or chromosomal abnormalities. There has been only one previous report dealing with this entity.

GENETIC AND MORPHOLOGICAL STUDIES OF LONG-TERM LYMPHOCYTES IN CULTURE. Jack D. Singer, George F. Smith, Shanta Sachdeva, Jackson W. Chen, Parvin Justice, and David Y.Y. Hsia. Loyola University-Stritch School of Med., Department of Ped., Maywood, Illinois.

Heparinized blood was collected from a XXX female. Lymphocytes were separated and established in long-term culture.by techniques that will be discussed. In order to study the morphology of lymphocytes in long-term culture, the following procedures were carried out. The lymphocytes were centrifuged and the cell button was washed several times with phosphate buffered saline. Air dried preparations were stained by Giemsa (pH 7.7), Leishman, and Wright staining procedures.

There were a number of different cell types observed, namely small, intermediate, and large lymphocytes. The small lymphocytes constitute the major part of the population - 72%. These cells have a very high nucleus to cytoplasmic ratio. The nucleus is usually dark with condensed chromatin. The cytoplasm, which is confined to a narrow rim around the nucleus is moderately basophillic. The intermediate lymphocytes constitute 22% of the population. This cell has a mean nuclear diameter of 17.95 μ. These cells contain more cytoplasm than the small cells. In addition, their chromatin is less condensed and there is an increase in cytoplasmic granularity. The large lymphocytes - 6%, have a mean nuclear diameter of 30.95 μ. The cytoplasm in these cells is variable. The chromatin in the nucleus is loosely packed and there are large numbers of cytoplasmic granules.

Cytogenetic and biochemical studies were carried out in order to ascertain the genetic stability of these long-term lymphocytes in culture.

NIEMANN--PICK DISEASE TYPE D : MORPHOLOGICAL AND BIOCHEMICAL STUDIES. Matthew W. Spence, Wei H. Chou, and Anthony J. Lewis. Depts. of Paed. & Path., Dalhousie Univ., and The Nova Scotia Path. Inst., Halifax; and Yarmouth Regional Hosp., Yarmouth; Nova Scotia, Canada. (Intr. by Richard B. Goldbloom).

Information on the chemical pathology in type-D Niemann--Pick disease (NPD) is very sparse, and the morphologic changes have been (briefly) described in only one report (Crocker & Farber, Medicine, 37:1, 1958).

Tissues were studied histologically in three cases and were chemically analyzed in detail in one. The patients were of one kindred.

HISTOLOGY: Moderate numbers of foamy, vacuolated cells were seen in spleen, lymph node, bone marrow and lung. Enlarged, vacuolated neurones with eccentric nuclei were visible in the cerebrum and upper spinal cord, as well as in the ganglion cells of the intestinal myenteric plexus.

DETAILED CHEMICAL ANALYSIS: Spleen showed the greatest chemical changes, consisting of a twofold increase in cholesterol, neutral glycolipids, and total phospholipids, and a threefold increase in acidic glycolipids, due to an increase in all normal types of splenic gangliosides. The phospholipids included 26% sphingomyelin phosphorus (normal, 14.6%) and 10% lyso-bis-phosphatidic acid (LBPA) phosphorus (normal, 0.3%); sphingomyelin was of normal fatty-acid and long-chain-base composition. Liver showed major increases in cholesterol and LBPA and minor increases in neutral glycolipids; sphingomyelin was normal in amount. Despite the severe psychomotor retardation and the histologically detectable swollen neurones, brain showed few abnormalities -- a twofold increase in gray-matter neutral glycolipids and a trace of cholesterol esters in white matter. Gray matter sphingomyelin was not increased.

Although the morphological and chemical changes are much less severe than in classical NPD, they fit the same general outline of tissue lipid defects and correlate with the more protracted clinical course of this variant.

RUSSELL (R) DWARFISM AND CYSTIC FIBROSIS (CF) IN A TWIN. Lynn M. Taussig, Glenn D. Braunstein, Beverly White, and Richard Christiansen. (Intr. by Paul A. di Sant'Agnese), NIH, Bethesda, Md.

Detailed dermatoglyphic, chromosomal, endocrine, and craniofacial analyses were done on a 6 yr-old white male twin with nearly all the characteristics of the R variant (no asymmetry) of the Russell-Silver (R-S) dwarf who also has CF (elevated sweat electrolytes, pancreatic insufficiency, and chronic pulmonary disease). He has increased atd angles (75^{o} and 76^{o}), increased whorls on fingers and toes, increased total ridge count, and a unilateral simean crease. Increased digital whorl patterns and total ridge counts were also noted in the father and a male sibling; the latter also had a unilateral simean crease. The patient's twin sister, while having similar facial features, is otherwise normal and has normal dermatoglyphics. Karyotyping was normal and blood group analysis was unrevealing. Both parents gave a family history of short stature. Urinary and plasma gonadotropins measured on 5 consecutive days, growth hormone levels determined by arginine hydrochloride infusion and insulin-induced hypoglycemia, plasma cortisol levels, and tests of thyroid function were normal. There was no precocious puberty. Measurements of skull and facial bones revealed that the craniofacial dysostosis present in the R-S syndrome is due to a significantly shortened posterior cranial bone and uniform reduction in the dimensions of the maxilla and mandible with the mandible abnormally positioned forward. Five permanent teeth are congenitally absent. The concordance of the R-S syndrome in monozygotic twins (Rimoin, 1969), its nonconcordance in fraternal twins, and the finding of isolated stigmata of this syndrome in relatives of affected patients indicate that the R-S syndrome is probably transmitted as a dominant gene, most likely as a fresh mutation, but familial inheritance is also possible. The presence in this patient of neonatal edema, cubitus valgus, heart murmur, hypertelorism and several distinctive dermatoglyphic abnormalities again raises the question of the association of the R-S syndrome with the Turner-Noonan phenotype. The occurrence of the R-S syndrome and CF in the same patient may be coincidental.

EXTRA VERTEBRAE, ESOPHAGEAL ATRESIA, AND TRACHEO-ESOPHAGEAL FISTULAE. Roger E. Stevenson (Intr. by R. Rodney Howell). Univ. Texas Med. Sch. at Houston, Dept. Ped., Houston, Texas.

We have found extra vertebrae in 75% of infants with esophageal atresia and tracheo-esophageal fistulae. Forty-four infants in whom the type of tracheo-esophageal anomaly had been documented surgically and complete x-rays of the spine were available were included in the study. Five patients had only esophageal atresia, 36 had esophageal atresia with tracheo-esophageal fistulae, and 3 had tracheo-esophageal fistulae without esophageal atresia. In 33 of these 44 patients an excessive number of thoracic and/or lumbar vertebrae were found.

	Number of Patients	Number of Patients With Extra Vertebrae
Esophageal Atresia Alone	5	4
Esophageal Atresia With Tracheo-Esophageal Fistulae	36	26
Tracheo-Esophageal Fistulae Without Esophageal Atresia	3	3

The presence of these additional vertebrae indicates that an excessive number of somites developed during embryonic life. This lends support to the theory that tracheo-esophageal anomalies result from a growth disturbance during early embryonic life in which the tracheal anlage (ventral foregut) grows at an augmented rate which exceeds that of the esophageal anlage. It is proposed that both mesoderm and endoderm share in the tissue augmentation, ultimately resulting in vertebral hypersegmentation and tracheo-esophageal anomaly respectively. Since thoraco-lumbar somitization is complete prior to actual separation of the trachea from the foregut, the etiologic factor(s) must operate at an earlier time. This reason coupled with recent report of familial recurrences of tracheo-esophageal anomalies suggests genetic transmission. All types of these tracheo-esophageal anomalies studied could have a common pathogenetic mechanism.

CLINICAL AND GENETIC DATA
ON TWELVE NEW CASES OF
TYPE D NIEMANN-PICK DISEASE

BY JOHN A. TIBBLES & J. PHILLIP WELCH
INTRA. BY RICHARD B. GOLDBLOOM
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The Nova Scotian type of Niemann-Pick Disease (Type D)* has been reported previously in only eight patients, all tracing their ancestry to a Nova Scotian Acadian French deme. We have discovered twelve additional patients, and examined the five who were alive during the study.

Transient jaundice marked the first year of life in at least five patients, and intellectual development appeared normal until school age. The onset of long tract signs was followed by progressive mental retardation, and ultimately by seizures. Age at death ranged from eleven to fifteen years.

Clinical enlargement of the liver and spleen was variable. Macular degeneration was not a feature. Diagnosis was usually confirmed by bone marrow examination, though three were negative on the first occasion. Some adult carriers showed marrow histology indistinguishable from clinically affected children. Liver histology was diagnostic in all three children biopsied.

Family investigations revealed that all twelve of these new patients were members of the same large kindred, as were four of the eight patients reported previously. All affected members of this kindred can be traced to an Acadian who settled in this region in 1691. The mode of inheritance is consistent with an autosomal recessive disorder. A province-wide survey revealed no affected individuals unrelated to this kindred, suggesting that the condition probably resulted from a single initial mutation.

*CROCKER. A.C. J. NEUROCHEM. 7: 69. 1961

RUSSELL-SILVER SYNDROME: 8 CASES, ONE WITH XX/XY MOSAICISM. Rawatmal B. Surana, John D. Bailey, Margaret W. Thompson and Patrick E. Conen. The Hospital for Sick Children, and the University of Toronto, Toronto, Canada.

More than 50 cases of the Russell-Silver syndrome which combines features originally described by Russell, and by Silver and associates have been described.

We report clinical, cytogenetic and dermatoglyphic studies on 8 additional patients; 5 females and 3 males from newborn to 16 years of age. Birth weights ranged from 1170 to 2300 g. Body asymmetry (originally reported by Silver) was noted in 5 patients; 2 of these also had short upper extremities with impaired supination-pronation (originally reported by Russell). The 5 patients whose intelligence was tested had IQ's of 60, 60, 80, 95 and 117. Two of 3 patients tested had an abnormal IVP.

Chromosomal preparations were made from lymphocyte cultures in 7 cases and from fibroblast cultures also in 2 of these. Karyotypes of 5 patients were normal. One phenotypic male had an XX/XY complement; blood serum groups and red cell enzyme studies in this patient gave no evidence of two different red cell populations.

Dermatoglyphics of 6 patients (5 with asymmetry) were normal, with no unusual discrepancy in patterns and ridge counts between right and left sides, suggesting that the asymmetry developed after the eighth week of gestation. If this finding is confirmed in other cases, it might suggest a search for etiological factors operative after the first trimester.

A review of 13 reported cases with XX/XY mosaicism disclosed none with clinical features of Russell-Silver syndrome or with body asymmetry. Several types of chromosomal anomalies have been reported in individuals with body asymmetry but none had XX/XY mosaicism.

GROWTH AND BEHAVIORAL CHARACTERISTICS OF CHILDREN WITH XYY CHROMOSOMES: A LONGITUDINAL EVALUATION. Richard P. Toister and William W. Cleveland, Dept. of Peds., Univ. of Miami Sch. of Med., Miami, Florida.

Since the XYY karotype was first described in 1961, a great deal of attention has been focused on the behavioral characteristics of these affected males. The current study involved four patients, one (GJ) initially diagnosed at age 6 mos because of suspected mongolism, two at age 5 1/2 (WM) and 7 years (FW) because of the recognized association of radio-ulnar synostosis and abnormalities of sex chromosomes and one at age 3 1/2 (KE) because of delayed language development. Longitudinal evaluations of intelligence and growth as well as reports of behavior at home and in school were recorded over a period of 4-7 years. Intellectual scores ranged from borderline to average with some intra-subject variability on serial testing: CJ 80-92; FW-77; WM 67-96 and KE 70-94. Growth patterns were at the following percentiles: CJ,50th; FW,50th; WM,90th and KE,80th. A behavioral checklist demonstrated increased areas of impulsivity and agressiveness for three patients, while one was described as "shy" and "passive". Three of the four have had significant behavior problems at home and in school; one has been legally confined at age 11 to a correctional institution.

These data indicate that in the XYY genotype: 1) the anatomical phenotype including growth is variable, 2) IQ is generally below average and 3) very significant behavior disturbances are present in 3 of 4.

HEMATOLOGY

First Session

A SIMPLE MICRO-METHOD FOR THE SIMULTANEOUS DETERMINATION OF HEMOGLOBINOPATHY AND GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY. Lance Sieger and Myron Karon. Division of Hematology, Childrens Hospital of Los Angeles and Department of Pediatrics, University of Southern California School of Medicine.

Erythrocyte glucose-6-phosphate dehydrogenase (G-6PD) deficiency is as prevalent as sickle cell trait in certain segments of the population. It predisposes to a significant hemolytic anemia, and has been associated with neonatal jaundice and with chronic non-spherocytic hemolytic anemia. The association with S hemoglobin is of major clinical significance.

A rapid, simple, and inexpensive method to screen for the occurrence of G-6-PD deficiency concurrently with hemoglobin electrophoresis has been developed. This test utilizes commercially prepared agarose plates on which 1 microliter samples of 50% hemolysates of unwashed red cells sedimented from capillary blood are electrophoresed in pH 8.6 Barbital buffer. Fluorescent staining technique utilizing NADP and glucose-6-phosphate is used to develop the enzyme pattern after electrophoresis. The enzyme is seen as a fluorescent band. Hemoglobin bands can be read directly without staining. The entire method requires only one hour from the time of sample application.

Using the above screening procedure on fifty patients, we have been able to detect AA, AS, AC, and SC hemoglobins, and detect G-6-PD deficiencies as well as differentiate A and B variants of the enzyme. To date we have been unable to distinguish clearly heterozygote G-6-PD deficient persons from normals. This test offers several advantages over other commonly used screening procedures permitting differentiation between sickle cell anemia and trait and other abnormal hemoglobins. It offers quick detection of two common hematological abnormalities utilizing a single micro-sample, making the test especially useful for smaller pediatric patients from whom venous blood often is difficult to obtain.

INFECTION AND SPLENIC FUNCTION IN SICKLE CELL ANEMIA. Maria L. Falter, Margaret G. Robinson, Ok S. Kim and Suat Ch. Go. S.U.N.Y., Downstate Medical Center, Brooklyn, N.Y., Department of Pediatrics and Nuclear Medicine.

Children with sickle cell disease are very prone to infections. In the child of pre-school age overwhelming pneumococcal septicemia or meningitis is a frequent cause of death. When exposed to massive bacterial invasion, they are unable to cope with it, reacting like splenectomized individuals. The rapidly fatal course in some sicklers suggests a defect in primary body defenses related to decreased splenic function. In a group of 10 sicklers we performed splenic functional studies to determine their usefulness in selecting high risk patients. 9 splenectomized and 10 normal children served as controls. The phagocytic function of the spleen was tested by ^{99m}Tc uptake. As a second splenic function the release of factor VIII (AHG) after adrenaline infusion was measured. Splenic uptake of ^{99m}Tc was absent or decreased in the sicklers and normal in the control group. A significant difference in the ability to release AHG was found between the normal group and the sicklers and splenectomized patients. (see table). We reviewed the clinical courses of the sickle cell patients attempting to correlate the results of both tests to the number of severe infections in each patient. 3 children with absent ^{99m}Tc uptake and inability to raise AHG, had had frequent severe infections at a young age. Out of 6 children with decreased ^{99m}Tc uptake and either normal or absent rise in AHG, only one child developed severe infections. The results of this study seem to warrant further investigation as to the value of the 2 tests applied concurrently in the detection of high risk patients.

Percent rise of factor VIII after adrenalin infusion

Subjects	range %	mean %	p
Normal	45 to 365	191.8	
Sicklers	-90 to 172	34.8	.003
Splenectomized	-60 to 171	48.4	.006

(Supported by USPHS grant #RR-318-07 A-1)

THE EFFECT OF CYANATE ON THE SURVIVAL OF SICKLE RETICULOCYTES. Blanche P. Alter, Yuet W. Kan and David G. Nathan. Children's Hosp. Med. Ctr. and Harvard Med. Sch., Boston, Mass. 02115.

Cyanate prevents sickling in vitro, and apparently prolongs the survival of ^{51}Cr tagged sickle erythrocytes in vivo. This apparent prolongation of survival should be interpreted with caution because the effects of cyanate on ^{51}Cr binding to sickle and fetal hemoglobin containing RBC are unknown, and because comparison of the effect of CNO^- on RBC survival to control RBC survival must be performed sequentially. To avoid these difficulties, we have studied the survival of sickle reticulocytes utilizing radioactive amino acids which are incorporated into hemoglobin. Two informed adult patients with sickle cell disease were studied. In each study, two 50 ml samples of blood were incubated separately with ^{14}C and ^{3}H-leucine for two hours, after which 50 mM cyanate was added to 1 aliquot for an hour. The cells were then washed and reinfused. Frequent venous samples were obtained and the specific activities of ^{14}C and ^{3}H in the hemoglobin were followed. In both cases, the $T_{\frac{1}{2}}$ of the carbamylated cells was twice that of the control cells, but remained below normal. The control $T_{\frac{1}{2}}$ was 10 days, and the cyanate-treated $T_{\frac{1}{2}}$ 23 days. We conclude that cyanate does indeed prolong sickle reticulocyte survival. In addition this method provides a generally useful measurement of the influence of drugs bound to red cells on reticulocyte life span. The labels are incorporated into the hemoglobin molecule of the reticulocyte and, most important, simultaneous comparison of the survivals of the same cohort of drug-treated and control cells is achieved.

POTASSIUM THIOCYANATE (KCNS) AS AN INHIBITOR OF SICKLING OF ERYTHROCYTES. Robert L. Kaufman and Harold S. Zarkowsky (Intr. by William S. Sly). Washington Univ. Sch. Med., St. Louis Children's Hosp., Dept. of Ped., St. Louis.

Potassium cyanate (KCNO) has been shown to inhibit sickling of sickle cell erythrocytes in vitro (PNAS 68:1180, 1971) and to prolong the in vivo survival of such cells (PNAS 68:2791, 1971). Because KCNS was formerly used widely in man as a treatment for hypertension, its effects on sickling were studied.

Red blood cells from patients with known sickle cell disease were washed twice in phosphate buffered saline (PBS) and resuspended at a hematocrit of 25% in PBS alone, or PBS containing 50 mM KCNO or 50 mM KCNS. These mixtures were incubated for 60 min in air at 37°C and then deoxygenated with 95% nitrogen, 5% carbon dioxide for 20 min except for experiment 2 which was deoxygenated 10 min. Cells were fixed in 6% formalin in normal saline. Cells at risk were those sickled in PBS alone minus those irreversibly sickled (ISC). The results calculated for each of three patients are shown below. Experiments 3 and 4 involve the same patient at two different times but show similar degrees of protection by both agents in each experiment.

	% Sickled				% Protection	
	ISC	PBS	KCNS	KCNO	KCNS	KCNO
1.	9	80.7	59	52.2	31	40
2.	2.1	60.4	32.4	21.8	48	66
3.	13.7	79.8	69	60.8	16	29
4.	5	46	38	35	19	27

When KCNS was used for antihypertensive therapy in the range of 1-1.5 mM, it caused only infrequent side effects. Normal levels are 0.05 mM and rise to 0.10 mM with cigarette smoking or significant dietary intake of Manioc derivatives or certain other vegetables. KCNS joins KCNO as a potential treatment of sickle cell disease.

GLUTATHIONE INSTABILITY OF CYANATE TREATED RED BLOOD CELLS IN VITRO Bertil E. Glader, Linda Winn and Marcel E. Conrad (Intr. by David G. Nathan) Walter Reed Army Institute of Research, Washington, D.C.

Cyanate (CNO) is being considered as a possible therapeutic agent in the treatment of occlusive sickle cell disease. Preliminary reports have suggested that in vitro incubation of sickle erythrocytes with 50 mM CNO will enhance the survival of these cells in vivo. When red blood cells from normal adults were incubated with 10 or 50 mM CNO, there was a time and concentration dependent inhibition of glucose-6-phosphate dehydrogenase (G6PD). Corresponding to this enzyme inhibition, there was inhibition of the resting and stimulated (ascorbate and methylene blue) hexosemonophosphate shunt. Reduced glutathione (GSH) was also depressed after CNO incubation. This decrease in GSH could not be accounted for by an increase in oxidized glutathione (GSSG). Washing CNO treated cells and then reincubating for one hour allowed GSH levels to return to normal. This reversible reaction which occurred without an increase in GSSG suggested that S-carbamylation of GSH occurred with the formation of S-carbamylglutathione. In contrast to the changes in GSH after treatment with CNO, the inactivation of G6PD following CNO was not reversible, and this would be consistent with N-carbamylation of the enzyme. When CNO induced G6PD deficient red blood cells with regenerated normal levels of GSH were stressed with 20 mM ascorbate, their GSH was labile as compared to similarly treated controls. These studies indicate that CNO is capable of inducing a G6PD deficiency with an associated GSH instability in normal red blood cells. Whether or not these in vitro observations will limit the clinical usefulness of CNO remains to be assessed in vivo.

RED CELL OXYGEN (O_2) CONSUMPTION AND HYDROGEN PEROXIDE (H_2O_2) FORMATION. Fred Lipschutz, Bertram Lubin and Frank A. Oski. Univ. of Pennsylvania Sch. Med., Children's Hosp., Phila., Pa.

Red cells consume small quantities of O_2 under normal in vitro conditions. Factors regulating O_2 consumption and its metabolic consequences have been poorly defined. Red cell O_2 consumption was measured in the erythrocytes of adults, newborn infants and subjects with reticulocytosis. The red cells of the newborns (37.5 microliters/10^{10} cells/hour) and the patients with reticulocytosis (52 microliters) consumed significantly more O_2 than did the cells of the adults (13.6 microliters). When red cells were incubated with aminotriazole and N-ethylmaleimide and catalase inhibition was used as a measure of H_2O_2 formation it was found that H_2O_2 formation paralleled red cell O_2 consumption. Incubation of red cells in the presence of NADPH, adenosine diphosphate (ADP) and ferric chloride ($FeCl_3$) produced a 2 to 5 fold increase in O_2 consumption. This was not observed when the compounds were incubated with the cells individually. The combination of NADPH, ADP and $FeCl_3$ also produced a 37% increase in red cell Cl^4O_2 production, while NADPH alone produced a 2.1% and ADP-$FeCl_3$ produced a 5.8% increase. These findings suggest that the young red cells of the newborn may be susceptible to a auto-peroxidation because of their increased O_2 consumption and H_2O_2 formation at a time when their detoxifying mechanism for H_2O_2 is not fully developed (low glutathione peroxidase and catalase activity) and the natural antioxidant, Vitamin E, is present in low concentration. The stimulation of O_2 consumption by NADPH, ADP and $FeCl_3$ suggests the presence of a membrane oxidase, illustrates another mechanism of serum control of red cell metabolism and may explain why the administration of iron to Vitamin E deficient infants may initiate a hemolytic episode.

HEMOGLOBIN BARTS AND ALPHA THALASSEMIA IN THE NEGRO NEWBORN. Shlomo Friedman, Jean Atwater, and Elias Schwartz. (Intro. by Robert L. Brent), Jefferson Med. Col., Cardeza Fndn. and Dept. of Ped., Philadelphia, Pa.

The incidence of elevated levels of Hb Barts in Negro newborns has been reported as 2-7%, associated in some instances with unexplained familial microcytosis and hypochromia. We have studied capillary blood from 555 Negro newborns by starch gel electrophoresis. Hb Barts was visible in the patterns of 44.5% of the infants, moderate amounts being present in 3.2%, small amounts in 12.0% and trace amounts in 29.3%. Quantitation of Hb Barts by carboxymethyl (CM) Sephadex chromatography showed 2.0-9.3% Hb Barts in infants with moderate amounts, 1.1-1.7% in those with small amounts, and 0.2-0.9% in those with trace amounts. The latter did not differ from the values found in infants without visible Hb Barts.

Globin synthesis was studied in 9 of the 18 infants who had more than 2% Hb Barts at birth. Peripheral blood was incubated with ^{14}C-leucine, the α, β, and γ chains separated by chromatography on CM cellulose in 8M urea, and the $\alpha/(\beta+\gamma)$ ratios determined. In 7 infants studied by 4 days of age, $\alpha/(\beta+\gamma)$ ranged from 0.88 to 1.10 (mean = 0.97 ± 0.08 (1 S.D.)), indicating balanced globin synthesis. Repeat studies on 3 of these infants plus 2 others at 5-11 months of age showed α/β ratios from 0.65-0.81 (mean = 0.73), indicating deficient synthesis of α chains. These infants had microcytosis and hypochromia despite iron therapy. Studies of 3 of the mothers of this group showed ratios of 0.77-0.86, also indicating decreased α chain synthesis.

This study demonstrates for the first time that levels of Hb Barts above 2% in the newborn Negro infant are associated with biochemical evidence of decreased α chain synthesis later in infancy. The balanced globin synthesis in the affected newborn is unexplained, but may be related to the switchover from fetal to adult Hb production. Further studies of the Negro infants with 1.1-1.7% Hb Barts will indicate whether they have a milder form of α thalassemia similar to that found in other racial groups.

RED CELL δ-AMINOLEVULINIC ACID DEHYDRASE (ALAD) ACTIVITY AS AN INDEX OF BODY LEAD BURDEN. Phillip I. Nieburg, Barbara F. Oski, David Cornfeld, and Frank A. Oski. Children's Hospital, Phila., Penna.

Measurement of red cell ALAD activity has been found to be useful for the detection of lead poisoning. This enzyme is inhibited by lead and thus an inverse correlation between blood lead levels and red cell ALAD activity exists. During a survey of 420 children, a number of subjects were found to have blood lead and red cell ALAD values that were disparate. Nineteen patients were studied in detail in an attempt to resolve these disparities and further validate the red cell ALAD assay as a reflection of body lead burden. Studies included a blood count, blood lead determination, a test for urinary coproporphyrin, a skeletal survey, and a 24 hour urine assay for lead after the administration of EDTA, 25mg. per Kg., at 8 hour intervals for a period of one day. Red cell ALAD activity was found to be significantly correlated ($p < 0.001$) with both the urine lead concentration and the 24 hour total lead excretion. The blood lead level did not correlate significantly with either of these parameters. In children with positive x-rays, red cell ALAD activity was significantly less and urinary lead excretion significantly greater than in those with equivocal or normal x-rays. The mean blood level, however, was similar for all three groups. These studies demonstrate a precise correlation between red cell ALAD activity and body lead burden. In patients with discrepancies between blood lead and red cell ALAD values the red cell ALAD assay appears to be superior to the blood lead level for purposes of predicting the body lead burden.

EFFECT OF pH ON GLYCOLYSIS IN THE ERYTHROCYTES OF THE NEWBORN INFANT. Frank A. Oski and Susan F. Travis. Univ. of Pennsylvania Sch. Med., Children's Hosp. of Philadelphia, Philadelphia, Pa.

Previous studies have shown that the erythrocytes of the newborn infant consume less glucose than would be anticipated for their young mean cell age. The effect of pH on glycolysis was examined in an attempt to identify rate controlling factors. The red cells of adults, newborn infants, and subjects with reticulocytosis had maximal glycolytic rates at a pH of 8.2 to 8.3. The washed red cells of 14 adults, 14 newborn infants and 6 subjects with reticulocytosis were studied at pH 7.2, 7.4 and 8.2 in a glycine buffer containing phosphate, 4.5 mM, and the ratios of the glycolytic rates at 7.4/7.2, 8.2/7.4 and 8.2/7.2 were examined in conjunction with analysis of glycolytic intermediates. The red cells of the infants had significantly greater increments in glycolytic rate when the ratios of 8.2/7.4 and 8.2/7.2 were contrasted with those of adults, and at 8.2/7.4 with the subjects with reticulocytosis indicating that their cells had a far greater capacity for glycolysis than is normally exhibited at pH 7.4. In all cells, with an increase in pH, there was a fall in red cell levels of glucose-6-phosphate, fructose-6-phosphate, and ATP and an increase in the levels of the triose phosphates and 2,3-DPG indicating a relief of phosphofructokinase inhibition and the emergence of the glyceraldehyde-3-phosphate dehydrogenase or phosphoglycerate kinase (PGK) steps as rate limiting. The rise in 2,3-DPG in the newborns was not as great as that observed in the reticulocytosis group suggesting an NAD lack or increased flow through the PGK step because of low ATP levels. These studies underscore the fact that the red cells of the newborn differ in their metabolism of glucose from cells of the normal adult and are metabolically unlike young erythrocytes produced at any other period of life.

HEMATOLOGY

Second Session

A DEFICIENCY IN THE PHAGOCYTOSIS STIMULATING TETRAPEPTIDE TUFTSIN FOLLOWING SPLENECTOMY. Andreas Constantopoulos*, Victor A. Najjar and Thomas F. Necheles*. Tufts University School of Medicine, Division of Protein Chemistry, and the Department of Pediatrics, Boston Floating Hospital for Infants and Children, Boston, Massachusetts 02111

We reported earlier a deficiency of the tetrapeptide tuftsin (Thr-Lys-Pro-Arg) in three families with a history of repeated and severe infections. Its extreme severity is manifested in the first few years of life. The peptide isolated from these patients was not only inactive, but inhibited the biological activity of tuftsin and therefore is presumed to be abnormal. We now report the complete absence of tuftsin after interruption of splenic function. These include patients with splenectomy comprising eight cases of hereditary spherocytosis, three cases of β-thalassemia, and three cases of Hodgkin's disease. Splenectomy in two cases following rupture of the spleen, proved an exception. Normal levels were obtained, presumably due to the well-known implantation and growth of splenic tissue in the peritoneal cavity. Similar deficiency of tuftsin was encountered following infarction of the spleen in two cases of sickle cell anemia, and extensive splenic infiltration in six cases of myelogenous leukemia. Tuftsin acts in hormone-like quantities and is presumed to be synthesized in the spleen. It could well explain the frequency and severity of infections in young splenectomized patients. Supported by PHS Grant AI-09116

FREE ERYTHROCYTE PROTOPORPHYRIN CONCENTRATION: A PROMISING SCREENING TEST FOR LEAD POISONING. Sergio Piomelli and Bernard Davidow. Dept. of Ped., N.Y. Univ. Sch. of Med. and N.Y. City Food and Drug Laboratory, New York.

Lead poisoning is known to result in a striking increase in free erythrocyte porphyrins (FEP). A simple test has been devised to quantitate FEP from 20 micro liters of blood and its correlation with blood lead level has been investigated.

In a test tube 20 micro liters of blood are pipetted into 0.1 ml of saline. Then 2 ml of a mixture of Ethyl Acetate and Acetic Acid (4:1) and a trace of Celite are added. The tube is agitated for 10" on a Vortex mixer and quickly centrifuged. The supernatant is decanted and mixed again with 2 ml of HCl 1.5 N. The HCl phase is then read in a spectrofluorometer at an excitation wavelength of 405 mμ and emission wavelength of 615 mμ. The concentration of FEP is calculated by comparison with a standard of protoporphyrin IX. Alternatively, 20 micro liters of blood are pipetted on a piece of Whatman 3 MM paper and dried. Then, at time of analysis, 200 micro liters of H_2O are added to the cut paper and the specimen is tested as above. The results with either method duplicate well. The FEP concentration is expressed as μg/100 ml of RBCs, by relating to the hematocrit. FEP concentration remains stable for at least a week in the refrigerator.

In a preliminary survey FEP concentrations were measured by either method in 120 blood specimens with lead levels between 10 and 100 μg/100 ml. The concentration of FEP was linearly correlated to Pb concentration ($r = 0.6$; $p = <.001$). All of the 29 samples containing over 50 μg of Pb were clearly identified by their increased FEP content. The FEP were increased in 12/18 samples with 35 to 50 μg of Pb and in 4 out of 73 samples with less than 35 μg of Pb.

A larger scale survey is in progress, but on the basis of these preliminary results, the FEP concentration appears to be a sensitive index of lead intoxication and a very promising screening test.

Surface-associated Disorders of Human Neutrophil Function. PJ Edelson,DP Stites,HH Fudenberg. Dept of Medicine, UCSF, San Francisco, Calif. (spon.:M.M.Thaler) Neutrophil function was studied in three patients with chronic recurring infections. All showed a normal neutrophilia with infection. Chemotaxis was assayed in a Boyden chamber using an E.coli filtrate stimulus. Control cells gave a chemotactic index (CI)=80 wbc/5 hpf. Patient CI were: T.C.=9, M.K.=14, B.S.=18. Random migration in capillary tubes was grossly abnormal: M.K.(2mm), T.C.(0mm), B.S.(0mm), control(16mm). Adherence to a nylon fiber column was abnormal only for M.K.(64.3%adherence; control 97±2%). Reduction of nitro-blue tetrazolium by neutrophils was normal in M.K.,T.C. A Rebuck window in M.K. showed no cells at 8 hrs, and a neutrophil response at 24 hrs. M.K. and T.C. killed S.aureus normally, but showed abnormal killing of E.coli and S.marscesens. Defects were not correctible by normal serum,nor could patients' serum affect normal cells' responses. Immunoglobulins and opsonins were normal and all patients phagocytized yeast particles normally. These patients emphasize the variety of defects observable in neutrophil function, and are separable from those patients whose defects are serum dependent. These studies suggest that certain neutrophil defects may involve surface-associated events in the phagocytic process.

QUANTITATION OF BACTERICIDAL CAPACITY IN NORMAL AND ABNORMAL HUMAN NEUTROPHILS C. C. Clawson, John E. Repine and James G. White. Univ. of Minnesota, Dept. of Pediatrics, Minneapolis.

The in vitro tests of phagocytosis and bacterial killing now widely employed use a ratio of about one microbe to one neutrophil. Under these conditions the test is best suited to revealing a major qualitative defect such as probably exists in chronic granulomatous disease (CGD) of childhood. It is postulated that other neutrophil abnormalities may occur in which there is a quantitative deficiency of ingestion or of the granules or granular components essential for bacterial killing. An example of such conditions may be the Chediak-Higashi syndrome in which much of the granular material is confined to giant granules that do not take part in degranulation into phagosomes. A test system has been developed which stresses the ability of neutrophils to ingest and kill increasing multiples of bacteria. Several samples of washed neutrophils at 4 x 10^6 ml. are exposed to ratios of S. aureus ranging from 10 to 200 bacteria to one neutrophil. These mixtures are tumbled for 20 min. to allow contact and ingestion of the organisms. Incubation at 37° C is continued for another 40 minutes. The total number of bacteria surviving at 60 minutes is determined by lysis of the neutrophils with distilled water followed by quantitative plate culturing, and compared to the number in the initial inoculum. This test provides a quantitative evaluation of the mean bactericidal capacity per cell in a neutrophil population. Normal cells ingest and kill predictable numbers of bacteria per neutrophil depending on the bacterial concentration to which they are exposed. The test has been applied to a variety of clinical conditions in which quantitative defects of neutrophil function were suspected. These include the Chediak-Higashi anomali, diabetes mellitus, leukemias, CGD, and variants of CGD. Quantitative deficiencies in bacterial killing have been identified in the Chediak-Higashi syndrome and diabetes. Tests of neutrophils from CGD provide a new perspective of the cellular abnormality in this disease.

DEFICIENCY OF NATURALLY OCCURRING ANTICOAGULANTS IN NORMAL AND SICK INFANTS. Chularatana Mahasandana and William E. Hathaway. Univ. of Colorado Med. Ctr., Dept. of Ped., Denver, Colorado.

At least two physiologic anticoagulants (antithrombin III, AT-III and anti-activated factor X, anti-Xa) have been described in man. These substances are probably alpha 2-globulins and have been shown to inhibit specific steps in the coagulation process. Since evidence for hemorrhagic tendencies, hypercoagulability and disseminated intravascular coagulation (DIC) is frequently seen in sick newborns, it was considered important to measure the activity of these anticoagulants in the neonatal period. Defibrinated citrated plasma was used for the AT-III assay (modified from von Kaulla) and the anti-Xa assay after Biggs. Cord blood from 48 normal infants (45 term and 3 premature) and 20 infants from high risk pregnancies (toxemia, 3rd trimester bleeding, diabetes mellitus, premature labor) as well as venous blood from 5 infants with respiratory distress syndrome (RDS) were studied. AT-III and anti-Xa levels were significantly ($p = <.001$) decreased in the normal cord blood as compared to normal adult controls. Two of the 20 high risk infants (both small for gestational age) showed very low amounts of AT-III; the remainder of the high risk group were like the normal infants. None of these infants became seriously ill or died. The five premature infants who developed RDS during the first day of life also had severely decreased AT-III levels; clotting studies of three of these infants were compatible with DIC. In general the level of AT-III and anti-Xa tended to parallel each other in the same infant.

In conclusion, (1) antithrombin III and anti-activated X (as measured by coagulation techniques) are deficient in normal newborn infants; (2) the level of activity of AT-III and anti-Xa are similar in the same infant; and (3) sick infants with RDS and/or DIC have lower amounts of the anticoagulants than normal infants.

THE PROSPECTS FOR CURABILITY OF CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA (ALL). Joseph V. Simone, Rhomes J.A. Aur, H. Omar Hustu and Donald Pinkel. St. Jude Children's Research Hosp., Memphis.

For the past 10 years we have used multiple drug chemotherapy combined with "prophylactic" central nervous system radiotherapy in an attempt to establish a significant cure rate for childhood ALL. In the 1962–65 series 17% of patients have been leukemia-free for 7 years (JAMA *216*:648, 1971). In the 1967–68 study 55% of patients have been leukemia-free for 3½ years (Blood *37*:272, 1971). An important question now is whether one can anticipate permanent cure in these children. In an attempt to determine the answer we analyzed the records of all children with ALL admitted to studies at this hospital from 1962–1970 with regard to complete remission duration and relapse rate during 1) the 2–3 years of therapy and 2) the years following cessation of therapy.

During the 2–3 years of therapy, patients surviving in continuous complete remission decreased exponentially, *i.e.*, the log of patients in remission *vs.* time described a straight line. After completion of therapy, however, relapse rarely occurred. Thus, after 2–3 years of complete remission in the 1962–65 series, therapy was stopped in 7 patients and all remain in complete remission for an additional 3–5 years. In the 1967–68 study 20 patients were in continuous complete remission for 2½–3 years when therapy was stopped; all but one have been in complete remission for an additional 6–20 months. These results indicate that after 3 years of combination therapy with multiple drugs and "prophylactic" central nervous system irradiation, the number of patients in remission stabilizes and the chance of relapse is small. These data suggest 1) that the first 2–3 years of therapy are critical and may be sufficient in the management of ALL, and 2) that there is a good possibility of permanent cure in these patients. (Supported by NIH Grants CA-08480 and CA-07594, and by ALSAC.)

EFFECTS OF CATIONIC POLYPEPTIDES ON AFIBRINOGENEMIC AND THROMBASTHENIC PLATELETS. James G. White, Univ. of Minnesota Sch. of Med., Dept. of Ped., Minneapolis.

Cationic polypeptides (C.P.) cause immediate, irreversible aggregation of normal platelets. Adenosine diphosphate, calcium, energy metabolism of the cell, and alterations in discoid shape are not required for this action, and the agents are reported not to stimulate the platelet release reaction. (Jenkins et al: Blood, 37:395, 1971). The present study has examined the influence of polybrene (P.B.) and polylysine (P.L.) on normal (N), afibrinogenemic (A) and thrombasthenic (T) platelets with the techniques of electron microscopy (E.M.) and nephelometry. Unstirred samples of N,A, and T citrate platelet-rich plasma (C-PRP) were incubated at 37 C with either PB or PL at concentrations of 0.1, 0.5, and 1.0 mg/ml and fixed at 15, 30, and 60 minutes for E.M. C.P. were taken up by the platelets and transferred to intracellular organelles. Subsequently, the cells lost their discoid shape, developed pseudopods, underwent internal transformation, and discharged secretory organelles. Granules and dense bodies stabilized by C.P. remained relatively intact during extrusion. Aggregation did not occur. N, A, and T platelets responded identically. Addition of PB or PL to stirred samples of A C-PRP on the aggregometer produced slightly delayed, irreversible aggregation, suggesting that fibrinogen may accelerate the reaction but is not essential. PB and PL did not cause immediate aggregation of T platelets, but induced a shape change like that produced in samples of T platelets by collagen. Failure of C.P. to cause immediate aggregation of T platelets provides a new test for this disorder. Effects of C.P. on immediate aggregation cannot be due to neutralization of surface charge alone, since T platelets which fail to aggregate have the same net negative charge as N cells and respond to C.P. in the same manner as N cells during incubation.

ANTIGENIC DISPARITY BETWEEN LEUKEMIC LYMPHOBLASTS AND NORMAL LYMPHOCYTES IN IDENTICAL TWINS. Jaw J. Wang, Tin Han, and Lucius F. Sinks. Roswell Park Mem. Inst., Dept. of Ped., Buffalo, New York.

In vitro lymphocyte stimulation by autologous leukemic cells has recently been described, indicating that there is a histoincompatibility between these two types of cells. We now report mixed cell interaction between lymphocytes from the normal identical twin and leukemic lymphoblasts from the other twin with acute lymphoblastic leukemia (ALL).

A 26 month old white male, the first sib of identical twins was diagnosed as ALL in October 1969. Complete remission was induced by prednisone and vincristine. In November 1970, bone marrow examination showed complete replacement by lymphoblasts. The other identical twin was periodically examined and blood counts and bone marrow examination showed no evidence of leukemia. Studies for precise zygosity of the twins, including fingerprint analysis, blood grouping study and HL-A typing indicate that they are monozygotic twins.

Blastogenic response of lymphocytes was determined by measuring ^{3}H-thymidine incorporation in duplicate cultures containing equal number of reactive lymphocytes and irradiated syngeneic lymphocytes or leukemic lymphoblasts incubated for seven days. Both one-way mixed lymphocyte reactions between normal twin and the other twin with ALL in remission were nonreactive, confirming monozygosity of these twins. However, lymphocytes from the normal identical twin were unequivocally stimulated by irradiated leukemic lymphoblasts from the leukemic twin at the time of relapse of his disease while receiving Methotrexate (7-fold increase of ^{3}H-thymidine incorporation over the appropriate controls). This reaction indicates that there is an antigenic disparity between these two types of cells. It is possible that leukemic lymphoblasts may acquire new surface antigens or the surface antigens of lymphoid cells may alter during the process of leukomogenesis.

ABNORMAL PLATELET AGGREGATION AND THROMBOSIS - A FAMILIAL DISORDER Harold S. Margolis* and James J. Corrigan, Jr. Department of Pediatrics, University of Arizona Medical Center, Tucson, Arizona.

In vitro adenosine diphosphate (ADP) induced platelet aggregation by turbidimetric technique is presently in use to evaluate one parameter of platelet function, but it is not known whether increased in vitro platelet aggregation can be translated into a "thrombotic tendency" in vivo. ADP induced platelet aggregation can be inhibited in vitro by adenosine triphosphate (ATP) or by adenosine; the mechanism of this phenomenon being only theoretical. In this study an eight year old negro boy was evaluated because of recurrent thrombophlebitis without any known predisposing factors. A strong family history of thrombotic episodes was present on the maternal side, with the mother of the child requiring caval ligation for recurrent pulmonary emboli. Detailed studies including coagulation factor assays, anti-thrombin titer, anti-urokinase level, fibrinolytic studies, and a negative acid hemolysis test failed to provide an explanation for the thrombotic episodes. The bleeding times, platelet adhesiveness, clot retraction, prothrombin consumption and platelet factor 3 availability were normal. Citrated platelet rich plasma from both the child and his mother consistently exhibited 85–95% ADP (2.1×10^{-6}M), collagen, and thrombin (0.25U) induced platelet aggregation and no subsequent disaggregation (N=40–60%). Prior addition of ATP resulted in only 10–40% inhibition of aggregation with ADP. Normal platelets and two asymptomatic 90% aggregators exhibited 80% inhibition with ATP. Aspirin therapy in the mother resulted in normal aggregation studies. An incomplete ATP inhibitory mechanism is suggested from these results which may be due to a greater than normal platelet release of ADP, inadequate plasma metabolism of ADP, or actual inability of ATP to inhibit ADP induced aggregation.

HEMOSTATIC EFFICACY OF PLATELET TRANSFUSIONS - EFFECT OF STORAGE AND ASPIRIN. Marie J. Stuart, Scott Murphy, Milton H. Donaldson, Audrey E. Evans, Frank H. Gardner and Frank A. Oski. Univ. of Pennsylvania Sch. Med., Philadelphia, Pa. (Intr. by D. Cornfeld)

The demonstration that platelets (plts) circulate after transfusion does not guarantee that they will be hemostatically effective for the recipient. The efficacy of transfused plts was therefore evaluated in thrombocytopenic recipients by determining template bleeding times (BT's) at 1 and 3 hours post plt infusion. The recipients were all leukemics with plt cts less than 20,000/cu.mm. and BT's > 20 mins. If the plt ct was elevated above 50,000/cu.mm. by fresh plts, or plts stored at 22° C for 18 to 24 hrs, BT's were normalized to < 10 mins by 1 hr post-infusion using fresh plts (5 studies), or by 1 to 3 hrs post-infusion using stored plts (5 studies). If the plt ct was elevated to only 40,000 to 50,000/cu.mm. by stored plts the BT was normalized in 2/7 such studies. The efficacy of fresh plts obtained from donors given 600 mgm aspirin (ASA) 1, 12 and 36 hrs prior to donation was similarly evaluated. Plts for infusion were suspended in plt poor plasma from a donor not treated with ASA to avoid the infusion of free ASA or ASA bound to plasma protein. When ASA was taken 36 hrs prior to donation, donor plts were demonstrated to be as effective as fresh unaspirinized plts; ie, by normalizing BT's to < 10 mins by 1 hr post infusion. When ASA was taken 1 to 12 hrs prior to donation a shortening of BT to < 12 mins was observed by 3 hrs post infusion in 5/6 studies. It appears therefore that aspirinized plts are hemostatically effective to varying degrees in the recipient. Donors ingesting ASA 36 hrs or more prior to donation may be accepted as plt donors for the support of thrombocytopenic recipients. The situation among donors taking ASA in the 36 hours prior to donation requires further clarification.

TRANSFUSIONS OF ANTIGENICALLY COMPATIBLE PLATELETS FOR THERAPY AND DIAGNOSIS OF ISOIMMUNE NEONATAL THROMBOCYTOPENIA. L. Sue McIntosh, Richard T.O'Brien and Howard A. Pearson, Yale Univ. School of Medicine, Dept. of Pediatrics, New Haven Connecticut.

Isoimmune neonatal thrombocytopenia purpura is a not uncommon, often familial disease resulting from maternal-fetal incompatibility for specific platelet antigens. It is associated with significant mortality and morbidity. Despite the prognostic importance of establishing this diagnosis with certainty, it has usually been made only by clinical exclusion because the special techniques for measuring platelet antigens and antibodies are available in only a few centers. Therapy has been somewhat controversial although exchange transfusions and corticosteroids may be of some value. We wish to report the use of differential platelet survival studies as a diagnostic procedure for establishing the diagnosis of isoimmune neonatal thrombocytopenia and to suggest that transfusions of antigenically compatable platelets (usually maternal) constitute the most effective therapy for this disorder. A diagnosis of isoimmune neonatal purpura was suspected in three infants on clinical grounds (no organomegaly, normal maternal histories and platelet counts, normal bone marrows but with variable numbers of megakaryocytes). Random donor platelets had markedly shortened survival (12-36 hrs.) while compatible platelets obtained by plasmaphoresis survived for 5 - 7 days. Subsequent serologic studies revealed Pl^{A-1} incompatibility in one case and strong, but as yet unclassified maternal isoantibodies directed at the infants' and paternal platelets in the other two. One infant had neutropenia which was shown to be due to a concommitant and unrelated leukocyte antibody. The pattern of normal survival of maternal platelets but reduced survival of random donor platelets is characteristic of isoimmune disease. In contrast to this, in neonatal purpura secondary to maternal I.T.P. both maternal and donor platelets will have shortened survival. In thrombocytopenia secondary to megakaryocytic hypoplasia both types of platelets will have normal survival. In the thrombocytopenia of infection both types will have normal survival unless D.I.C. or hypersplenism is present.

HEMATOLOGY

Read by Title

SCREENING DEFECTIVE HEMOSTASIS IN SICK NEWBORNS
Arturo J. Aballi, Avelina Maralit, Hedda Acs, and Fernando Costales, Queens Hospital Center, Dept. of Pediatrics, Jamaica, New York.

In a three year period screening for hemostatic defects was carried out in 186 sick newborns, 87 of which had a fatal outcome. All had received vitamin K. Of the total 108 had RDS, 38 infection, 26 anoxia or massive aspiration, and 14 miscellaneous conditions. 144 weighed less than 2000 gms. Studies included prothrombin time (PT), partial thromboplastin time (PTT), plasma recalcification time (PRT), factor V, platelets, bleeding time (B.T.), euglobulin clot lysis (ECL) and Fi test in serum (Fi). Evaluation of results was based on previous findings in thriving neonates. In 76 cases more than one study was done. ECL was seldom abnormal and is excluded from further considerations. In 74 babies with moderately severe illness only a few had significant coagulation changes. The percentage of alterations in this group were as follows: PT 8, PTT 15, PRT 5, factor V 2, platelets 24, Fi 4, and B.T. 0. In 86 fatal cases and 26 severely ill infants, the coagulation defects were frequent as demonstrated by the following figures: PT 60%, PTT 72%, PRT 40%, factor V 50%, platelets 48%, Fi 44% and B.T. 37% abnormal tests. All differences between these two groups were highly significant and most of their p values were <.001. Changes were not detected early. Severely ill babies who recovered showed rapid improvement of coagulation tests. In those whose condition deteriorated greater alterations became evident. In 40 fatal cases where hemorrhage was found post mortem results of tests showed greater abnormalities than in 30 without hemorrhages. In the former group PT was altered in 80%, PTT in 79%, PRT in 51%, factor V in 68%, platelets in 61%, Fi in 49% and B.T. in 47%. In those without hemorrhages the proportion of abnormalities was as follows: PT 48%, PTT 65%, PRT 23%, factor V 24%, platelets 12%, Fi 37% and B.T. 20%. Differences for factor V and PT showed p values of <.002. It is concluded that defective hemostasis plays a definite role in the majority of hemorrhagic lesions observed in the newborn infants.

POSTNATAL FETAL (F) AND ADULT (A) HEMOGLOBIN (Hb) SYNTHESIS IN PRETERM NEWBORN INFANTS IN RELATION TO POSTCONCEPTIONAL AGE (PA) H. Ward, (Intr. by J.R. Ducharme) Univ. of Montreal, Hopital Ste-Justine. During intrauterine life the sequential appearance of F & A Hb is believed to be under genetic control. The percentage of F Hb being synthesized is high during early gestation and decreases with increasing gestational age (GA). The relative rates of F & A Hb being synthesized in relation to GA have been reported previously. The present study was carried out with two goals in mind, first to determine F & A Hb synthesis postnatally in preterm infants born after 27-32 weeks of GA and compare their postnatal Hb synthesis with that which occurs in utero and second to measure F & A Hb synthesis in the infants born at 27-32 weeks of GA at their PA corresponding to term and compare the results with that of the term babies studied at birth. Reticulocytes from neonates born at 27-32 weeks of gestation whose clinical assessment of GA correlated with the maternal history were incubated at 3-4 week intervals in an amino acid mixture containing ^{14}C leucine. The cells were washed, lysed and the hemolysate purified by passage through a Sephadex G-25 column. The purified Hb solution was subject to column chromatography on DEAE A-50 which provided a separation of A & F Hb fractions. Liquid scintillation counting of the A & F fractions was then carried out. In the infants born between 27-32 GA there was a slow transition towards A Hb synthesis during the first postnatal month. At a PA of 35-36 weeks F Hb synthesis was 80% (SD5%). Then as the PA of term approached there was a rapid transition towards A Hb synthesis. At a PA of 38-42 weeks the percentage of F Hb being synthesized was 51% (SD16%) compared to 62% (SD8%) in term newborn infants (P <.05). Since during extrauterine life F Hb is less effective than A Hb for transporting oxygen to the tissues, infants born at 32 weeks or less of GA maintain this disadvantage several months after birth.

THE PREVALENCE OF ANEMIA AMONG PRE-ADOLESCENT AND YOUNG ADOLESCENT URBAN BLACK AMERICANS. Kenneth Brown, Bertram Lubin, Robert Smith and Frank Oski. Univ. of Pa. Sch. Med., Children's Hosp., Phila.

Numerous surveys have provided information as to the prevalence of anemia in infants and young children but few studies have been performed among pre-adolescents and adolescents. A survey of 1806 black junior high school students was conducted. Studies included electronic determination of hemoglobin (Hb), hematocrit, red cell count and indices, a sickle cell prep and a G-6-PD screening test. The children with G-6-PD deficiency (12.9%) and sickle cell trait (8.3%) did not differ hematologically from the remainder of the group. Two definitions of anemia were employed. One was the guidelines of the National Nutrition Survey where anemia is defined as a Hb value of less than 11.5 gm% for females ages 12-15 yrs and for males of 12 yrs while the minimum Hb value for males 13-15 yrs is 13.0 gm%. By these criteria the incidence of anemia among males ranged from 13.1% at age 12 to 50.6% at age 13, and 18.4% at age 15. In females the incidence ranged from 11.4% at age 12 to 27.3% at age 15. The Pearson criteria for anemia was also employed which is similar for females but for males is defined as a Hb of less than 11.5 gm% at ages 12 and 13 and less than 12.0 gm% at ages 14 and 15. By these criteria the incidence among males was 9.8% at age 13, 18.8% at age 14 and 5.8% at age 15. In an attempt to determine if children with Hb values just below Pearson's limit of normality were truly abnormal, the red cell indices of these groups were compared with those in the high normal range. In every instance the MCH and MCV values of the children with the lower Hb values were significantly less and indicative of hypochromia and microcytosis. These studies indicate that iron deficiency anemia is a very common entity among black, urban, adolescents.

IMPAIRED ADP RELEASE FROM PLATELETS OF NORMAL TERM NEWBORNS. Donald G. Corby, Florence H. Shigeta, Thomas F. Zuck (Intr. by William E. Hathaway). Fitzsimons Gen. Hosp. and University of Colorado, Denver, Colorado.

Several reports indicate that platelets from normal newborns respond differently to epinephrine and collagen than do platelets from normal adults. It has been postulated that this defect is an expression of impaired ADP release. (Corby, DG and Shulman, I, J. Ped. 79:307, 1971.) The current studies were undertaken to test this postulate.

At delivery, blood from normal term newborns was drawn from an umbilical cord vein, and maternal blood from an antecubital vein. All mothers denied taking for 10 days prior to delivery drugs known to affect platelet function. Aggregation in response to epinephrine (5.5 uM) and collagen (1:1), release of ADP and ATP into the supernatant plasma following aggregation, and total ADP and ATP content following platelet lysis was measured in PRP ($3x10^6/mm^3$) of both sample populations. Aggregation of maternal platelets was normal, confirming the absence of membrane inhibitory drugs. By contrast, platelets of newborns showed marked impairment of aggregation to both agents. The ADP and ATP released into the maternal supernatant plasma during aggregation was normal. By contrast, in response to epinephrine, newborn platelets released about 20 times less ADP and ATP than their mothers. Similarly, in response to collagen, 4.5 times less was released by newborn platelets. The ADP and ATP content of lysed PRP did not differ significantly between the two sample populations.

These data are in accord with previous aggregation studies of platelets from normal newborns, and confirm the postulate that the functional defect is indeed impaired capability to release endogenous ADP. Although this impairment has not been related to neonatal hemorrhage by these studies, it would appear that to avoid intensification of the defect the use of drugs known to inhibit ADP release from platelets should be limited in the neonatal period and during labor to the extent practical.

SERIAL OBSERVATIONS ON MONOCYTE FUNCTION IN CONGENITAL NEUTROPENIA. Flossie Cohen, Carol O. Matlen, Chung W. Kim, Barbara G. Rowe, Mary F. Locniskar, and Wolf W. Zuelzer. Children's hosp. of Mich. and Wayne State Univ. Sch. of Med. Dept. of Pediatrics, Detroit, Michigan.

The course of congenital neutropenia may depend largely on differences in the behavior of monocytes. Recent reports concerning monocyte function are conflicting. Serial studies in a 2 year old W.M. without demonstrable PMNLs in the blood, permitted evaluation of an essentially pure monocyte population independent of possible effects of manipulative procedures for separation. The following observations were made:

1) Over a period of 9 months, the intracellular killing ability tested against a stock strain of S.Aureus and a strain obtained from one of the patient's abscesses, improved steadily, reaching that of normal PMNLs >85% "kill"in 90 minutes. Ratio of phagocytes to bacteria 5:1. NBT was normally reduced.

2) When Lysostaphin (99% killing efficiency) was added to the test system, the intracellular viable count was more than 10 times higher at any test period than that of PMNLs. This indicated a slower rate of intracellular kill, despite a comparable if not better phagocytic ability for the test organism.

3) Both phagocytosis and intracellular kill of S.Aureus by the patient's monocytes were retarded by normal serum. Suggesting that the patient's serum possessed a factor enhancing his monocyte function.

4) The patient's serum retarded phagocytosis and killing ability of normal PMNLs.

5) Patient's serum generated no chemotactic factor for normal PMNLs. Observations 4 and 5 suggest lack of factors for PMNL function or inhibitory substances.

6) Although at no time bands or PMNLs were seen in bone marrow or blood, serial skin windows revealed the greatly delayed appearence of mature PMNLs in small numbers.

JUVENILE RHEUMATOID ARTHRITIS: HYPOFERREMIA AND ANEMIA. Inta J. Ertel and Jack C. Bass (Intr. by W. A. Newton, Jr.), Ohio State Univ., Coll. of Med., Children's Hosp., Dept. of Ped., Columbus.

The anemia in rheumatoid arthritis has been observed to be hypochromic but one with a poor response to dietary iron supplements. The present study investigates the hypoferremia and anemia in 17 children with juvenile rheumatoid arthritis.

The disease activity was evaluated by the usual clinical and laboratory criteria. The children demonstrated a spectrum of rheumatoid activity varying from acute disease with systemic involvement to those of arthritis in remission. All patients had complete hematologic studies and in addition the use of the differential ferrioxamine test for measuring chelatable body iron was evaluated. All 17 patients had normal serum folic acid, B-12, haptoglobin levels and bone marrow morphology. All demonstrated trace to moderate amounts of stainable iron in the bone marrow. Eight children showed no anemia and these children all had mild disease activity or were in remission.

Three children were found to be anemic. All three of these children had active disease, low serum iron and reduced iron binding capacity. Their serum copper and ceruloplasmin levels were high. In addition, chelatable body iron was high in one of the three but was normal in the other two children.

The remaining six patients all showed evidence of active arthritis, yet they all had hemoglobins between 12.3 and 13.8 g %. Serum iron levels in this group of patients, however, ranged from 15 to 55 ug % and none of them had elevated iron binding capacities. Five children in this group had normal iron stores and one had markedly elevated chelatable body iron. Oral iron therapy had no effect on the serum iron of any of these children. This study demonstrates that hypoferremia is a common finding in juvenile rheumatoid arthritis whether associated with anemia or not. Further, hypoferremia can co-exist with adequate body stores and is unresponsive to iron therapy.

CLINICAL SIGNIFICANCE OF FIBRINOLYTIC SPLIT PRODUCTS IN SERUM. James J. Corrigan Jr. and Bobbie M. Bell* Dept. of Ped. Univ. of Ariz. Med. Ctr. Tucson, Arizona.

Activation of the fibrinolytic mechanism yields an enzyme, plasmin, which degrades fibrin into soluble fragments called fibrinolytic split products (FSPs). Since disseminated intravascular coagulation (DIC) is one mechanism by which FSPs are produced their presence in serum has been equated with this diagnosis. The purpose of this study was to measure FSPs in the serum of 220 children with a variety of disorders, with and without DIC, and 106 normals by simple radial immunodiffusion and the tanned human red cell hemagglutination inhibition assay (HAIA). Serum was obtained from blood clotted in a sterile glass tube containing epsilon aminocaproic acid. Platelet counts and assays of the plasma coagulation factors were also performed. Antisera to human fibrin was produced in rabbits, absorbed against pooled normal human serum and the same lot used for all determinations. The sera from normal children had no FSPs when measured by radial diffusion and 0 to 4 micrograms per milliliter detected by the more sensitive HAIA. FSPs were found in 29% of all sick children with the highest levels noted in DIC. FSPs were present in 14% of other inflammatory disease states and in 37% of the cases with heart disease all without other laboratory evidence for DIC. In addition, the results showed that when FSPs were present by the radial diffusion technique 98% had abnormal amounts by HAIA. Conversely, if FSPs were not detected by radial diffusion only 62% had normal amounts by HAIA, whereas 38% were elevated. The data indicate that the HAIA is a sensitive method for detecting FSPs in children. The data also suggest that with the more sensitive methods FSPs can be found in serum in pathologic states without overt DIC indicating that other laboratory studies are necessary to diagnose this event.

MULTIPLE PRIMARY CANCERS ASSOCIATED WITH RETICULUM CELL SARCOMA. Inta J. Ertel, Ala B. Hamoudi, Stella B. Kontras, William Clatworthy and W.A. Newton, Jr. Ohio State Univ., Col. of Med., Dept. of Ped., Children's Hosp., Columbus, Ohio.

A Caucasion girl developed multiple intestinal polyps at the age of 10 yrs, adenocarcinoma of the large bowel at age 12, hemangioma of the hand at age 14, mediastinal reticulum cell sarcoma at age 15, epidermoid carcinoma of the scalp at age 18, choroidal tumor of the eye at the age of 20, and pleomorphic glioma of the cerebrum at age 21. The patient had prior splenectomy for hereditary spherocytosis and tonsillo-adenoidectomy on two occasions because of recurrent otitis media. At the time of her death at the age of 21 she had had local recurrence of the adenocarcinoma of the large bowel, but no distant metastases of any of her other cancers. She always showed a moderate serum IgA deficiency, but her circulating lymphocytes were present in the usual numbers and showed normal responsiveness to phytohemagglutinin stimulation.

The patient's only sibling developed reticulum cell sarcoma (RCS) of the mediastineum at the age of 15 years. He had absent serum IgA. His RCS metastasized widely and he died 11 months after the onset of his neoplasm. The brother had no other primary tumors.

The development of multiple primary neoplasms at a young age suggests altered host defense mechanisms to cancer. The IgA deficiency may well have been the signal of a more extensive immune deficiency which permitted prompt and extensive metastases in the boy, but which in the girl allowed new neoplasms to develop.

If one were to postulate a single hereditary deficiency in both children; the striking differences in the courses of their disease suggest that the host mechanism which permits development of new primary neoplasms in one child may in another child lead to distant metastases of a single tumor.

INCREASED CALORIGENESIS AND RED CELL 2,3-DIPHOSPHOGLYCERATE(2,3-DPG). J. N. Desai and N. T. Shahidi, Univ. of Wis., Univ. Hosp., Dept. of Ped., Madison.

Increased erythrocyte 2,3-DPG has been observed in thyrotoxicosis and following administration of thyroid hormones. In vitro studies have revealed increased synthesis of 2,3-DPG following incubation of red cells with L-thyroxine(T4), triiodothyronine(T3), and a weak calorigenic congener, 3,5-diiodothyronine. It is, however, not clear whether the in vivo increase in 2,3-DPG is the result of this direct effect or due to increased oxygen demand caused by calorigenesis. To ascertain this, 4 hypothyroid Rhesus monkeys (^{131}I method) were placed on 0.05 mg/day of T4 and 3 similar hypothyroid primates were given identical doses of the congener, 3,5-diiodothyronine. Baseline weight, hematocrit, MCHC, red cell volume(RCV) and red cell 2,3-DPG were recorded in all primates before and during therapy. Despite marked deficiency in RCV as seen below, the baseline 2,3-DPG in these primates was not elevated suggesting decreased oxygen demand.

Rh monkeys(No.)	Hct mean ± SD	MCHC mean ± SD	2,3-DPG mean ± SD	RCV mean ± SD
Hypothyroid(7)	37.7 ± 4.2%	29.7 ± 1.7%	4167±574mμm/ccRBC	16.0 ± 3.0ml/kg
Normal(10)	39.0 ± 4.0%	33.0 ± 2.0%	4920±255 "	23.0 ± 2.0 "

All primates treated with T4 showed a slow but steady rise in 2,3-DPG and weight loss, whereas those receiving 3,5-diiodothyronine showed no significant change in 2,3-DPG or weight. The mean values after 5 weeks of therapy are as follows:

Group	Mean 2,3-DPG	% increase	Mean wt	% wt loss
T4	6356mμm/ccRBC	56.7%	5.55 kg	22%
diiodothyronine	4339 "	0%	8.38 kg	0.3%

The above data indicate that the increase in 2,3-DPG by thyroid hormones in vivo may be the result of increased oxygen demand caused by these hormones rather than their direct effect on the red cell.

BETA THALASSEMIA IN THE AMERICAN NEGRO. Shlomo Friedman, Robert W. Hamilton, and Elias Schwartz. Jefferson Med. Col., Cardeza Fndn. and Dept. of Ped., Philadelphia, Pennsylvania.

Homozygous β thalassemia is usually a much milder disease in the Negro than in Caucasians. The difference in severity is not related to differences in red cell morphology or levels of Hb F and Hb A_2 in homozygotes or heterozygotes of the two groups.

We have studied globin synthesis in 5 homozygotes and 21 heterozygotes from 6 Negro families in order to compare β chain production with that found in Caucasian β thalassemia. Peripheral blood was incubated with ^{14}C-leucine, the α and β chains were separated by urea CMC chromatography and the β/α ratios were calculated. The results in the homozygotes did not differ in the 2 groups (Negro β/α mean = 0.21, Caucasian = 0.24; no values above 0.25). There was a marked difference in heterozygotes of the 2 groups. The Negro patients had a mean β/α of 0.88 with a range from 0.52 to 1.41, while 10 Caucasians had a mean β/α of 0.57 with a range from 0.41 to 0.69. The ratio in 21 controls was 0.99 ± 0.05 (1 S.D.). Eleven of twenty-one Negro heterozygotes with high Hb A_2 and definite morphologic abnormalities had ratios in the normal range or above, while no Caucasian heterozygotes had similar unusual results. In one large Negro family with a δ chain variant it could be shown that the factor responsible for the unusual ratios was not linked to the δβ loci.

Studies in our laboratory and those previously reported indicate that the incidence of α thalassemia in the American Negro may range from 2-15%. The presence of α thalassemia may modify the clinical and biochemical expression of β thalassemia. The mild nature of β thalassemia in the Negro may thus be due to a high incidence of α thalassemia or to another undefined factor.

FREE ALPHA CHAIN POOL IN THE BONE MARROW. Frances M. Gill and Elias Schwartz. Jefferson Med. Col., Cardeza Fndn. and Dept. of Ped., Philadelphia, Pa.

A small pool of free α chains is present in human peripheral-blood red cells. We have studied bone marrow samples to determine the presence of such a pool in red cell precursors and its significance in hemoglobin synthesis. Bone marrow samples from 7 patients with thalassemia and 3 controls were incubated with ^{14}C-leucine. Globin chains were separated by chromatography on carboxymethyl cellulose (CMC) in 8M urea, and the β/α ratios were determined. An aliquot of fresh radioactive hemolysate from each marrow sample was also separated by chromatography on Sephadex G-100 into a hemoglobin tetramer peak and a dimer-monomer peak. The tubes comprising each peak were pooled, carrier hemoglobin added, and the α and β chains separated by CMC chromatography. The excess α chain radioactivity in the dimer-monomer peak was compared to the total radioactive α chain present in both peaks.

Total globin synthesis in the bone marrow was balanced in all patients studied (mean β/α = 1.02 ± 0.07 (1 S.D.)), as previously described in heterozygous β thalassemia. In the 3 control patients, the pool of free radioactive α chain averaged 5.8% of the total radioactive α chain. The mean pool size was larger in patients with disorders of β chain synthesis: 50.2% in 2 patients with high Hb A_2 β thalassemia, 16.5% in 4 patients with Hb S-β thalassemia, and 13.1% in 1 patient heterozygous for both β and α thalassemia.

Similar studies were performed on peripheral blood samples of 4 newborn infants. The total (γ+β)/α ratio in each infant was normal. In 2 controls the α chain pool averaged 6.1%, while 2 infants with α thalassemia trait had α chain pools of zero and 0.9%.

Despite balanced globin synthesis in bone marrow or peripheral blood samples of 14 patients, there was a marked variation in the size of the free α chain pool. In heterozygotes for β thalassemia the pool is much larger than normal, while in infants with α thalassemia there is a marked decrease in the size of the pool. These findings support that concept that free α chain may be involved in stimulating the compensatory synthesis of β chain which occurs in the bone marrow of patients with heterozygous β thalassemia.

ANEMIA AND ABNORMAL IRON METABOLISM IN LYMPHOID HYPERPLASIA. L. R. Hyman, N. T. Shahidi and L. Tyson, Univ. of Wis., Univ. Hosp., Depts. of Ped. and Nuclear Med., Madison.

The association of hyperplasia of lymphoid tissue and increased serum immunoglobulins with hypochromic microcytic anemia and hypoferremia has been reported on several occasions, but the pathogenesis of the anemia remains obscure. An 8 year old boy with marked tonsillar hypertrophy, marked splenomegaly, chronic microcytic hypochromic anemia (Hgb: 7.5gm%), hypoferremia (Serum Fe: 20 μg%), high iron binding capacity (450μg%), elevated serum IgG (1989mg%) and IgA (477mg%) globulins, and increased serum haptoglobin (223mg%) was studied. Long-term oral iron therapy was ineffective, and parenteral iron dextran produced a transient rise in hemoglobin. Extensive search for occult blood loss yielded negative results. Bone marrow smear contained no demonstrable iron. Ferrokinetics revealed a rapid iron clearance ($t_{\frac{1}{2}}$ = 16 min.) and rapid red cell ^{59}Fe incorporation (93% at 4 days). Liver and spleen scan using Tc-99m sulfur colloid showed no abnormality except for splenomegaly. Histological examination of tonsils, adenoids, mesenteric and small bowel lymph nodes, appendix and spleen showed diffuse lymphoid hyperplasia. Iron stain for hemosiderin in all tissues was negative. Total body ^{59}Fe studies using a Whole Body Counter were performed. The percent ^{59}Fe retention and organ distribution was followed in the patient over 5 months. During this period there was no significant body iron loss. The organ distribution revealed a gradual increase of radioiron in the hepato-splenic axis. Following splenectomy, there was no significant alteration of radioactivity of the hepato-splenic axis, suggesting that the liver was the primary site of radioiron accumulation. The above data suggest that the anemia in this patient was the result of a defect in iron re-utilization. The accumulation of ^{59}Fe in the liver suggests that this organ may be the major site of the defect in iron exchange in this patient.

EFFECTS OF CYANATE ON THE CLOTTING PROTEINS AND PLATELETS. Margaret W. Hilgartner, Denis R. Miller. New York Hospital-Cornell University Medical Center, Dept. of Pediatric Hematology, New York, N.Y.

Cyanate reacts with uncharged amino groups of various proteins in a specific irreversible carbamylation reaction. The preclinical evaluation of cyanate to treat sickle blood requires investigation of the immediate effect of the cyanate molecule on the clotting process and the further effect of carbamylation on the clotting proteins and platelet functions. Fresh normal platelet-poor plasma was incubated with NaNCO to give final concentrations of 1mM, 10mM and 100mM with comparable controls of NaCl in PBS. The screening tests PT, PTT and TT and assays for Factors I, II, V, VII, IX, X and XI were done at 0', 30' and 60' incubation. An immediate rise in the clotting times was seen in the PT and PTT over controls which progressed with time. The greatest changes occurred with highest concentration, with little or no change occurring with the 1mM additive. No immediate changes were seen in the TT. After 60' incubation with 100mM NaNCO prolongation of the TT to 40 sec. occurred, but no change with 1mM was noted. No changes were found immediately or with incubation in the levels of Factors I, II, V, VIII and XI. Changes were seen immediately in the levels of Factors IX (greatest degree with 100mM, minimal changes with 1mM NaNCO) and with time in both Factors IX and X. Platelet Factor 3 release, measured by the Kaolin clotting time, was grossly inhibited by KNCO at 100mM (clotting time doubled) but was not affected by lower concentrations. ADP aggregation was partially affected by 100mM KNCO. Epinephrine response was partially affected by 10mM KNCO and completely inhibited by 100mM KNCO. There appears to be an immediate effect of the cyanate molecule on coagulation and a dose-related effect of carbamylation on platelet function and the coagulation mechanism.

THE TRANSPLACENTAL PASSAGE OF FETAL LEUKOCYTES INTO THE MATERNAL BLOOD. Sanford Leikin and Jacqueline Whang-Peng, George Washington Univ. Sch. of Med., Children's Hosp., Washington, D.C., and Natl. Cancer Inst., Bethesda, Md.

During and after pregnancy lymphocytoxic and blocking antibodies against paternal transplantation antigens appear in the maternal blood. There is also evidence for some degree of maternal immunologic inertia against the transplantation antigens of the conceptus. The antigenic message prompting these maternal immunologic changes could be either cellular or subcellular. It is known that trophoblasts can be detected in the blood of pregnant females. To determine the possible contribution of fetal leukocytes to these immunologic processes, a search was made for male karyotypes in phytohemagglutinin-stimulated leukocyte cultures from the blood of pregnant and postpartum females. Sixty-five cultures obtained during pregnancy were examined. Thirty-four males were delivered. More than 0.5% male karyotypes were found in six cultures. In each instance a male infant was born. In eight cultures 0.5% male karyotypes were found. Six of these pregnancies resulted in a male infant. The incidence and percentage of male karyotypes was greatest in the cultures obtained during the first trimester.

In five of six mothers of a male infant male karyotypes were found when the blood was obtained immediately post partum although none of these mothers had male chromosomes in their prepartum blood, suggesting that transplacental hemorrhage at delivery may be an important mechanism for the passage of fetal leukocytes into the mother. In addition, we found that male karyotypes could be detected in maternal blood for at least 24 weeks post partum. Our results indicate that fetal leukocytes can traverse the placenta and enter the maternal circulation during pregnancy and delivery. The passage of these cells may be important in the immunologic phenomena of parity related to paternally derived transplantation antigens.

MACROPHAGE INHIBITORY FACTOR: John C. Houck and Catherine M. Chang, Children's Hosp., Washington, D.C. and George Washington Univ., Washington, D.C., 20005.

One of the most important factors released from transforming lymphocytes is macrophage inhibitory factor (MIF). We have recently developed a very rapid and exceedingly sensitive assay for this factor. Peritoneal exudates are prepared in rabbits by IP injection of glycogen in the usual fashion. These cellular exudates were then diluted and placed in Leighton tubes. After 1 hr. the tubes were rinsed with Medium 199 and only the macrophages remained adhered to the glass. After 18 hrs. at 37°C in Medium 199 containing 20% calf serum the macrophages have distributed themselves evenly over the botton of the Leighton tubes. At this time, one or two "troughs" are created in the macrophage monolayer by scraping with a small spatula. The cells are again rinsed with medium and at 4 hrs. the number of macrophages which have crawled into these "holes" are counted using a ruled eye-piece. By 24 hrs. the defect in the macrophage monolayer is essentially repaired.

Human lymphocytes in culture were transformed by exposure to phytohemagglutinin (PHA) and the supernatant medium added at various dilutions to this macrophage system. It was notable that as little as .02ml of the supernatant from transformed cultures would inhibit approximately 50% of the migration of macrophages after 4 hrs. into the scraped hole. Further, isotonic saline extracts of spleen and thymus from calf indicated that a significant amount of MIF activity could be demonstrated only in the thymus of these animals. The thymus of immature guinea pigs contained no MIF activity until these animals had been immunologically sensitized, however. The properties of this MIF activity are: 1) it is thermostable; 2) it is destroyed by incubation with chymotrypsin; 3) it is non-dialyzable and 4) it is inactivated by exposure to neuraminidase. These four properties of MIF have been described by David et al to be characteristic of MIF.

This method is at least 50 fold more sensitive than the existing technique and requires only 4 hrs incubation.

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CONGENITAL NEUTROPENIA: A DEFECT IN STEM CELL MATURATION. Pierre L'Esperance, Richard Brunning, Byung H. Park, W. Douglas Biggar and Robert A. Good. Depts. Path., Pediatrics & Lab. Med., Univ. of Minnesota, Minneapolis, Minn. 55455.

Congenital neutropenia is characterized by severe and persistent neutropenia, recurrent infections, and often fatal septicemia. The pathogenesis of this disease is unknown. We have studied two infants with a severe form of congenital neutropenia manifesting within three days of life. The peripheral blood count showed no neutrophils, increased eosinophils and monocytes. Lymphocyte and platelet counts were normal. Repeated bone marrow examinations revealed a marked depletion of neutrophil precursors with the promyelocyte being the most mature cell noted. The Rebuck skin window test showed no neutrophil migration. Epinephrine and steroid stimulation failed to mobilize any neutrophils into the circulation. In in vitro culture using soft agar for colony formation, their bone marrow cells failed to show any maturation of neutrophil precursors while eosinophils and macrophages developed normally in the presence of normal plasma as well as autologous plasma. Furthermore, their plasma was found to support normal growth and maturation of control human bone marrow cells. The colony stimulating activity of their urine was normal when tested with mouse bone marrow cells in culture. The monocytes of these patients seemed to play an important compensatory role in phagocytosis since an increased reduction of nitroblue tetrazolium dye by those cells correlated well with episodes of bacterial infection. In addition, these monocytes ingested and killed staphylococcus 502A normally in vitro. These data suggest that the basic disorder of this form of congenital neutropenia resides in a primary defect of the neutrophil stem cell maturation. However, a deficiency of the microchemical environment cannot be excluded.

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IMMUNOTHERAPY OF ACUTE LYMPHATIC LEUKEMIA (ALL) by Brigid G. Leventhal, Roger H. Halterman and Ronald B. Herberman, NCI, NIH, Bethesda, Md.

Patients with previously treated ALL in relapse were given asparaginase 15,000 IU/m^2/day for 28 days either alone or in combination with 5 day courses of actinomycin D, 0.4 mg/m^2/day. Complete remission was achieved in 5/8 on asparaginase alone and 7/7 on the combination. At remission patients were randomized to therapy with 1. Pasteur Institute BCG, 75 mg freeze dried weekly for 4 weeks by scarification plus cell inoculation or 2. monthly courses of methotrexate (MTX) 15 mg/m^2 for 5 days followed in 10 days by cell inoculations every other day x 4. Cell inoculations were intradermal with $4x10^7$ leukemia cells from a single allogeneic donor. The 5 patients on BCG had remissions of 53+,58+,79,108+ and 189+ days while the 5 on MTX had remissions of 7+,63, 64,126 and 134+ days. Median remission on a previous asparaginase protocol was 64 days. The skin reactions of these patients were tested to PPD, SKSD, mumps, candidin and leukemic blast cell membranes. All patients had at least 1 positive skin test before therapy but all were tuberculin negative; 2/5 patients on BCG and 1/5 on MTX have not had repeat skin tests; 3/3 on BCG and 1/4 on MTX developed positive skin reactions to tuberculin; 1/3 on BCG and 1/4 on MTX developed positive skin tests to immunizing blast cell preparations. Two on each regimen converted to positive with candida. Blast transformation in vitro was measured to PPD, SLO, smallpox, candida, PHA and allogeneic cells; 3/3 BCG patients showed a 6-10 fold increase in reactivity to PPD; 2/5 showed an increase in reactivity to immunizing blast cells of 8 and 30 fold. There was no effect on the response to PHA or other antigens. The patients on MTX showed an initial depression of in vitro response immediately after MTX with a rebound at 9-17 days to 6-22 times baseline in response to candidin, and 1-10 to SLO and PPD. The response to immunizing blast cells went up in 3/4 to 3,3, and 31 times baseline. There was no significant change in the PHA response. We conclude that BCG did not show a general adjuvant effect although it did produce specific immunity to tuberculin. MTX augmented responses to all antigens. It may be that a judicious combination of chemotherapy and adjuvants will give better immune responses to tumor than either modality alone.

CORRELATION OF FETAL HEMOGLOBIN (FH) DETERMINATIONS WITH THE CLINICAL SEVERITY OF SICKLE CELL ANEMIA (SSA). Thomas D. Miale, Lourdes Guerrero, and Gerald E. Bloom. Univ. of Fla. Sch. of Med., Dept. of Ped., Gainesville, Fla.

Previous studies have presented conflicting evidence concerning the correlation of fetal hemoglobin levels with the severity of symptoms in patients with sickle cell anemia. In order to determine whether FH levels may be a factor influencing severity, the quantity and distribution of FH in eighteen American Negro patients with SSA were evaluated. Quantitative FH values were obtained by alkali denaturation, corrected for methemoglobin formation. The distribution of FH among erythrocytes was determined by the acid elution staining technique.

Two patient groups were recognized: eleven mildly affected individuals, aged 3 to 23 years; and seven severely affected individuals, aged 4 to 12 years. Frequency and duration of crises, growth and development, and severity of anemia were the parameters utilized in patient selection. The mean and range of quantitative FH levels in the mildly affected group were 12.2% (3.1--19.3) as contrasted with 4.0% (1.4--5.8) in those who were severely affected. The distribution of FH patterns was heterogenous in all eighteen patients. These findings indicate that SSA patients with minimal symptoms have higher levels of FH than those with severe manifestations. FH levels may be of predictive value in appraising the clinical course of SSA patients.

THE ROLE OF HEMOGLOBIN OXYGEN IN THE HEMOLYSIS OF VITAMIN E DEFICIENT HUMAN ERYTHROCYTES. Bertram Lubin, Mitchell Fromm and Frank Oski. Univ. of Pennsylvania Sch. Med., Children's Hosp. of Philadelphia, Philadelphia, Pennsylvania

Although it is recognized that hydrogen peroxide is capable of generating free radicals that serve to initiate the sequence of lipid peroxidation in the hydrogen peroxide hemolysis test in vitamin E deficiency, the source of the molecular oxygen required to continue the reaction has been undefined. Hydrogen peroxide hemolysis tests employing red cells in the oxyhemoglobin (HbO_2) and carboxyhemoglobin (HbCO) state, were performed in 11 infants with vitamin E deficiency. Simultaneous measurements of lipid peroxides and specific changes in membrane fatty acids were performed. With HbO_2 cells hemolysis averaged 75.9%. In the HbCO cells hemolysis was significantly reduced averaging only 9.9%. Accompanying these changes were a reduction in lipid peroxidation. In the presence of HbCO, hydrogen peroxide did not produce any alteration in polyunsaturated fatty acids, while in its absence arachadonic (20:4) and docosahexaenoate (22:6) decreased 49 and 68% respectively. These studies demonstrate that the source of molecular oxygen required for the propogation of lipid peroxidation of long chain unsaturated fatty acids in the red cell membrane is derived from hemoglobin and not the atmosphere, and again illustrates that the hydrogen peroxide itself only initiates the reaction and is not exclusively responsible for the membrane damage.

CONGENITAL DYSERYTHROPOIETIC ANEMIA: REPORT OF 2 CASES. Sharon Murphy and Frank Oski. Univ. of Pennsylvania Sch. Med., Children's Hosp. of Philadelphia, Philadelphia, Pennsylvania

A new category of congenital anemias has recently been described which is characterized by erythroblastic multinuclearity, erythroid hyperplasia with ineffective erythropoiesis, unconjugated hyperbilirubinemia and characteristic serologic abnormalities. We wish to describe 2 patients who represent opposite poles on the spectrum of severity of this disorder. One has been severly anemic (Hb 5-7) and transfusion-dependent since birth and has a Thalassemic-like facies. The second patient is only mildly anemic (Hb 10-11) and otherwise healthy. Both patients have splenomegaly. Peripheral smears show aniso- and poikilocytosis, and bone marrow aspirates on both patients demonstrate marked erythroid hyperplasia with 50% normoblasts on differential count, 20% of which are multinuclear or multilobulated. The first patient has also been shown to have increased plasma iron disappearance (32 min), decreased iron reappearance (27% at Day 8), markedly increased (10X) fecal urobilinogen excretion, and decreased survival of autologous ^{51}Cr rbc's ($T_{\frac{1}{2}}$ 11 days). The second patient has numerous typical Gaucher cells on marrow aspirate, an acquired abnormality. Serologic abnormalities demonstrated include increased susceptibility to lysis by acidified sera and increased susceptibility to lysis and agglutination by anti-c and anti-I antisera. Previous reports have emphasized genetic factors, but the parents and siblings of our patients are normal. Underlying abnormalities of both the nucleus and/or the cell membrane are possible explanations for this uncommon congenital anemia; but at present, the pathophysiology of this dyserythropoietic state remains obscure. This syndrome should be considered in patients with Thalassemia-like red cell morphology, ineffective erythropoiesis and splenomegaly.

SUBCELLULAR DISTRIBUTION OF ^3H-BILIRUBIN IN HUMAN PLATELETS. Harold M. Maurer, Joyce Caul, and A. Hossaini. (Intr. by J. A. Wolff), Medical College of Virginia, Richmond, Virginia.

We have previously demonstrated that free indirect-reacting bilirubin influences platelet function in vitro. In its presence, human platelets stain yellow, aggregate and release adenine nucleotides. The subcellular distribution of ^3H-bilirubin in washed human platelets was studied. Platelet suspensions were incubated with ^3H-bilirubin and then washed to remove excess radioactivity. Platelets were disrupted by sonication and subcellular fractions separated by sucrose density gradient ultracentrifugation. The morphology of each particulate fraction was verified by electron microscopy. Approximately 19% of the original ^3H-bilirubin was incorporated into platelets. The major portions of radioactivity taken up were contained in the granule and mitochondrial fraction (46%), and the soluble (cytoplasmic) fraction (42%). Membranes played a minor role in the binding of ^3H-bilirubin (6%). Our studies indicate that bilirubin accumulates intracellularly in platelets, and binds to intracellular platelet structures. It may thus exert an influence on multiple cellular processes. One such effect may be the release of adenine nucleotides stored in α-granules.

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EFFECTIVE INTENSIVE COMBINATION TREATMENT OF METASTATIC CHILDHOOD TUMORS. Jorge A. Ortega, Georges Rivard and Myron Karon. Division of Hematology, Childrens Hospital of Los Angeles and University of Southern California School of Medicine, Los Angeles, California.

The goal of therapy in childhood malignancy is the complete eradication of tumor without serious morbidity to the host. Since agents which are active when used singly produce additive therapeutic effects when used in combination, the effect of intensive chemotherapy using three agents was investigated in children with malignant tumors. The intent was to deliver maximally tolerated treatment in as short an interval as possible. The results indicate that such an approach is feasible and effective. Twelve children with metastatic tumors (8 rhabdomyosarcoma; and 1 each of embryonal carcinoma, dysgerminoma, retinoblastoma and synovial sarcoma) were treated with courses of drugs in the following manner: dactinomycin 60Qug/M2/day I.V. days 1 through 4; cytoxan 300mg/M2 on days 1,4, and 7; and vincristine 1.5 mg/M2 I.V. on days 1 and 7. Courses were repeated every 3 to 4 weeks depending upon recovery of the bone marrow. All patients had inoperable primary and/or metastatic disease at the time chemotherapy was initiated. Following 4 to 6 courses of chemotherapy 4 of these patients underwent surgery that resulted in complete excision of the original lesion. All four are alive and free of disease at 10,13,24 and 34 months. Of the remaining 8 patients, 7 are clinically free of disease. One patient with rhabdomyosarcoma had progressive disease while receiving combination treatment. All 12 patients are alive with survival times which range between 2 and 34 months (median, 13 months).

12/12 patients developed alopecia. 9/12 patients nausea and vomiting which did not require drug interruption. 5 patients developed WBC less than 1500 cells/cu.mm, usually by day 10 but recovered by day 21.

Intensive combination therapy with dactinomycin, cytoxan and vincristine is effective treatment for a wide variety of metastatic childhood tumors. The use of such agents singly for children in such instances may no longer be justified. Additional improvements in the prognosis can be expected with the development of additional agents that can be added to such combination regimens.

HEMATOCRIT AND PLASMA IRON VALUES OF POVERTY-AREA CHILDREN* by G. M. Owen, A. H. Lubin, P. J. Garry and J. M. Swartz, Ohio State Univ., Col. of Med. Children's Hosp., Dept. of Ped., Columbus, Ohio and Minnesota Systems Research, Inc., Minneapolis.

In March and April, 1968, 36 Children and Youth (C&Y) Projects simultaneously determined hematocrits of 5,000 poverty-area children (65% Negro) between 1 and 5 years old [Rep. No.: 8-9 (ld) Systems Development Project, Univ. of Minn.]. For 1,935 children 1-2 years old and 1,159 children 4-5 years old in that non-random sample, mean hematocrits were 33.5 and 36.1%, respectively. One-fourth of 1-2 year olds and 1/20 of 4-5 year olds had hematocrits < 32%. During 1971, 20 C&Y Projects determined hematocrits of a non-random sample of 1,200 children (65% Negro) 1-5 years old. Plasma irons were determined in a central laboratory. Data pertaining to 1-2 and 4-5 year old C&Y registrants (1971) are compared below with data pertaining to 1,500 non-poverty children (10% Negro) included in a cross-sectional sample (J Pediat 79:563, 1971) of U.S. preschool children examined in 1969 and 1970 in a Preschool Nutrition Survey (PNS).

		Hematocrit		Sat. transferrin	
		Mean	< 32%	Mean	<16%
1-2 years:	C&Y	35.3	12%	14.9	60%
	PNS	35.6	6%	16.5	45%
4-5 years:	C&Y	36.6	2%	23.5	25%
	PNS	37.0	2%	23.6	30%

Anemia among preschool children in poverty areas appears to be less prevalent in 1971 than in 1968. Young poverty-area children have significantly more iron deficiency than do affluent children, but by age 4 or 5 years, iron deficiency does not seem to be related to socioeconomic status.

*Supported by Grant MC-R-390050-06-0 from MCHS, DHEW.

THE RELATIONSHIP BETWEEN ERYTHROCYTE CATALASE ACTIVITY AND BLOOD LEAD CONCENTRATIONS. Qutub H. Qazi and Helouise C.C. Mapa, Dept. of Ped., Downstate Medical Center, Brooklyn, New York (Introduced by S. Fikrig)

Catalase is an iron-containing enzyme which is widely distributed in mammalian tissues and is most abundant in liver, kidney and erythrocytes. During the present investigation catalase activity was assayed by the method of Takahara et al (J. Clin. Invest., 40:2199, 1960) in blood samples from 54 children seen for possible lead poisoning in the Pediatric Out-patient clinic.

*Blood Lead Conc. mg/100 ml.	Number of Children	Hemoglobin Conc. gm% Mean ± S.D.	Catalase Activity K-cat Mean ± S.D.
0.05 or less	25	11.8 ± 1.3	5.30 ± 1.13
0.06 or greater	29	11.8 ± 1.4	4.45 ± 1.47**

*New York City Health Department Laboratory

**$P < 0.025$

Our data reveal that erythrocyte catalase activity is lower in children with blood lead levels of 0.06 mg/100 ml. or higher. The significance of this finding remains to be clarified. Decreased life-span of red cells and iron-deficiency anemia which occur in lead burdened children could be ruled out as causative factors since catalase activity is independent of erythrocyte age and the two groups of children in the present study did not differ in their hemoglobin concentrations. Although lead is known to be a potent inhibitor of enzymes that are dependent on the presence of free sulfhydryl (SH) groups for their activity, the catalase activity is only slightly affected by high concentrations of SH reagents such as p-chloromercuribenzoate.

There is a significant increase in coproporphyrin excretion in the urine in acatalasic patients as well as in those with lead intoxication. We are, at present, looking into this relationship between the two conditions.

FERROKINETIC STUDIES IN SYNDROME OF CONGENITAL IRON OVERLOAD (HEPATO-CEREBRO-RENAL SYNDROME OF ZELLWEGER). Howard A. Pearson, Joseph Chusid, Richard T. O'Brien and Richard P. Spencer. Departments of Pediatrics and Nuclear Medicine, Yale University School of Medicine, New Haven, Connecticut.

The hepato-cerebro-renal syndrome is a rare multi-system defect in which there is marked iron deposition in many organs. Iron metabolism in this syndrome has not been quantitatively assessed, prompting ferrokinetic studies in an 8 week old female. Serum iron was high with near saturation of iron binding capacity (S.I., 282 µg/100ml; T.I.B.C., 296 µg/100 ml). Clearance of radioiron from the plasma was rapid; PIDT 1/2, 64 min. (normal, 90-120 min.). Plasma iron turnover was greatly increased, P.I.T., 2.17 mg/kg/day (normal, 0.4 - 0.6 mg/kg/day). Fe^{59} utilization by RBC was low, 33% at 7 days (normal 70-90%). Absorption of orally administered iron was normal at 10%. Organ uptake of Fe^{59} was determined by surface counting. Sacral marrow up-take was less than normal, but there was normal release of this activity into the blood corroborating effective red cell synthesis. Abnormal hepatic accumulation of Fe^{59} was noted. Treatment with desferrioxamine (DFO) produced increased ferriuria and a significant decrease in serum iron. A surprising observation was a high level of free iron in the cerebro-spinal fluid. This was 62µg/100ml initially, and fell after DFO treatment. At autopsy, markedly increased deposits of iron were noted in reticuloendothelial elements of liver, spleen and bone marrow. Ferrokinetics in the Zellweger syndrome differ from those in both idiopathic hemochromatosis or transfusional hemosiderosis complicating red cell aplasia or thalassemia major. There appears to be active uptake of iron into a hepatic compartment. However, iron can be mobilized by chelating agents. Transport of iron across the intestinal mucosa is normal. These studies suggest that the basis of the iron overload may be an increased avidity of the reticuloendothelial system for iron. The high levels of free CSF iron could theoretically be of importance in the genesis of neurological dysfunction.

THE EFFECT OF 11-KETOPREGNANOLONE(11-KP) ON RED CELL VOLUME(RCV). L. M. Rao and N. T. Shahidi, Univ. of Wis., Univ. Hosp., Dept. of Ped., Madison.

Certain nonmasculinizing 5βH steroids, such as 11-KP, are known to increase porphyrin synthesis by stimulating δ-aminolevulinic acid synthetase. Stimulation of hemoglobin synthesis by these hormones has been assessed in short-term experiments using red cell ^{59}Fe uptake and have yielded conflicting results. In this study, the effect of 11-KP on RCV was evaluated by ^{51}Cr method. For this, a group of 12 Sprague-Dawley female rats received 20 mg/kg of 11-KP intraperitoneally 3 times a week for 6 weeks. The second group(11) received similar doses of testosterone propionate(TP) for the same period. The third group(15) received both 11-KP and TP, and a fourth group(13) was given the vehicle alone. Each animal received 2 mg iron dextran i.m. at the beginning of the experiment. The RCV and the wet weight of the kidney, liver and spleen were recorded in each animal at the end of 6 weeks. The data as shown below revealed a significant increase in RCV in the 11-KP treated group as compared to the controls ($p \leq .05$). RCV in the TP treated group was, however, significantly greater than in the 11-KP group ($p \leq .001$). The highest RCV was obtained in the group receiving the combined 11-KP and TP. While there was a significant increase in kidney mass in the TP treated group ($p \leq .001$), 11-KP had no effect on the weight of this organ, suggesting a different mode of action. Neither hormone exerted any effect on the weight of the liver or spleen.

Group (No.)	RCV (mean ± 1SD)	Kidney (mean ± 1SD)
11-Ketopregnanolone(12)	26.16 ± 1.53 ml/kg	0.63 ± 0.01 gm/100gm body wt
Testosterone(11)	29.83 ± 2.14 ml/kg	0.79 ± 0.05 "
Testosterone + 11-keto-pregnanolone(15)	30.65 ± 3.65 ml/kg	0.78 ± 0.07 "
Controls(13)	24.87 ± 0.95 ml/kg	0.64 ± 0.04 "

In view of the above data, the efficacy of 11-KP alone or in combination with TP deserves investigation in refractory anemia in man.

COORDINATED THERAPY OF RETINOBLASTOMA. Charles B. Pratt, David Meyer, H. Omar Hustu, and Warren W. Johnson (Intr. by Donald Pinkel). St. Jude Children's Research Hosp., Memphis.

In an attempt to provide optimal therapy for children with retinoblastoma, a coordinated multidisciplinary treatment program using all known effective modalities has been initiated. The aims are to provide therapy and to quantitate its results according to the stage of the tumor at diagnosis.

Thirteen children, age 2 months to 4 years, with a confirmed diagnosis of retinoblastoma, were admitted to this study between April, 1970, and November, 1971. Six children had unilateral tumor, 7 had bilateral disease. Extent of disease was staged as: I-tumor confined to the retina, II-tumor confined to the globe, III-extraocular extension of tumor (regional), or IV-generalized disease. Therapy included surgery, $^{60}Cobalt$ therapy, cryotherapy, light coagulation and vincristine-cyclophosphamide (VCR-Cyclo) combination chemotherapy. Five of the patients with unilateral tumor had disease confined to the globe; one patient had tumor which also involved lymphatics along the dura. Each has had a complete clinical regression following enucleation with durations of response ranging from 3 to 19 months. Each of the patients with bilateral tumor has had complete clinical regression, one following bilateral enucleation, one following light coagulation, and 4 following the combination of VCR-Cyclo chemotherapy, radiotherapy and cryotherapy after enucleation of the more severely affected eye. One patient who was treated without enucleation responded for 6 months; he expired with tumor of the nasopharynx 15 months following diagnosis.

Coordinated utilization of all treatment modalities is well tolerated and offers prospects of improving survival and maintaining sight of more children with retinoblastoma. (Supported by USPHS Grant CA-08480, and by ALSAC.)

FREE BILIRUBIN AS AN INDEX OF RESERVE BILIRUBIN-ALBUMIN BINDING CAPACITY. David Schiff, George Chan, and Leo Stern. McGill Univ.-Montreal Children's Hosp. Research Inst.

Bilirubin-albumin binding can be measured by a number of methods. The commonly used HBABA dye binding method is nonspecific for bilirubin and competing anions (1). In the presence of high unconjugated bilirubin, the Sephadex G-25 elution technique gives a qualitative assessment, i.e. the presence or absence of free bilirubin. The present study demonstrates the use of the Sephadex G-25 elution technique as a quantitative indicator of reserve bilirubin-albumin binding. Fifteen sera from 7 infants with bilirubin concentration ranging from 6.9 to 23.0 mg% were assayed. 0.5 µl aliquots of a freshly prepared 5 mg/ml bilirubin solution was added to 0.5 ml of the icteric plasma in increasing amounts to the point of yielding free bilirubin. At least 3 points between bilirubin-albumin molar ratio of 1 and 2 were obtained. Plotting the absorbance of free bilirubin obtained against the amount of bilirubin added, yielded a straight line in all the sera studied, enabling an estimation of the amount of bilirubin concentration increase that a specific infant could tolerate before the appearance of free bilirubin. Application of this quantitative measure would permit a more meaningful approach to neonatal hyperbilirubinemia, the indications for and timing of exchange transfusions, and prevention of kernicterus.

1. Chan, G., Schiff, D., and Stern, L.: Competitive binding of free fatty acids and bilirubin to albumin: Differences in HBABA dye versus Sephadex G-25 interpretation of results. Clinical Biochemistry 4:208, 1971.

A NEW, NON-ISOTOPIC METHOD FOR DETERMINING PLATELET SURVIVAL - RECOVERY OF PLATELET AGGREGATION FROM ASPIRIN EFFECT. Allen D. Schwartz (Intr. by Howard A. Pearson) Yale Univ. Sch. of Med., Dept. of Ped., New Haven, Conn.

Acetylsalicylic acid causes a permanent defect of the platelet release mechanism resulting in a measurable abnormality of platelet aggregation. This platelet function is not corrected until a significant number of undamaged platelets enter the circulation. A new method of estimating platelet survival was devised by taking advantage of this transient effect of aspirin on platelet aggregation. Blood samples were collected from subjects prior to the ingestion of medication in order to document normal platelet aggregation. Following ingestion of 10 grains of aspirin, the study was repeated at 24 hour intervals until the pattern of aggregation had returned to normal. Platelet aggregation was measured on a platelet aggregometer using aqueous epinephrine as the aggregating agent in a final concentration in platelet rich plasma of 4×10^{-5}M. In twenty control subjects platelet aggregation returned to normal 4 to 7 days following aspirin ingestion. Five patients with normal platelet counts, but a history of thrombocytopenia, were thought to have decreased platelet survival. These subjects corrected the drug-induced aggregation defect in 2 to 3 days. Two of these patients had a history of ITP, one had a diagnosis of systemic lupus erythematosis, one had Evans' syndrome, and one had cardiac valvular disease. One patient with moderate thrombocytopenia and a massive spleen due to thalassemia major had complete return of platelet function in two days. One patient with sickle cell anemia, mild thrombocytopenia and a large spleen had complete return of platelet function in 5 days, suggesting splenic pooling rather than increased platelet destruction to be the etiology of the thrombocytopenia. The aggregation recovery time following aspirin ingestion appears to be a simple method of determining increased platelet turnover with small amounts of blood without exposing the patient to radioactive materials. In addition it may permit differentiation between thrombocytopenia due to increased platelet destruction and thrombocytopenia secondary to platelet pooling within the spleen.

ERYTHROCYTE PYRUVATE KINASE (PK)ACTIVITY IN LEUKEMIA. Voravarn S. Tanphaichitr and Jan van Eys. Intr. by David T. Karzon. Departments of Biochemistry and Pediatrics, Vanderbilt University, Nashville, Tenn. 37232

The existence of low red cell PK activity unrelated to the hereditary type of PK deficiency has not been extensively explored, though a few scattered reports exist in the literature indicating that the PK activity in erythrocytes is low in acute leukemias. We have restudied the erythrocyte PK activity in various types of hematological malignancies. The results showed that red cell enzyme levels in acute leukemias are significantly lowered. This was most pronounced in acute myelomonocytic leukemia (112.76 $\pm$6.05 I.U./100 ml RBC) compared to normal controls (147.34 $\pm$3.09 I.U./100 ml RBC). This difference is significant at the $p < 0.0005$ level. The levels in acute lymphocytic leukemia are only moderately lower than controls (127.31 $\pm$9.19 I.U./100 ml RBC). Erythrocyte PK activity in polycytemia vera is significantly elevated (165.39 $\pm$15.62 I.U./100 ml RBC). No significantly different red cell PK activity was observed in chronic lymphocytic or chronic myelocytic leukemia. The same results were also obtained when the enzyme activity was expressed per gram of hemoglobin or per 10^{10} erythrocytes. In two families with one member suffering from acute myelogenous leukemia no evidence of familial PK deficiency was seen. Nevertheless, the consistent association between AML and levels of red cell PK in the heterozygous range for the genetic deficiency raises the possibility of a correlation between these diseases. This study was materially aided by the finding that differential inhibition of WBC PK activity can be achieved by using unbuffered washing of the cells, hemolysis in water only, and using TRIS buffer rather than the usual triethanolamine buffer with EDTA during the assay. (Supported by an Institutional Grant of the American Cancer Society and a grant of The John A. Hartford Fndn, Inc.)

COAGULATION CHANGES AND INTRACRANIAL BLEEDING IN SICK NEWBORN INFANTS. Elsa Sell, Norman Dyer, Eugene Dolanski, Jean-Pierre Relier, Alex Tsiantos, Mildred Stahlman, A. Bertrand Brill. Dept. Ped. and Radiology, Vanderbilt Univ. Sch. Med., Nashville, Tenn.

The role of the hemostatic mechanism in the pathogenesis of intracranial hemorrhage in newborn infants is not yet clear. 50 newborn infants at risk of developing intracranial hemorrhage were evaluated. Platelets, factors II, V, VIII and fibrinogen and fibrin split products were determined initially; the infants had received buffer and IV fluid as needed, but no blood or blood by-products before the initial study. All infants were transfused with Cr50 tagged red cells after the initial study and follow up studies were drawn in 30 babies. In no infant was the amount of blood transfused sufficient to give an increase of 50% over the initial value for any coagulation factor. Of the 50 infants, 26 lived and 24 died. Autopsies were performed in 18 and significant intracranial bleeding was found in 12. The timing of the intracranial bleed was estimated from the ratio of Cr to iron present in the clots as previously reported. Initial platelet counts and fibrinogen levels were different in infants who survived and those who died. 37 infants with more than 150,000 platelets had 65% survival; 13 infants with less than 150,000 platelets had 83% mortality. There was a 70% survival in 30 infants with fibrinogen above 150 mg%, and 70% mortality in 20 infants with fibrinogen less than 150 mg%. Of the infants with intracranial bleeding, 10 were male, 8 were less than 1500 gms, and 8 were less than 34 weeks gestation. 10 had reduced fibrinogen levels, 9 had reduced platelets, and 6 had low factor V or VIII at some time. In 2 infants with time of intracerebral bleeding known, both had thrombocytopenia and reduced factor V near the time of bleeding and subsequently fibrinogen remained normal in one and increased from a reduced level in the other, and factor VIII was low normal initially and reduced after the time of bleeding.

ERYTHROCYTE VOLUME AND DEFORMABILITY IN ABETALIPOPROTEINEMIA. Phillips P. Wedemeyer, (Intr. by Richard H. Michaels), Univ. of Pittsburgh Sch. of Med., Children's Hosp. of Pittsburgh, Dept. of Ped., Pittsburgh.

Patients deficient in betalipoprotein have red cells whose surface is covered with multiple knob-like projections (acanthocytes). This abnormal shape requires an increased ratio of surface area to contained volume. The lipid content per cell, one measure of surface area, is normal suggesting that the volume of the cell (CV) must be decreased.

We have recorded the frequency distribution of CV's in two affected brothers using a calibrated Coulter B counter. The median CV is normal or slightly increased over controls. The distribution curve is skewed toward cells of increased volume.

The deformability of RBC's suspended in Isoton was measured by filtration through calibrated G-E Nucleopore filters (mean pore size 2.8 microns) under negative pressure. Over 95% of the patient cells (controls >90%) passed this filter.

These results indicate that the CV of acanthocytes in abetalipoproteinemia is not decreased and would suggest that the lipid content per unit of surface area is decreased. This membrane alteration, although associated with an abnormal cell shape, is not associated with a decrease in cell deformability.

MARROW TRANSPLANT WITH GRAFT ACCEPTANCE IN AN IDENTICAL TWIN WITH ACUTE LEUKEMIA. Kenneth A. Starling, John M. Falletta, Donald J. Fernbach, Baylor Col. of Med., Dept. of Ped., Houston, and Evan M. Hersh, Univ. of Texas M.D. Anderson Hosp. and Tumor Inst., Houston. (Intr. by Mary Ann South)

A 3½-year-old girl, one of identical twins, was diagnosed as having acute leukemia in January, 1969. Identity was established by history of common placenta, HLA typing and 24 red cell antigens. Bone marrow and peripheral blood studies on the well twin were normal and have remained so. Mixed lymphocyte cultures have shown no stimulation of the sick twin's lymphocytes by the well twin's lymphocytes, but they were stimulated by other mitogens. The well twin's peripheral lymphocytes were stimulated x 10 by the peripheral lymphocytes and x 7 by the bone marrow from the sick twin.

The twin with leukemia received chemotherapy according to Southwest Cancer Chemotherapy Study Group protocols until a relapse on 9/20/71. She then received prednisone, vincristine, daunomycin, and L-asparaginase therapy for reinduction. At the end of this time, her bone marrow was in complete remission, but was markedly hypocellular and all therapy was discontinued on 10/25/71. On 11/3/71 the sick twin received 2.72×10^9 bone marrow cells intravenously from her twin. The marrow was collected in heparin and infused directly. In an attempt to provide an immunological marker for evaluation of graft acceptance, the well twin was immunized to keyhole-limpet hemocyanin (KLH) and to yellow fever one month prior to the marrow infusion.

The patient has been in continuous remission on no drugs since 11/3/71. She was febrile for 10 days following the graft procedure, but was asymptomatic. Six days after the graft she developed a diffuse interstitial pneumonitis which cleared spontaneously. A full thickness graft from the well twin was accepted, while a graft from an unrelated donor was rejected in 33 days. On 1/3/72, a KLH skin test applied to the twin with leukemia was strongly positive at 24 hours, and was still positive at 48 hours. KLH antibody titers were also positive. The positive skin test and KLH antibody titers are strong evidence for graft acceptance.

THE ROLE OF PROPHYLACTIC TRANSFUSIONS IN HOMOZYGOUS SICKLE-CELL DISEASE. James A. Wolff, Glenn Reeves and Anneliese L. Sitarz. Coll. of Physicians and Surgeons, Columbia Univ., The Babies Hosp., Dept. of Ped., New York City.

The effect of prophylactic transfusions on the course of S-S disease has been studied in seven children. Three subjects received only simple transfusions; one received only partial exchange transfusions, and three received simple transfusions following a prior period of partial exchange transfusions given at 4-9 week intervals. The ages of the patients at onset of the program ranged from 2½ to 16 years. Duration of treatment was 8 months to 6½ years. Three subjects were selected for prophylactic transfusion because of frequent crises without cerebrovascular accidents (CVAs); two because of a recent CVA, and two because of recent CVA and a moderate number of other crises. Mean Hgb levels were 2.0 Grams higher during the transfusion period than before; mean reticulocyte counts were elevated during the study period (14.1) and only slightly lower than before (18.5). The S Hgb level varied, as did the reticulocyte count, directly with the duration of interval between transfusions. In most subjects the S Hgb level was 60-80% just prior to transfusion, and 25-50% immediately afterwards.

None of the four patients with prior CVA have had a second such episode. Only one subject demonstrated striking decrease in number of crises. Four of the others showed no decrease. No difference in effect of partial exchange versus simple transfusions was noted. One of the seven subjects developed hepatitis during the study period. It is concluded that prophylactic transfusions, as used in this study, have a limited role in S-S disease which must be balanced against the added risks of iron overloading and possible increased incidence of hepatitis.

THE STABILITY OF RED CELL ADENOSINE TRIPHOSPHATE (ATP) DURING SICKLING. Harold S. Zarkowsky*, Wash. Univ. School of Med., Dept. of Ped., St. Louis. (intro. by Arthur L. Prensky).

A burst in lactate production and a greatly increased flux of potassium accompany the sickling of red cells from patients with sickle cell anemia (J. Gen. Phys. 39:31). The stability of red cell ATP during sickling was evaluated to assess the metabolic injury due to sickling, since Prankerd reported a decrease in ATP in sickled cells (Clin. Sci. 14:381). The level of ATP in sickle cells was significantly greater than that in normal cells (1.57 mM/L cells ± .28 vs. 1.19 ± .28) which reflects a younger cell population and suggests that no major irreversible loss occurs from in vivo sickling. Samples of whole blood from patients with sickle cell disease were deoxygenated by flushing 95% N_2/5% CO_2 gas into shaking flasks. Neutralized perchloric acid filtrates were prepared before incubation and after 30 or 60 minutes, at which time more than 50% of the cells had sickled.

Experiment:	1	2	3	4	5
Initial ATP (mm/L cells):	1.27	1.42	1.41	2.07	1.32
Deoxygenated ATP (mm/L cells):	1.54	1.97	1.60	2.05	1.52

In order to determine whether the above findings could represent ATP loss into plasma, immediately after deoxygenation plasma was separated from cells. No ATP was detected in the plasma. The maintenance of ATP levels indicates that no major disruption of energy production occurs during sickling.

DEVELOPMENT OF INTESTINAL ADENYL CYCLASE AND ITS RESPONSE TO CHOLERA TOXIN. Frank M. Torti, Stephanie Jaksina and Richard J. Grand, Children's Hosp. Med. Ctr., Boston

The developmental pattern of adenyl cyclase from fetal day 17 to 10 days postnatally was studied in fetal intestine obtained during timed pregnancies in white New Zealand rabbits. Intestinal membranes were prepared and assays performed by methods of Kimberg (JCI 50:1218, 1971). Adenyl cyclase activity was comparable in jejunum and ileum at all time points. Basal enzyme specific activity (μmoles cAMP formed/min/mg protein) was already present by fetal day 17 (0.028) and showed a 4-fold peak rise by 22-23 days (0.104). By 28 days the basal activity had fallen toward adult levels (0.023) and remained constant throughout gestation and the first week of life. At all time points fluoride-stimulated activity was 3-5 times the basal values. When intestinal segments were incubated in vitro with purified cholera toxin, adenyl cyclase activity in subsequently prepared membranes was tripled but was not further stimulated by fluoride until day 26 when fluoride produced increases over those achieved with toxin. Phosphodiesterase activity did not change during gestation. Lactase activity in whole intestinal homogenates prepared from the same fetuses showed the expected rise beginning on fetal day 25. The data show that intestinal adenyl cyclase responds to cholera toxin quite early in gestation, and that the peak in the development of the unstimulated enzyme occurs before the time of appearance of villi or of an enzyme marker for microvilli. The results support the concept that adenyl cyclase is present in plasma membrane other than the brush border.

GASTROENTEROLOGY AND ENZYMOLOGY

First Session

JEJUNAL IMMUNOGLOBULIN A (IgA) SYNTHESIS IN CYSTIC FIBROSIS (CF). Z. Myron Falchuk and Lynn M. Taussig (Intr. by Paul A. di Sant'Agnese). NIH, Bethesda, Maryland.

Immunologic abnormalities have recently been described in patients with CF. Accordingly, we have evaluated local IgA production by jejunal mucosa in vitro in seven patients with CF, three patients with hereditary pancreatitis (HP), and 12 normal subjects. IgA synthesis in biopsy specimens obtained perorally was assessed by measuring ^{14}C-L-leucine incorporation into IgA. Incorporated counts binding to specific anti-IgA antibodies covalently linked to bromacetyl cellulose constituted a measure of IgA production. The patients with CF were 14.5 to 41 years of age and their Shwachman scores ranged from 52 to 88. Pancreatic enzymes were absent in all CF patients and in 2 of 3 HP patients.

Mean IgA production in CF patients (20,400 ± 9,300 cpm/mg protein, mean ± SD) was significantly greater than normal (6400 ± 2500) ($p < 0.001$), while in HP patients it was not significantly different from normal (8700 ± 2200). Three of 7 biopsies from CF patients revealed increased numbers of plasma cells on histological examination. There was no correlation between locally produced IgA and serum IgA levels, age, Shwachman score, severity of lung disease, type of bacteria in sputum cultures, or roentgenographic abnormalities of the small bowel.

These results may indicate that patients with CF are under an increased local antigenic stimulus, perhaps due to an altered gastrointestinal bacterial microenvironment. Alternatively, these findings are compatible with the suggestion that immunologic factors play a role in the pathogenesis of CF as suggested by the fact that IgA has been found in the sterile maconium of newborns with CF (Rule et al., Pediatrics, 1971).

MECHANISM OF ANTIGEN UPTAKE FROM THE SMALL INTESTINE: Effect of oral and parenteral immunization. W. Allan Walker, Kurt J. Bloch, Laura M. Davenport and Kurt J. Isselbacher. Harvard Medical School, Mass. Gen. Hosp., GI Unit and Arthritis Unit, Boston, (Intr. by J. Warshaw)

Macromolecules such as food proteins and bacterial enterotoxins can be taken up in antigenic and biologically active quantities by the adult human small intestine. To determine the mechanism of uptake, horseradish peroxidase (HRP) (M.W. 40,000) absorption was studied in adult rat small intestine using the in vitro everted gut sac technique. HRP uptake was noted to be an energy dependent pinocytotic mechanism similar to that of immunoglobulin absorption in neonatal mammalian intestine. To determine the effect of immunization on antigen uptake, germ free and conventional rats were fed either 1 mg/ml of HRP or bovine serum albumin (BSA) for two week periods. After a specific antibody response was noted in intestinal secretions and serum, the in vitro uptake of ^{125}I-HRP and ^{125}I-BSA was measured. A significant decrease in the uptake of HRP in HRP-immunized and BSA in BSA-immunized animals was noted when compared to controls. However, no difference in BSA uptake was noted in HRP immunized animals nor HRP in BSA immunized animals. This suggested that uptake may be influenced by a specific antibody response. Furthermore, BSA and HRP uptake were decreased in parenterally immunized animals only after extensive antigen stimulation causing a hyperimmune state. Since systemic antibodies are more likely to gain access to secretions at high serum concentrations, the observation that antigen uptake was decreased by oral immunization and by extensive parenteral immunization suggests that secretory antibodies may be more important than serum antibodies in preventing antigen uptake. These findings have potential clinical therapeutic application in preventing milk allergy and toxic diarrheal states. (Work supported by U.S. Medical Research and Development Command Contract DAD 17-70-C-0113).

INTESTINAL LACTASE ACTIVITY IN PRETERM, NORMAL AND IUGR RAT PUPS AT BIRTH. M.K. Younoszai. Univ. of Iowa Coll. of Med., Univ. Hosp., Dept. of Ped., Iowa City, Iowa 52240.

In rats fetal and fetal small intestinal growth is retarded when maternal dietary protein is restricted during pregnancy (Younoszai, Ped. Res. 5:386,1971). In such intrauterine growth retarded (IUGR) rat pups histochemical methods demonstrated intestinal enzyme abnormalities (Schrader,et al, J. Nutr.99:401, 1969). The present study compares intestinal lactase activity in preterm (P), control (C) and IUGR rat pups that had not suckled. Dams of P and C pups were fed ad lib. during pregnancy a diet with 26% protein and those of IUGR pups a similar diet with 6% protein. P pups were delivered on the 21st day and C and IUGR pups on the 22nd day of gestation. The small intestine was removed within half an hour of delivery and divided into three segments, proximal, mid and distal thirds, and frozen immediately. Body weight (g, mean±S.E.) was greater ($p<0.01$) in C than in P or IUGR pups (P=5.3±0.1, C=6.1±0.1, IUGR=4.4±0.1). Total intestinal protein (mg) was also greater ($p<0.01$) in C pups (P=10.2±0.3, C=15.9±0.5, IUGR=11.3±0.5). Similarly total intestinal lactase activity, TLA (μmoles lactose hydrolyzed/min) was greater ($p<0.01$) in C pups (P=1.07±0.03, C=1.40±0.08, IUGR= 1.14±0.08). Intestinal lactase specific activity, LSA (μmoles lactose hydrolyzed/min per g protein) in the proximal segments were about the same in the P and IUGR pups and slightly lower in C pups (P=137±8, C=106±6, IUGR=122±8). In all pups LSA was 2-3 times higher in the proximal than in the distal third. These findings suggest that in IUGR pups, in contrast to intestinal growth and some other mucosal enzymes LSA is unaffected; the lower TLA is chiefly due to smaller intestinal size in IUGR than in C pups.

DISACCHARIDASE ACTIVITIES IN BRUSH BORDER MATERIAL OBTAINED BY INTESTINAL PERFUSION IN THE NORMAL INFANT. R. Torres-Pinedo and Carmen Lugo-de-Rivera. Gen. Clin. Research Center and the Dept. of Pediatrics, School of Medicine of the Univ. of Puerto Rico, San Juan, Puerto Rico.

A segment of the jejunum of infants recovered from diarrhea was perfused during 1 hour with Krebs-Henseleit buffer. The perfusate was collected over EDTA and its contents separated by differential centrifugation. Light, phase contrast and electron microscopy of the pellets revealed abundant brush borders (400 xg) and microvilli (73,000 xg). Disaccharidase activities (invertase, lactase, maltase) were measured in the pellets and supernatants. About 30% of the total activities were recovered in the sediments, while the rest remained soluble. Enzyme specific activities were higher in the microvillous fractions. Further purification was obtained by separation of the microvilli in Ficoll density gradients. Distribution of enzymes and proteins in the particulate sub-fractions was identical to that of a microvillous preparation obtained from mechanically disrupted brush borders of guinea pig's jejunum.

The method is useful for biochemical appraisal of brush border activity in the infant.

SULFATED PRIMARY BILE SALTS: A NEW METABOLIC PATHWAY IN CHOLESTASIS. M. Michael Thaler, Adolf Stiehl, and William H. Admirand (Intr. by M. M. Grumbach), Depts. of Ped. and Med., Univ. of California, San Francisco.

The synthesis, turnover and sulfation of bile salts were studied in a four-year-old child with chronic severe cholestasis due to intrahepatic biliary atresia. Metabolites of orally administered ^{14}C-cholate and ^{3}H-chenodeoxycholate were extracted from serum and urine, and identified by thin-layer chromatography. The presence of sulfate esters of these primary bile salts was confirmed with infrared spectrometry. The sulfate esters were then solvolyzed and quantitated by gas-liquid chromatography.

Of the total bile salts synthesized daily, 32% were excreted in the urine. Sulfated bile salts accounted for 76% of the total urinary bile salts. In contrast, less than 5% of the bile salts in serum were sulfated. Thus, the renal clearance of bile salt sulfates was approximately 100 times greater than the clearance of non-sulfated bile salts. Within 12 hours after oral administration of ^{14}C-cholate and ^{3}H-chenodeoxycholate, half of the radioactivity present in the urine was in the sulfate fraction, indicating that bile salt sulfates were rapidly formed and excreted in the urine.

These findings indicate that sulfation and urinary excretion of bile salt sulfates represents a new and quantitatively important pathway of bile salt metabolism in cholestasis. Supported by USPHS Grants HD-03148 and AM-13857.

IMPAIRED ABSORPTION OF 3-O-METHYL GLUCOSE IN BILE LIGATED RATS. Claude C. Roy, Reuben S. Dubois, Guy Laurendeau, Victor Ling and Claude L. Morin, Univ. of Montreal, Hôpital Ste-Justine, Dept. of Pediatrics.

On the basis of D-xylose absorption tests, monosaccharide transport is assumed to be unimpaired in patients with biliary atresia. The absorption of 3-O-methyl glucose (3 MG) was studied 48 hours after bile ducts ligation in Sprague-Dawley rats weighing 150 to 220 g. using two different in vitro techniques. There was no difference in weight loss between the bile ligated rats and the sham animals. Total bilirubin concentration averaged 7.2 mg% in the former and .8 mg% in the latter. Twenty cm segments of upper jejunum were completely removed from the animals and perfused extracorporeally through the superior mesenteric artery. The intestinal lumen was infused at a rate of 1 ml/min. with 100 mg% of 3 MG and 2μCi of the labelled substrate and the total portal venous effluent was collected at one min. intervals for 30 min. The % min. absorption in 12 experimental animals (23.1±1.3) was significantly lower ($P<.001$) than in 12 controls (36.6±3.8). Comparable results were obtained using everted segments of proximal jejunum. The distribution ratios developed by intestinal rings after a 40 min. incubation period showed a significant decrease ($P<.05$) in the intra-cellular accumulation of 3 MG in 6 bile ligated animals (3.6±0.5) as compared to 6 controls (7.1±1.4). Moreover, tissue accumulation of the substrate was lower (0.8 versus 1.6) as early as 5 min. after the start of the incubation suggesting a reduced influx. In view of our recent report that jejunal segments from bile fistula rats, in whom bile salt depletion is countered by a 48 hour sodium taurocholate infusion, absorb 3 MG less efficiently (Nature 225: 1055, 1970), the present study suggests that, in cholestatic conditions, bile salts may exert an inhibitory effect on the monosaccharide transport system.

FETAL BILE SALT FORMATION. R. Lester, J. M. Little, R. Greco, G.J. Piasecki and B. T. Jackson. (Intr. by R. Klein) Depts. of Med. and Surgery, Boston University School of Medicine, Boston, Massachusetts.

What is the source of fetal bile salt? Is it synthesized by the fetus or transferred to the fetus from the mother? This problem was studied in thoroughbred pregnant Beagle dogs using established surgical techniques.

Fetal synthesis was measured in 4 fetal dogs, with vascular and biliary catheters, injected with cholesterol-4-^{14}C, and maintained in utero with external biliary drainage for 36-53 hrs. Basal excretion = 0.37 μmoles/Kg/hr and rose as high as 3.2 μmoles/Kg/hr in response to pool depletion. 1.1-4.7% of precursor was incorporated into fetal bile salt; 62-92% in cholate(CA), 8-38% in chenodeoxycholate(CDCA) and none in deoxycholate (DCA). Similar results were obtained after injection of cholesterol-4-^{14}C into 7 fetuses with the biliary tree intact.

Maternal to fetal transfer was studied in 4 pregnant adult dogs receiving intraduodenal cholate-2,4-^{3}H. The appearance of labeled bile salt in 27 fetuses was measured. 0.02-0.05% appeared in fetal bile as CA and derivative DCA over 5-7 days. In maternal bile, 2/3 of the label was in CA and 1/3 in DCA; but in fetal bile, 1/3 was in CA and 2/3 was in DCA. A similar study of maternal to fetal transfer of chenodeoxycholate-24-^{14}C in 2 adults and 12 fetuses showed that CDCA transfer was 5 times that of CA and DCA combined.

Conclusions: 1) The secondary bile salt in fetal bile comes exclusively from the mother, and dihydroxy bile salts are transferred in greater amounts than trihydroxys. However, 2) fetal CA synthesis is 1.6-11.5 times greater than CDCA synthesis, and 3) it can be estimated that the rate of total fetal bile salt synthesis is at least 1 1/2 times maternal to fetal transfer. Therefore, 4) bile salt synthetic mechanisms are sufficiently developed in the near-term fetal dog to facilitate the transformation to independent existence after birth.

HUMAN AMNIOTIC FLUID (AF) ISOAMYLASE. Robert O. Wolf and Lynn M. Taussig (Intr. by Paul di Sant' Agnese). NIH, Bethesda, Maryland.

An investigation of the amylase concentration and isoenzyme pattern in AF was performed since the source of AF amylase has been in doubt. Amylase isoenzyme patterns in human AF have not been examined previously. Eleven AF samples were obtained at various times during gestation by amniocentesis and at delivery by transvaginal needle aspiration. Homogenized placenta, fetal urine, and adult serum, duodenal fluid, and parotid saliva were also studied. Total AF amylase concentration was measured by a saccharogenic method. Disc polyacrylamide gel electrophoresis was used to separate the isoamylases and the various bands were identified by squeezing the enzyme-containing polyacrylamide gel column against a starch agar film (Wolf and Taylor, Amer. J. Clin. Path., 1968). The isoenzymes of amylase were allowed to react with the starch substrate; 15 min. at room temperature for saliva and duodenal fluid and 6 hrs. at 37°C in a moist box for urine, serum, placenta, and AF. After incubation, the zymograms on the starch slides were developed in an iodine solution. The concentration of AF amylase rises during gestation and may be as high as 120 Somogyi units/100 ml at term; the range of values at any gestational age is wide. The AF amylase isoenzyme pattern was nearly identical to that of fetal urine and revealed distinct salivary (at least 5 bands) and pancreatic (at least 1 band) components. Homogenized placenta was similar to that of adult serum and different from AF indicating contamination of the homogenate by maternal blood; previous studies have also shown that placenta probably does not contain amylase. Maternal proteins (except for IgG) are not known to cross the placenta. The similarity of the AF and urine patterns indicate fetal origin of AF amylase. In contrast to previous beliefs, it appears that the pancreas and salivary glands of the fetus function early in intrauterine life (as early as 18 weeks).

INTERRUPTION OF THE ENTEROHEPATIC CYCLE OF BILE ACIDS BY UNABSORBED FAT. Andrée Weber, Liette Chartrand, Micheline Ste-Marie and Claude C. Roy, Univ. of Montreal, Hôpital Ste-Justine, Dept. of Pediatrics.

The physiologic role of bile acids on the digestion and absorption of fat is well known; however, the influence of unabsorbed fat on the enterohepatic circulation of bile acids (B.A.) has not been explored. A drop in the coefficient of fat absorption from 97 to 85% in 16 prematures fed long chain triglycerides (TG) instead of medium chain TG was associated with a significant ($P<.01$) increase in fecal B.A. measured by the enzymatic method and expressed in mg/Kg/72 hrs. The close correlation between fecal fat and B.A. prompted the study of 18 controls, 13 untreated celiac and 10 cystic fibrosis (C.F.) children on a normal long chain TG diet. Despite steatorrhea, B.A. values in celiacs (25.7±5.2) were not significantly different from those obtained in controls (18.3±1.9). However, they were much lower than in C.F. (125.0±16.1). Since the fecal sequestration of B.A. increased linearly with the degree of steatorrhea in C.F. but not in celiacs, it is suggested that a causal relationship may exist between unabsorbed fat, associated with intraluminal types of fat malabsorption, and intestinal reabsorption of B.A. Because daily B.A. synthesis equals fecal B.A. excretion and assuming that the basal synthesis rate in C.F. corresponds to fecal B.A. values in controls, the average loss in C.F. is interpreted in terms of a 7 fold increase over the basal synthesis rate. Interruption of the enterohepatic cycle, in certain cases, may be severe enough to exceed the capacity of the liver to synthetize B.A. and lead to a contraction of the pool.

Supported by the Medical Research Council of Canada grant MA 4433 and by Mead Johnson Co.

GASTROENTEROLOGY AND ENZYMOLOGY

Second Session

CHARACTERIZATION OF NEWBORN FECAL LIPID. J. B. Watkins, R. Lester, C. M. Bliss and R. M. Donaldson. (Intr. by R. Klein) Dept. of Med., Boston University School of Medicine, Boston, Massachusetts.

Adequate fat absorption in the neonate is essential for the achievement of optimum growth and development. We have examined fecal lipid excretion utilizing newly developed fractionation techniques in 2 groups of normal infants, ages 3-11 days and 48-70 days, with the same formula and fat intake per Kg. Fecal lipid was partitioned by solvent extraction into four fractions: neutral lipids, insoluble divalent soaps, water soluble fatty acids, and bound lipids. Identification and quantitation of the individual lipid species present in each fraction was then performed by thin layer chromatography.

The newborn infants excreted a greater amount of fat (0.81 g/Kg/day) than the older infants (0.35 g/Kg/day). In both groups, fecal lipid was composed primarily of neutral lipids (56%, avg., range 36.7-78%); however, newborn fecal lipid contained a significant proportion of diglycerides and monoglycerides (13% of the total lipid excreted), while no glycerides were found in the older infants' stools. In both groups, insoluble divalent soaps comprised the other major fraction (29%, avg., range 21-46%). Fatty acid analysis of this fraction by gas liquid chromatography showed that it was comprised primarily of long chain saturated fatty acids.

The demonstration of glycerides in fecal lipid establishes that lipolysis is defective in newborn infants. Identification of long chain saturated fatty acids in the insoluble divalent soap fraction documents the association between calcium and saturated fatty acid excretion. Furthermore, the presence of fecal monoglyceride, while possibly the result of bacterial hydrolysis of triglycerides, suggests that lipid micellization and/or mucosal transport is insufficient for optimal lipid absorption. The results establish that the intraluminal phase of lipid absorption is not fully developed in the full-term newborn infant.

BLOOD AND FECAL LIPIDS IN LOW BIRTH WEIGHT INFANTS FED A CORN OIL AND A CONVENTIONAL FORMULA. Billy F. Andrews, Vichien Lorchirachoonkul and Roger J. Shott. Univ. of Louisville Sch. of Med. Dept. of Ped., Louisville, Ky. (Introduced by William G. Thurman.)

Twenty low birth weight infants 1200-1700 Gms were randomly assigned to groups fed Similac (I) and CP 5027 B (II) containing corn oil at 24 cal/30 cc up to 200 cc/Kg/day to test whether there would be differences in absorption or blood levels of lipids. Blood studies were performed on a three hour fast on the morning of the second day of a three day stool collection. Two infants were removed from the study. Results for mean values are summarized as follows:

	7d		14d		21d	
	A	B	A	B	A	B
Total Lipids in mg%	633	619	549	497	572	503
Cholesterol in mg%	176	128	184	126	171	133
Per cent Fat Excreted	35	38	22	30	25	28

No statistical difference was detected for gain in weight, length or head circumference. Although there was no statistical difference in per cent fat excretion between groups, fat absorption increased with maturity even with greater intake. These results indicate infants have a capacity to absorb rather large quantities of fat. The observation of persistently lower cholesterol values in the corn oil fed group demonstrates the potential for reduction of cholesterol by diet even for the newborn.

INHIBITION OF HEPATIC MICROSOMAL MIXED FUNCTION OXIDASE (HMMFO) BY CHLORAMPHENICOL (CH). Jacob V. Aranda*, Stuart M. MacLeod*, Kenneth W. Renton*, and Norman R. Eade* (Intr. by Mary E. Avery). McGill Univ., Dept. of Pharmacology and McGill Univ. - Montreal Children's Hosp. Research Inst., Montreal.

CH decreases hepatic drug biotransformation as shown by prolongation of $T\frac{1}{2}$ of Tolbutamide, Diphenylhydantoin and dicoumarol in man. This is presumed to be due to inhibition of HMMFO and glucuronyl transferase. To test this hypothesis, measurements of the hepatic microsomal electron transport components - NADPH oxidase, cytochrome (cyt.) c reductase, cyt. P-450 and cyt. P-450 reductase and of representative oxidative pathways, Aminopyrine N-Demethylation (AMP-ND) and Aniline hydroxylation (AN-OH) from adult rats were made. The data showed a significant in vitro inhibition of NADPH oxidase, P-450 reductase and AMP-ND. Rats pretreated with CH 100 mg/kg/d and 200 mg/kg/d I.P. for 3 days both showed inhibition of P-450 reductase and AMP-ND, ($P<0.025$). The data confirm previous suggestions that CH inhibits HMMFO. CH should be cautiously used when administered concomitantly with other drugs that undergo hepatic biotransformation especially in instances where HMMFO is immature, as in the newborn.

	Control (10)	CH In Vitro (10)	Pre-Rx CH (5) 100 mg/kg/dx3	Pre-Rx CH (5) 200 mg/kg/dx3
NADPH oxidase	7.07±.45	4.65±.36**	7.02±.97	6.59±.60
cyt. c red'ase	118.5±7.3	105.2±7.5	112.3±15.5	98.9±5.9
cyt. P-450	0.385±.02	.362±.03	0.354±.1	0.396±.05
P-450 red'ase	6.81±.7	3.54±.41**	3.936±.95**	3.43±.53**
AMP-N-D	2.64±.12	.448±.1**	1.148±.27**	1.05±.17**
AN-OH	.397±.027	.335±.018	.437±.116	.306±.08

** $P<0.025$ as compared to control.
All values expressed as nmoles/mg protein/min.

CHOLESTERYL ESTER STORAGE DISEASES: STUDIES OF THE CHEMICAL AND BIOCHEMICAL ABNORMALITIES. Howard R. Sloan and Donald S. Fredrickson, NIH, Bethesda, Md.

Tissue accumulation of cholesteryl esters (CE) and triglycerides (TG) occurs in two rare human diseases, Wolman's disease (WD) and cholesteryl ester storage disease (CESD). The two disorders are quite different in clinical expression and life expectancy. The activities of cholesteryl ester hydrolase (CEH), triglyceride lipase (TGL) and monoglyceride lipase (MGL) and the lipid content have been determined in several tissues from one patient each with WD and CESD, and controls. In liver, spleen and lymph node, CE was elevated as much as 90-fold in CESD and 30-fold in WD; in spleen TG was 30-fold increased in CSED and 8-fold in WD. Tissue homogenates were incubated at pH 4 or 7.4-8.6 and 37° with ^{14}C-CE, -TG, and -MG and the ^{14}C-fatty acids liberated were quantified. Activities are expressed as picomoles of substrate cleaved per mg tissue per hour. The acid-CEH activities were: Liver: 6 controls - 110 ± 20 (mean ± S.D.), CESD - 1.0, WD - 0.4; spleen: 5 controls - 200 ± 20, CESD - 7.6, WD - 1.3; lymph node: 5 controls - 110 ± 50, CESD - 3.5, WD - < 0.1. The acid-TGL activities were: liver: 6 controls - 5,800 ± 3,600, CESD - 660, WD - 460; spleen: 5 controls - 19,400 ± 3,300, CESD - 1,100, WD - 220; lymph node: 5 controls - 10,430 ± 4,340, CESD - 663, WD - 274. These relative enzyme activities were not altered by correction to tissue protein instead of tissue weight. In the liver, acid-MGL activities were 29 and 11% of the normal value in CESD and WD, respectively. Activities of other lysosomal enzymes and of neutral CEH and TGL were normal in liver homogenates of CESD and WD. In CESD skin fibroblasts, acid-CEH and acid-TGL activities were markedly reduced; in the CESD aorta, acid-CEH activity was deficient. The chemical and enzymatic abnormalities in CESD and WD are similar; indeed they likely involve the same genetic locus. If the latter is true, the marked difference in phenotypic expression in the two disorders is presently without explanation. The intriguing possibility that both enzyme activities are associated with a common protein remains to be explored.

ANTIBIOTICS AND BILIRUBIN TRANSPORT. B.H. Doray and A.P. Bonin, (Intr. by J.R. Ducharme) Dept. of Ped. and Biochemistry., Univ. of Montreal and Hôpital Ste-Justine, Montreal. Several antibiotics are transported in the serum by albumin and may thus displace bilirubin bound to this protein. The albumin-bilirubin complex may be assessed by measuring absorption of serum diluted in buffer at 465nm. It is also possible to evaluate the amount of unbound bilirubin in separating serum through Sephadex G-25 and measuring bilirubin adsorbed on the column. Serums were obtained from icteric newborns at the start of their exchange transfusions and either Nafcillin, Kanamycin, Carbenicillin or Ampicillin were added in amounts equal to those used for therapy in the neonatal period. Out of a group of 32 studies, Nafcillin produced a decrease of absorption at 465nm in 5 cases having total bilirubins of 13, 19, 24, 8 and 22mg%, the last three having a conjugated to total bilirubin ratio ≥ 20%; the first two less than 5%. Among the 27 negative results with Nafcillin, only 2 had conjugated to total bilirubin ratio ≥ 5% (7%and 14%). Δ O.D. 465nm amounted to a percentage of total bilirubin displacement of 2.2% ± 0.2. Kanamycin was also studied in 33 serums, and the albumin-bilirubin complex was decreased by 2.95% in only one case. This specimen also had conjugated bilirubin over 20%. No effect was detected with Carbenicillin and Ampicillin in 27 and 33 samples respectively. 11 to 13 studies on each of the 4 antibiotics using Sephadex G-25 separation did not reveal any increase of unbound bilirubin. Although the danger for brain toxicity from the displacement of bilirubin in serums with a high conjugated bilirubin ratio is questionable, the same displacement in the last 2 cases (Bilirubin 8 and 22mg%), suggests a potential danger in icteric newborns. (Supported by Combined Canada and Quebec Health Programs, Grant no. 604-7-741

INTESTINAL AMINO ACID TRANSPORT IN HYPERPHENYLALANINEMIC AND HYPERTYROSINEMIC RATS. Flma Lifshitz and Raul A. Wapnir. Rosewood State Hospital and Univ. of Md. Sch. of Med., Dept. of Pediatrics, Baltimore, Maryland 21201.

In untreated phenylketonuric patients, the intestinal absorption of leucine, arginine, and tyrptophan is decreased. The intestinal absorption of aromatic amino acids was tested in rats in vivo, after induction of hyperphenylalaninemia or hypertyrosinemia. Female Wistar rats (80 gms) were made hyperaminoacidemic by an excess intake for 1 to 2 weeks of phenylalanine (Phe) or tyrosine (Tyr). Purina lab chow was fed to the control rats. The experimental animals received this diet supplemented with 7% Phe (HiPhe) or 7% Tyr (HiTyr). The animals were anesthesized with 1.5 gm/Kg of urethane. A 20 cm segment of the jejunum was cannulated. Krebs-Henseleit buffers with 1-10 mM Phe or 1 mM Tyr were perfused for 2 hrs. at a rate of 0.17 to 0.20 ml per min. The buffers contained 600 mg% polyethylene glycol as a marker. All animals on the HiPhe or HiTyr diets had 3-4 mM blood Phe or Tyr levels respectively at the beginning of the perfusion. A significant inhibition of the transport rates of 1 to 5 mM Phe occurred in rats made hyperphenylalaninemic (22 ± 3 vs 10 ± 2 mμ moles/min/cm $p<.001$). However, there was no inhibition for the transport of Tyr. Conversely, hypertyrosinemic rats, fed HiTyr diets exhibited an impaired intestinal absorption of 1 mM Tyr (4.1 ± .9 vs 2.8 ± .2 mμ moles/min/cm $p<.02$), and the transport of 1 and 5 mM Phe was not altered. The high circulating blood Phe acts as a non-competitive inhibitor of the intestinal transport mechanisms. The apparent Km for Phe was 6×10^{-3} M for both groups of rats. The maximum rate of Phe absorption in the HiPhe rats was 54% of the controls. These findings indicate that high circulating levels of Phe or Tyr may specifically inhibit the transport of the same amino acid at the intestinal mucosal interphase. The lack of cross inhibition for amino acid transport may be taken as evidence of the presence of specific binding sites on a common amino acid carrier in the small intestine. Supported in part by USPHS Grant HD-03959-03 and the Hartford Foundation.

THE EFFECT OF PREGNANCY ON DRUG METABOLISM. Hector Rodriguez, Charlotte S. Catz and Sumner J. Yaffe. Department of Pediatrics, State University of New York at Buffalo, School of Medicine, Children's Hospital of Buffalo, New York.

Although women take an average of 8.5 drugs during pregnancy, no comprehensive study of drug disposition during gestation has been carried out. This information is a prerequisite to rational therapy. Some metabolic pathways have been reported to be decreased toward the end of pregnancy, but systematic investigation has not been undertaken.

Pregnant Sprague-Dawley rats were assayed for several drug metabolic pathways in vitro in early (7 days), mid (14 days) and late (21 days) gestation. Activities in liver homogenates for type I oxidative substrates varied with drug substrate. For hexobarbital after a significant decrease at 7 days a progressive increase ensued reaching control values at term. For aminopyrine an initial increase was followed by a return to control activity at 14 and 21 days. Type II substrates (aniline) showed a continuous progressive decline throughout pregnancy. Nitro reductase (paranitrobenzoic acid) activity remained stable up to 14 days and decreased at term; whereas, azo reductase (neoprontosil) exhibited an 80% decrease at 7 and 21 days and only a 50% diminution at 14 days. Glucuronide conjugation (p-nitrophenol) was augmented early but greatly decreased in mid and late gestation. The differences observed at the three stages of gestation were statistically significant ($p<.01$).

The marked variations in drug metabolism throughout pregnancy which are substrate specific prevent the adoption of a uniform approach to drug administration during gestation. Therefore, each drug must be evaluated individually in order to obtain a reliable estimation of dosage.

Supported by USPHS Grant HD 04287.

TREATMENT OF CRIGLER-NAJJAR SYNDROME WITH AGAR. Ronald L. Poland*, Gordon B. Avery, Elizabeth Goetcherian*, and Gerard B. Odell. The Johns Hopkins University and Children's Hospital of the D.C.

A male infant whose lineage includes the originally reported cases of Crigler-Najjar syndrome was admitted on the 16th day of age with a serum bilirubin of 35.2 mg% (< 0.5 mg% direct reacting). Serum bilirubin was reduced to 15 mg% by two consecutive two-volume exchange transfusions and 24 hr/day phototherapy. Liver biopsy on the 44th day of age was histologically normal. The microsomal fraction had no bilirubin-UDP-glucuronyl transferase activity. Gall bladder bile contained 18.3 mg% total bilirubin of which 7.3 mg% was conjugated. Thin layer chromatography of the azo-derivative of the conjugated pigment showed an Rf of 0.56 unlike the glucuronide (Rf = 0.48). At 54 days of age the patient was begun on 3 weeks of night-time phototherapy at home and the serum bilirubin rose from 10 to 18 mg%. He was readmitted for a trial of agar therapy. Phototherapy was continued for 10 hr/day. A control period was followed by periods of oral agar therapy in increasing doses up to 1 mg/kg/day. The bilirubin binding properties of this USP Agar (k_a = 2.5 x 10^5; capacity = 1 mole bilirubin/50,000 gm Agar) were determined in vitro from adsorption isotherms standardized in this laboratory. Fecal bilirubin excretion increased from 1.2 to 3.0 mg/day with no change in bilinogens or bilins. Renal clearances (T_cH_2O) improved from 0.67 to 1.08 to 1.18 ml/100 ml GFR during three weeks of agar therapy. Phototherapy was reduced to 8 hr/day and serum bilirubin has been falling (low of 9.7 mg%) since initiation of 1 gm/kg/day agar dosage. Growth, development, and neurological examinations have been normal through 5 1/2 months of age. Tapering of phototherapy continues. Other liver functions remain normal.

ISOENZYMES OF ALKALINE PHOSPHATASE (AP) AND RELATED SEROLOGIC LIVER FUNCTION STUDIES IN NORMAL ADOLESCENCE AND IN CYSTIC FIBROSIS (CF). John Kattwinkel, Lynn M. Taussig, and Bernard E. Statland, (Intr. by Paul A. di Sant'Agnese), NIH, Bethesda, Md.

Serologic tests for liver function in children have been difficult to interpret because of the lack of good normal data in this age group. AP in particular is known to increase markedly during adolescence secondary to active bone growth, thus making interpretation of this test as a measure of liver function most difficult. An automated technique has been developed requiring 10 microliters of serum to examine total AP and its l-phenylalanine and urea stable components. This technique has been utilized as well as conventional methods for measuring 4 other serological parameters of liver disease: transaminases (SGOT,SGPT), 5' nucleotidase (5'N), and γ-glutamyl transpeptidase (γGTP). The sera of 50 normal controls (age 10-30) and 31 patients with CF were examined. It is well known that patients with CF may develop hepatic biliary cirrhosis which is often undetectable prior to postmortem examination but may lead to significant clinical problems during life. Our results disclose that total AP is a poor indicator of minimal biliary cirrhosis in childhood because of the masking effect of bone isoenzyme; normal values may exceed by a factor of 2 those previously reported. Determination of the liver fraction of AP, however, renders the test age-independent and unmasks a significant number of abnormal values. Of 31 CF patients studied, 10 had abnormal liver fractions while only 2 had abnormal total APs when compared with age-matched norms. Eight of these 10 patients also demonstrated slightly to markedly elevated transaminases, 5'N, and/or γGTP.

In summary, we have established new normal data for several serologic liver function studies in the 10 to 30 age group. Separation of AP isoenzymes discloses a normal peak of bone fraction during adolescence and distinguishes those patients with a significantly elevated liver fraction during puberty. We feel that AP during adolescence is of minimal value without concomitant isoenzyme determination and that, conversely, the liver fraction of AP can be a good determinant of early biliary cirrhosis in cystic fibrosis.

USE OF ANGER CAMERA IN EVALUATION OF EXCRETION OF I^{131} ROSE BENGAL FROM THE LIVER. Ruth C. Harris, M.D. and Philip M. Johnson, M.D. Columbia University College of Physicians and Surgeons, Departments of Pediatrics and Radiology, New York, N.Y.

Measurement of Rose Bengal excretion in stool and urine as an index of obstructive jaundice ignores the possibility of partial obstruction in the extrahepatic system, such as might exist with a common duct cyst or stenosis of a repaired extrahepatic bile duct anomaly. Following I^{131} tagged Rose Bengal injection, liver scans were repeated serially over 48 hours in 17 infants and children with various lesions to appraise the rapidity of uptake of radioactive dye and the speed of removal of material from the liver into the intestinal tract. Problem patients were studied: before surgery,-3 infants with parenchymal or obstructive disorders of the liver; following corrective surgery for common duct cysts,- 6 children, aged 4 mons. to 16 yrs.; 4 to 13 years after surgical procedures,-three with biliary atresia. Also included are one with intrahepatic atresia of 10 yrs. duration and examples of chronic hepatitis and metabolic disease.

In all patients but one with terminal hepatic failure, uptake of radioactive material by the liver was intense by 30 minutes. In patients manifesting good liver function all radioactivity had left the liver in 5 hours, with visualization in the colon by 24 hours. Suspicion of obstruction at the site of anastomosis seemed confirmed by local persistence of visualization in the gallbladder area for 24 hours in the 16 yr. old girl with slowly rising bilirubin and pruritis. Repeat study 6 mons later showed adequate, but slow, clearing from the liver. The pattern of excretion in the patient with intrahepatic atresia showed relatively poor uptake and slow elimination. Bile duct cysts may or may not be directly seen by this technique. The best uses are in the long term appraisal of reconstructive biliary surgery, with some parenchymal damage, to evaluate the possibility of local stasis, and the occasional bile duct cyst which shows a local accumulation of radioactivity.

ALTERATIONS IN THE RECTAL MUCOSA OF PATIENTS WITH PRIMARY IMMUNODEFICIENCY SYNDROMES (IDS). Marvin E. Ament, Hans D. Ochs. (Intr. by Starkey D. Davis). Univ. of Washington Sch. of Med., Depts. of Med. and Ped., Seattle.

The absence of plasma cells in some patients with primary IDS is well documented; however, a prospective study of rectal morphology in these patients has not been undertaken. Furthermore, rare cases of colitis have been described in these patients, but no attempt has been made to distinguish them from cases of idiopathic ulcerative colitis. Rectal biopsies from 34 patients with primary IDS were taken and matched with biopsies from 34 normal controls and 34 patients with inflammatory bowel disease. The biopsies were coded and read blindly in an attempt to separate patients with IDS from the 2 other groups by differences in morphology.

A total of 192 biopsies were reviewed with 97% agreement between the two reviewers. Plasma cells were absent or markedly decreased in all rectal biopsies from patients with IDS except in those of ataxia telangiectasia or IDS with normal immunoglobulins. Six of 8 patients with infantile X-linked agammaglobulinemia also demonstrated early crypt abscess formation. A single isolated early crypt abscess was found in biopsies from 2 of 19 patients with variable IDS. Sigmoidoscopic examination was normal in 3 patients with infantile X-linked agammaglobulinemia and early crypt abscesses.

Two patients with variable IDS and watery diarrhea demonstrated an edematous friable mucosa on sigmoidoscopic examination. Their rectal biopsies showed an edematous hypocellular mucosa with polys in the lamina propria but no crypt abscesses.

Rectal biopsies are useful in establishing the diagnosis of primary IDS. They are characteristic and can generally be distinguished from biopsies obtained from patients with inflammatory bowel disease. Early crypt abscess formation was found in 75% of patients with infantile X-linked agammaglobulinemia. The changes in the rectal mucosa of patients with primary IDS and colitis are unique and may give a clue to the mechanism of colitis.

GASTROENTEROLOGY AND ENZYMOLOGY

Read by Title

PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS. Mark Ballow, Carmi Z.Margolis, Bernard Schachtel, and Y. Edward Hsia, Yale Univ. Sch. of Med., Depts. of Ped. and Med., Div. of Med. Genetics, New Haven, Connecticut 06510.

Familial intrahepatic cholestasis is a cause of jaundice in infancy intermediate in severity between benign recurrent intrahepatic cholestasis and intrahepatic biliary atresia. The study of this condition and its complications in two affected brothers contributes to an understanding of its pathogenesis and of the classification of causes of cholestasis.

Two Puerto Rican brothers presented in early infancy with jaundice, hepatomegaly, and frantic pruritis. They both developed malabsorption, growth failure, rickets, and clubbing. They had fluctuating conjugated bilirubinemia (8 mg% to 50 mg%), markedly elevated alkaline phosphatase only partly responsive to anti-rachitic treatment, and normal serum cholesterol. Serum trihydroxy/dihydroxy bile acid ratios were 36.6/13.6 μg/ml and 14.4/23.8 μg/ml (normal: <3.5/<1.9 μg/ml). ^{131}I Rose-Bengal excretion was only 15.4% and 3.2%. At laparotomy both brothers had normal extrahepatic biliary systems, with attenuated intrahepatic bile ducts. Biopsies showed identical features of marked bile stasis, secondary centrilobular necrosis, and paucity of interlobular bile ducts. Cholestyramine is being given to lower their bile salts; medium chain triglycerides to overcome their malabsorption; and vitamin D to correct their rickets.

Retention of bile salt and bilirubin appears to be the primary defect in this syndrome, which is distinguished by its characteristic histology, with intact bile ducts, and absence of giant cells.

Progressive familial intrahepatic cholestasis probably represents an inborn error of hepatocellular bile excretion.

COMPARATIVE STUDIES OF ALBUMIN BINDING AND TOXICITY OF BILIRUBIN AND OTHER BILE PIGMENTS, Marilyn L. Cowger and Jung J. Lee, Albany Med. Col., Dept. of Ped., and State Univ. of New York, Dept. of Chemistry, Albany.

We have been studying the albumin binding characteristics of bilirubin (BR) in detail by optical rotary dispersion (ORD) and circular dichroism (CD) techniques as well as its toxic effects on mitochondrial reactions such as respiratory control, oxidative phosphorylation and swelling. A comparative study of two other major bile pigments closely related to BR, namely ℓ-stercobilin (SB) and biliverdin (BV) should help elucidate the mode of binding of bilirubin to albumin as well as aid in understanding the mechanism of toxicity. Furthermore, BV may be the first product formed by photo-oxidation of BR, so that knowledge of the own inherent toxicity of BV is important. It was found by ORD-CD studies that SB and BV bind to bovine serum albumin (BSA). In the presence of both SB and BV, SB bound preferentially to BSA. SB bound to BSA in a 1 to 1 ratio at pH 4.5. The binding constant of SB to BSA was estimated to be 1 x $10^{-1}M^{-1}$ with slight preferential binding to a dimer of BSA (2 x $10^{-1}M^{-1}$). This compares to a binding constant of approximately 6 x 10^6M^{-1} for BR at both pH 5 and 7.4. SB did not show any adverse effects on the aforementioned mitochondrial reactions. However, like BR, BV was inhibitory to substrate oxidations catalyzed by rat liver and brain mitochondria (K_m^{BV} = 16K_m^{BR}) but unlike BR, BV did not cause large amplitude irreversible swelling of mitochondria. Both BV and SB in high concentrations (~100 μM) diminished the swelling effect of BR. Unlike BR neither BV nor SB could be shown to form a lipid complex at least by spectrophotometric means. The results of these comparative studies implicate the importance of the lipophilic nature of BR both in its albumin binding characteristics and in its mode of toxicity. (Supported by NIH)

SERUM ALPHA 1 ANTITRYPSIN DEFICIENCY AND INFANTILE LIVER DISEASE. Blaise E. Favara, Ralph A. Franciosi and Arnold Silverman. (Introduced by Wm. E. Hathaway) Children's Hospital, Denver.

Two children with low serum levels of α1 antitrypsin and neonatal liver disease were studied. The first child had neonatal hepatitis at 6 weeks of age. At 12 years of age she had 28 mg% serum α1 antitrypsin (normal 200-400 mg%.) Biopsy revealed postnecrotic cirrhosis and intracellular hyaline masses. Ultrastructural studies showed nonspecific hepatocellular degeneration. Two siblings had low levels of α1 antitrypsin (56 mg% and 28 mg%) and the father had 168 mg% antitrypsin; a value in the carrier range. The mother and two other siblings had normal levels. No pulmonary disease was found in patient or family. Family history was also negative for liver disease and liver function studies were normal.

The second case, a boy, presented with jaundice at 3 weeks of age. α1 antitrypsin was 100 mg%. A liver biopsy at 10 weeks showed "neonatal hepatitis" with cholestasis. Ultrastructural studies showed numerous membrane bound masses of cytoplasmic amorphous material. A homogenate contained 0.7 mg of α1 antitrypsin/gm of liver tissue. (Control values 1.2-2.8 mg/g_m tissue.) Jaundice subsided by 6 months. Low levels of serum α1 antitrypsin persisted, (56 mg%) and a second biopsy was done at 13 months. Postnecrotic cirrhosis was present and small cytoplasmic hyaline masses were found. Ultrastructural studies revealed the same membrane bound material in the cytoplasm. A tissue homogenate demonstrated no α1 antitrypsin by immunoprecipitation technique, however, direct fluorescent antibody studies revealed positive granular deposits. The mother's serum α1 antitrypsin level was 152 mg%. No lung disease is manifest in the child or mother.

Deficiency of serum α1 antitrypsin associated with "neonatal hepatitis" and subsequent cirrhosis in children suggests a causal relationship. "Neonatal hepatitis" may be caused by the metabolic defect or subsequent liver disease in children with α1 antitrypsin deficiency may develope only with added insult of "neonatal hepatitis."

IN VITRO INDUCTION OF CHANGES IN ANTIGENIC AND MORPHOLOGIC CHARACTERISTICS OF ENTEROPATHOGENIC E. COLI.
Hsi-Yen Liu, M.D., Zsuzsanna Giday, Warren C. Eveland, Ph.D., Departments of Pediatrics and Epidemiology, University of Michigan. (Introduced by Wm. J. Oliver, M.D.)

By 1967, 12 pediatric patients with bovine milk associated lactose malabsorption and positive cultures of enteropathogenic Escherichia coli had been rendered "enteric-pathogen-negative" by dietary exclusion of lactose without accompanying antibiotic therapy. It was hypothesized, then, that the hosts' malabsorption of lactose might have provided the gut flora an abundance of antigenically significant galactose side chains on the bacterial lipopolysaccharide cell walls, thus, permitting agglutinability against specific "O" antibodies. To test the postulation, type O-55, B-5 E. coli, grown on trypticase soy agar from stock supply at the University of Michigan School of Public Health, were serially subcultured every 48 hours in beef extract-proteose-peptone base broth, with and without added 0.5% galactose, pH adjusted to 7.1, over an 11-day-period. Antigenic typing against specific antisera as well as smears for gram and F.A. staining were made of each culture at 48 hour intervals. Organisms grown without galactose lost their agglutinability against poly-A antisera but retained their agglutinability against O-55 antisera by the 5th galactose-free day and showed no morphologic alteration throughout the observation period; while those grown on galactose-containing media retained their agglutinability but became significantly longer, wider, thicker in cell walls and showed many regional punctate and segmental increases in cell wall F.A. and gram staining.

PANCREATIC EXOCRINE ENZYME DEFICIENCY ASSOCIATED WITH ASPHYXIATING THORACIC DYSTROPHY. Manouchehr Karjoo, C. Everett Koop, David Cornfeld, Philip G. Holtzapple. Dept. of Pediatrics, Univ. of Pennsylvania Sch. of Med. & The Children's Hosp. of Philadelphia.

A male infant was presented with small and narrow chest, tachypnea, repeated pulmonary infections, diarrhea and failure to grow. Studies revealed findings consistent with the diagnosis of asphyxiating thoracic dystrophy (ATD) and pancreatic exocrine insufficiency (PEI). Investigation included x-ray studies of chest and small bowel, stool fat analysis, small bowel biopsy, sweat electrolytes, stool trypsin, pancreatic exocrine function studies with secretin, enterokinase, and hematologic tests for neutropenia.

The progressive pulmonary difficulties and respiratory infections related to the chondrodystrophy were abated at 10 months of age by longitudinal separation of sternum and fixation by a George Washington bar. Pancreatic supplementation has corrected the diarrhea, steatorrhea and growth failure.

A younger brother was born with a milder degree of the congenital chest deformity but is free of pulmonary problems. His growth and development are normal and he is free of gastrointestinal disease.

This is the first successful surgical attempt for amelioration of the restrictive pulmonary problem, and the first description of the association of ATD with PEI.

INHIBITION OF INTESTINAL TRANSPORT BY SERUM FROM PATIENTS WITH CYSTIC FIBROSIS. Luis L. Mosovich, Charlotte S. Catz and Sumner J. Yaffe. Dept. of Pediatrics, State University of New York at Buffalo, Children's Hospital of Buffalo, New York.

An abnormal factor has been isolated from the serum of patients with cystic fibrosis. Experimental evidence in rats indicates that the factor inhibits transport in a variety of tissues (epithelial cells, parotid salivary gland and jujunum). On the other hand, it has also been implicated in the production of hyperpermeability of the isolated distal ileum in the rat. This was determined by increases in pressure caused by osmotically inducing flow of fluid into segments of the intestine previously bathed with CF serum. In order to clarify this apparent discrepancy, direct measurement of intestinal transport from mucosal to serosal side was measured employing the technique of everted intestinal sacs.

Sacs from SW mice fasted overnight were prepared and the transfer of water, sodium and glucose measured. Effect was determined by utilizing a 3:1 v/v incubation mixture of Krebs phosphate buffer and CF serum. Each experimental sac was compared to two others, incubated respectively in a similar mixture with serum from normal controls and serum-free buffer. With cystic fibrosis serum added, no changes in water or sodium transfer were recorded, but glucose transport was decreased 80% expressed as mg glucose transported/100mg tissue. Serosal/Mucosal ratios for glucose exhibited a small diminution in the presence of normal serum, but a marked decrease occurred with CF serum. Further experiments utilizing CF saliva may show an effect on sodium transport since the factor may be present in higher concentration in glandular secretions.

PHYSIOLOGIC DEFICIENCY OF PANCREATIC AMYLASE IN INFANTS: A FACTOR IN IATROGENIC DIARRHEA. Clinton B. Lillibridge and Philip L. Townes. University of Rochester School of Medicine and Dentistry, Genesee Hospital, Department of Pediatrics, Rochester, New York.

Selective deficiency of pancreatic amylase has been reported in only one patient (C. U. Lowe and C. D. May, Am J Dis Child 82:459, 1951). Despite the rarity of this deficiency in older infants and children, infants under six months of age normally have little or no pancreatic amylase. We have studied a child whose failure to thrive may be attributed to excessive starch intake during the period of physiologic amylase deficiency. During the first four months of life, the child had a severe, chronic diarrhea and gained little weight despite a high caloric intake. At age four months, he was hospitalized for evaluation of the failure to thrive. A duodenal aspirate, free of saliva and gastric contamination, contained normal trypsin, chymotrypsin, carboxypeptidase, and lipase activity, but no amylase activity. Other studies including duodenal biopsy, sweat electrolytes, lactose tolerance test, etc. all proved negative.

Before hospitalization, the child received 300 calories/kg/day. The child was placed on a low starch diet which provided 120/calories/kg/day. The change in diet resulted in excellent weight gain: 10th percentile to 75th percentile between ages of four and six months. On reevaluation at age twelve months, the duodenal aspirate contained 600 units of amylase/ml (normal 2000 units/ml). Salivary amylase was 120,000 units/ml. On immunoelectrophoresis, a weak amylase arch was detected; at age four months it was absent. The diet was liberalized to starch, and growth remained normal to the present time at age two years. These observations suggest that a fermentative diarrhea and failure to thrive may be iatrogenically produced by feeding starch to infants during the period of physiologic amylase deficiency.

LOW CHYMOTRYPSIN ACTIVITY IN CYSTIC FIBROSIS: ENZYME DEFICIENCY OR ENZYME DEFECT? Jack L. Neal, Ezzat A. Girgis and Mimi M. Belmonte, McGill University-Montreal Children's Hospital Research Institute, Montreal 108, Canada. (Intr. by C. Scriver)

The lack of enzyme activity in the stool of cystic fibrosis patients is usually attributed to a deficiency of enzyme caused by a blockage in the pancreatic duct. However, certain observations can be more readily explained on the basis of an enzyme defect rather than a deficiency. A blockage should lead to a parallel deficiency of trypsin and chymotrypsin, but the activity levels of these enzymes are not correlated until an age when appreciable pancreatic damage has taken place. Parents of C.F. children have enzyme activities significantly higher than other adults. This fact can hardly be reconciled with duct blockage. The response of stool enzyme activity to oral enzyme supplement is non-linear and seems to require a certain threshold enzyme level. The response threshold varies from patient to patient. Another assay based on inhibitor binding rather than substrate hydrolysis yields substantially higher ! values for stool chymotrypsin in C.F. patients than in normal children.

DISTRIBUTION AND QUANTITATION OF ALPHA$_1$ANTITRYPSIN IN DILUTE BIOLOGICAL FLUIDS: ITS LOCALIZED INCREASE IN TEARS OF PATIENTS WITH CORNEAL ULCERATION. Richard C. Talamo, Carol E. Langley, John C. Barber, Michael B. Berman, Newton E. Hyslop, Jr. Harvard Medical School, Children's Service and Department of Medicine, Massachusetts General Hospital and the Retina Foundation, Department of Cornea Research, Boston.

The alpha$_1$antitrypsin (α_1AT) is the major protease inhibitor of human serum. A severe inherited deficiency of this protein is associated with either familial infantile cirrhosis, familial emphysema, or, rarely, both diseases. This suggests that the α_1AT may normally be important in protecting tissues against enzymatic attack. Serum α_1AT is known to rise in normal individuals in response to inflammatory processes.

A sensitive agarose electroimmunodiffusion method has been used to study the distribution and quantity of α_1AT in a variety of body fluids. α_1AT was detected in all of 6 samples of colostrum, all of 3 cerebrospinal fluids, 2 of 8 parotid salivas, 1 of 3 urines, 1 of 2 tracheobronchial washings tested, in ug/ml quantities. In 20 amniotic fluids α_1AT was 54-1300 ug/ml. (Mean normal plasma α_1AT is 2.25 mg/ml.)

In tears from 12 eyes of normal individuals, α_1AT was detected in 4 samples in amounts up to 6.3 ug/ml. In tears from involved eyes of 5 patients with severe corneal ulceration, α_1AT levels were 11.7 to 75 ug/ml; the extent of the ulceration appeared to be correlated with the α_1AT level. α_1AT levels in the contralateral eyes were lower, ranging from 0 to 10.3 ug/ml. No elevations of serum α_1AT were noted in patients with severe ulceration and greatly increased tear α_1AT levels. In 2 of these patients serum levels were in the range of intermediate α_1AT deficiency.

α_1AT is widely distributed in human biological fluids and may elevate locally in tears to many times its normal level without an associated rise in serum α_1AT levels.

A NON-IMMUNOGLOBULIN VIRUS-BINDING SUBSTANCE IN HUMAN AMNIOTIC FLUID. Ruth B. Weisinger, Eugene Ainbender, M. Magda Hevizy, and Horace L. Hodes. The Mount Sinai School of Medicine. Dept. of Ped. New York.

The immunoglobulins of 50 amniotic fluids, 25x concentrated, were studied by radioimmunodiffusion (RID). All fluids had IgG, 90% had IgA and 20% had IgM. Specific binding of radioactive poliovirus (32P labelled) was demonstrated by IgG in 90% of the specimens and by IgA in 70% of the specimens. Only 2 fluids demonstrated IgM binding. In 80% of the fluids a non-immunoglobulin virus-binding substance was present on the radiograms.

The non-immunoglobulin virus-binding substance (NIVBS) has the following characteristics: When amniotic fluid is diffused in agarose, NIVBS moves just a short distance from the well. It is not removed from the agarose by extensive washing with 1% NaCl. It is not precipitated by any anti-immunoglobulin serum. It binds radioactive poliovirus producing a line seen only on the radiogram. NIVBS activity is not removed by dialysis of amniotic fluid or by heating the fluid to 56°C for 30 minutes. On radioimmunoelectrophoresis with 32P poliovirus, the substance appears as a short dense line slightly to the anode side of the antigen well. Sephadex chromatography shows that NIVBS has a molecular weight over 200,000. At 0.01M PO4 buffer pH 8.1 it is bound to DEAE, differing in this way from IgG.NIVBS can be eluted by 0.3M PO4 buffer pH 8.1. The binding of radioactive virus by NIVBS is decreased by pretreatment of the amniotic fluid with non-radioactive virus.

NIVBS was not related to the titer or immunoglobulin class specific poliovirus antibody of the amniotic fluid. In fact, one amniotic fluid which did not contain any specific polioantibody did contain the non-immunoglobulin virus-binding substance and this fluid neutralized poliovirus as demonstrated by standard tissue culture techniques.

EFFECT OF VITAMIN D AND CALCIUM ON AMINOACIDURIA AND INTESTINAL TRANSPORT OF AMINO ACIDS IN THE HOLTZMAN RAT. Claude L. Morin, Jean Léveillé, Victor Ling and Louis Dallaire. (Intr. by C.C. Roy), Univ. of Montreal, Ste-Justine Hospital, Department of Pediatrics, Montreal.

Generalized hyperaminoaciduria and hyperphosphaturia are associated with human vitamin D deficiency rickets and the effect has been reproduced in animals. The basis for the renal transport impairment was attributed to secondary hyperparathyroidism resulting from hypocalcemia (Grose and Scriver, Am. J. Physiol. 214: 370, 1968). In this study we attempted over a 16-week period to induce hyperaminoaciduria in rats with vitamin D deficient diets of varying calcium content (0.4% and 0.04%) so as to investigate the possibility of a concomitant defect in intestinal transport of amino acids. In doing so, observations on weight gain and calcium and phosphorus metabolism were made. Rats deprived of vitamin D and on a normal calcium diet (NCa-D) or a low calcium diet (LCa-D) developed hypocalcemia and hyperphosphaturia and impairment of growth. Animals fed a low calcium diet with vitamin D (LCa+D) were able to maintain growth and normal plasma calcium over the greater part of the study. Despite signs of secondary hyperparathyroidism, generalized hyperaminoaciduria was not in evidence in any of the groups. However, increased urinary excretion of lysine and taurine, as compared to controls (NCa+D), was demonstrated in the (LCa-D) group. The results failed to show any effect of vitamin D deficiency or secondary hyperparathyroidism on the intestinal transport of lysine, alanine and cycloleucine.

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COMBINED IMMUNODEFICIENCY MANIFESTED BY THE LETTERER-SIWE SYNDROME. Stephen D. Cederbaum, Gen Niwayama, E. Richard Stiehm, Robert C. Neerhout, Arthur J. Ammann and William Berman, Jr., Depts. of Psychiatry, Pediatrics and Pathology, Univ. of California, Sch. of Med., Los Angeles, and Dept. of Pediatrics, Univ. of California, Sch. of Med., San Francisco.

Three infants (one the offspring of consanguinous parents) are described in whom the clinical diagnosis of the Letterer-Siwe syndrome was suspected but in whom a diagnosis of combined immunodeficiency disease and in one case graft-versus-host reaction was made on post-mortem examination. Additional cases of this syndrome have been described as familial reticuloendotheliosis with eosinophilia (NEJM 273:427, 1965, and G. Omenn, personal communication). The outstanding clinical features included morbilliform rash, diarrhea, frequent infections, hepatosplenomegaly, normal or elevated lymphocyte counts, and eosinophilia. Immunoglobulin levels were variable. Post-mortem examination revealed thymic dysplasia with absent Hassel's corpuscles and absent germinal centers in peripheral lymphoid tissue with secondary histiocytic proliferation in these and other organs. Pneumocystis carinii infection was found in all three patients. The clinical picture of the Letterer-Siwe syndrome as well as the lymphocytosis in two instances and a normal in vitro phytohemagglutinin response in one instance, obscured the correct diagnosis. Potentially harmful transfusions and immunosuppressives were given and attempts to find a compatible bone marrow donor were not made.

The familial occurrence and consanguinity indicate that this is an inherited disorder. We propose that the combined immunodeficiency syndrome may regularly present as the Letterer-Siwe syndrome and that this presentation may be a relatively constant feature in individual families. One plausible explanation for this phenomenon would be a graft-versus-host reaction resulting from the engraftment of maternal immunocompetent cells in her immunodeficient offspring during gestation.

All patients presenting with the Letterer-Siwe syndrome should have the diagnosis of combined immunodeficiency excluded.

IMMUNOLOGY

First Session

SERUM AND SECRETORY ANTIBODY RESPONSE TO VIRAL INFECTIONS IN IMMUNOGLOBULIN DEFICIENCY SYNDROMES. Pearay L. Ogra and Margaret H. MacGillivray, Dept. of Peds., Sch. of Med., State Univ. of N.Y. at Buffalo.

Antibody response to polio, rubella and echoviruses was studied in the serum and nasopharyngeal secretions of patients with selective deficiency or total absence of γA immunoglobulin following intranasal immunization with inactivated poliovaccine, and after naturally acquired rubella and echovirus infections. The techniques of tissue culture neutralization, hemagglutination-inhibition, and radioimmunodiffusion and autoradiography were employed to determine the antibody response in γG, γA, and γM classes of immunoglobulin in serum and nasopharynx. Little or no poliovirus antibody response was observed in the serum after intranasal immunization with inactivated poliovaccine. Nasopharyngeal antibody response to poliovirus in γA deficient patients was characterized by the appearance of appreciable γG and low levels of γA class of antibody. The response appeared 1-2 weeks after immunization and persisted for as long as 3-4 months. The nasopharyngeal response in patients with total absence of γA was characterized by the regular appearance of significant amounts of poliovirus antibody which was essentially limited to γG and occasionally to γM class of immunoglobulin. The antibody appeared 2-4 days after immunization and persisted in detectable titers for approximately 3 months. Nasopharyngeal γA antibody response was conspicuously absent. Few patients with total absence of γA immunoglobulin who experienced natural infection with rubella or echovirus type 6, elicited an initial γM antibody response in the serum which was subsequently replaced by γG class of antibody. The nasopharyngeal response in these patients was characterized by the appearance of rubella and echovirus specific γG antibody which was detectable for as long as 7-8 months. No γA antibody activity was detectable in the nasopharynx. These observations may explain the apparent resistance to viral infections in patients with isolated immunoglobulin deficiency syndromes. It is suggested that a deficient or absent serum and secretory γA system may be effectively compensated by the local mucosal production of γG and γM antibodies.

MATERNAL INTRAUTERINE GRAFT OF B LYMPHOCYTES IN COMBINED IMMUNOLOGICAL DEFICIENCY DISEASE (CID). H.J. Meuwissen, R.J. Pickering, S. Litwin, and B. Pollara, (Intr. by H.S. Strauss), New York State Birth Defects & Kidney Disease Institutes, Albany, N. Y. and Cornell Medical Center.

CID is characterized by serious deficiency of the lymphocyte mediated-and humoral immune systems. Variants of this disease have been described in which plasma cells and normal or elevated gammaglobulin levels are present. Antibodies may or may not be found. We have studied a female infant (< 1 yr.) who manifested an absence of lymphocyte mediated immunity with extremely low lymphocyte levels and minimal response of these lymphocytes to phytohemagglutinin stimulation. Initially, IgG and IgA levels were normal but the IgM level was elevated. By the 11th month of postnatal life all immunoglobulins had decreased to low levels. Plasma cells were present in the bone marrow initially but disappeared later. On agarose electrophoresis the gammaglobulins appeared to be oligoclonal. Allotype studies showed maternal immunoglobulin G markers only. Antibody was produced in response to some antigens, not to others. By lymphocytotoxic testing, maternal lymphocytes could not be found in the circulation, and the circulating lymphocytes did not carry immunoglobulin surface markers. No response was observed to repeated fetal liver and thymus transplants, but a partial response to preparations containing transfer factor was noticed.

The most logical explanation of these facts is the hypothesis that clones of maternal B cells were established in this child's lymphoid system by intrauterine transfusion but were subsequently slowly rejected. These cells produced oligoclonal maternal gammaglobulins and were partially responsible for the child's clinical well being. Absence of all clinical criteria of graft-versus-host disease indicates that maternal T cells did not cross the placenta, were inhibited after crossing, or were rejected.

The proposed mechanism may be operative in other children suffering from this variant of CID. Supported by Grant No. 7RO1CA12241 from the National Cancer Institute.

FAMILIAL THYMIC APLASIA: ATTEMPTED RECONSTITUTION WITH FETAL THYMUS IN A MILLIPORE DIFFUSION CHAMBER. Russell W. Steele, Catherine Limas, Gary B. Thurman, Heinz Bauer, and Joseph A. Bellanti. Georgetown Univ. Sch. of Med., Dept. of Ped., Washington, D. C.

Immunologic studies of a 10 week old white female infant with hypocalcemic tetany and convulsions revealed impaired cell-mediated immune function. Normal serum immunoglobulin concentrations, a vigorous agglutination response to typhoid immunization, and normal numbers of circulating lymphocytes bearing membrane associated immunoglobulins ("B" cells) suggested adequate humoral immunity. However, histologic examination of lymph nodes by light, electron, and fluorescence microscopy demonstrated lymphocyte depletion in thymus-independent as well as thymus-dependent areas.

Thymus from a 13 week fetus was placed in a millipore diffusion chamber and implanted under the rectus sheath; such a chamber obviated the risk of a graft-versus-host reaction. Phytohemagglutinin (PHA) induced transformation of lymphocytes was demonstrated as early as 6 hours after implantation and uptake of 3H thymidine following PHA stimulation was normal at 8 days. This rapid reconstitution suggests the elaboration of a potent humoral factor as an important function of the thymus.

The infant expired from aspiration pneumonia 8 days after the thymus implant and post mortem examination confirmed the absence of thymus and parathyroid glands.

A maternal half-brother who had expired 5 years previously from P. carinii pneumonia at 4 months of age also had congenital absence of the thymus and parathyroid glands at necropsy. The mother was shown to have hypoparathyroidism and diminished cell-mediated immunity. This therefore represents the first familial cases of thymus and parathyroid aplasia.

PROLONGED SURVIVAL OF HEPATIC ALLOGRAFTS AFTER HOST LIVER ISCHEMIA. John R. Lilly, Kathryn D. Anderson, John C. Houck, Research Fndn. of Children's Hosp. of the D. C., Section of Surgical Research, George Washington Univ. Sch. of Med., Washington, D. C.

In previous laboratory experiments, we have shown that immature pigs subjected to liver ischemia by hepatic artery ligation and mesocaval shunt die in hepatic coma within 72 hours. Further, if after hepatic ischemia, homologous auxiliary liver transplantation is carried out, life is temporarily supported permitting recovery of the host liver and chronic survival after allograft removal. This communication reports the marked inhibition of immunologic rejection that was found in these experiments.

Non-immunosuppressed porcine recipients of heterotopic hepatic allografts begin to reject the graft 5 days after transplantation and complete rejection occurs within 10 days. In our experimental animals with host liver ischemia, a 2 to 3 fold delay in allograft rejection was found. In analyzing the serum from the animals, an as yet undetermined factor was present which profoundly interfered with PHA stimulation of the recipient (and normal porcine) lymphocytes. Three days after hepatic ischemia, ^{3}H-thymidine uptake by PHA cultured porcine lymphocytes fell from the normal of about 55,000 cpm/10^6 cells to below 1,500 cpm/10^6 cells. ^{3}H-thymidine uptake gradually returned to normal levels over the ensuing three weeks and were coincident with an increasingly aggressive rejection of the auxiliary liver transplant.

The biochemical changes consequent to hepatic ischemia in this experiment are similar to those seen in children with acute liver failure, and it is postulated that interference with normal immunologic defense mechanisms may be operative in such patients.

LYMPHOID INTERSTITIAL PNEUMONIA AND A DEFICIENCY IN THYMIC-DEPENDENT LYMPHOCYTES. Elton Dupree, Armond S. Goldman, Randall M. Goldblum and C. Wayne Smith. Shriners Burns Institute and The University of Texas Medical Branch, Department of Pediatrics, Galveston, Texas.

This is the first case of lymphoid interstitial pneumonia whose immunologic functions have been studied extensively. The patient, a 7-year-old girl, presented with chronic pneumonia, otitis media, mastoiditis, sinusitis and seborrhea. Humoral immunity, phagocyte functions and the number of marrow lymphocytes appeared normal. A defect in thymic-dependent lymphocytes (T-cells) was manifest in vivo by a lymphopenia, an absence of delayed hypersensitivity and a failure to reject a skin allograft, and in vitro by a shortened survival of blood lymphocytes, an accelerated synthesis of deoxyribonucleic acid by unstimulated lymphocytes and a decrease in antigen and mitogen stimulation of lymphocytes. The nodules of lymphocytes in the lung could be explained by infiltrating, non-sensitized lymphocytes which were incapable of eradicating the infecting organisms.

The thymus appeared normal except for enlarged Hassall's corpuscles. A relationship between the enlarged corpuscles and the deficiency of T-cells, such as an increased destruction of T-cells in the thymus, was suggested. Although lymphocyte studies of family members were normal, a genetic basis of the defect is suspected because of consanguinity in the family.

THE INCIDENCE AND MANIFESTATIONS OF COW'S MILK ALLERGY (CMA) IN AN UNSELECTED SERIES OF 787 NORMAL NEWBORNS. J. W. Gerrard, J. W. A. McKenzie, N. Goluboff, J. Z. Garson, C. Maningas, and M. K. Shokier, University of Saskatchewan University Hospital, Dept. of Pediatrics, Saskatoon, Sask.

787 normal newborns, delivered at University Hospital, have been followed for 12-36 months. CMA was demonstrated by the relief of symptoms when cow's milk and dairy products were removed from the diet, and by the return of symptoms on two separate occasions when they were reintroduced. 59 babies (7.49%) were found to have CMA. The main manifestations of CMA, singly and in combination, were diarrhea (24), vomiting (13), eczema (27), rhinorrhea (18), bronchiolitis (10) and asthma (7). Most babies had more than one symptom. Babies with CMA had more "colds", ear infections, attacks of bronchitis and bouts of vomiting and diarrhea than did normals. They had to visit their doctors on account of illness ($P<0.0001$) and be admitted to hospital for treatment ($P<0.005$) more frequently than was the case with non-allergic babies. Influence of breast feeding: this was not associated with decreased incidence of CMA, but it was associated with an increase in neonatal jaundice ($P<0.01$). Family history of allergy: the incidence of allergies was greater, but not significantly so, in the parents of babies with CMA. The mothers, whether of allergic or non-allergic babies, had a significantly greater incidence of eczema, urticaria, recurrent bronchitis, food and drug allergies and recurrent headaches than the fathers, ($P<0.001$). It is concluded that CMA is an important, relatively common and sometimes unrecognized cause of illness in infancy.

CELL-MEDIATED IMMUNE RESPONSES IN TRISOMY 21. Richard J. Bonforte, Photini Papageorgiou, and Lawrence R. Shapiro (Intr. by Philip R. Glade). The Mount Sinai Sch. of Med., Dept. of Ped., New York, N.Y. and The Cytogenetics Lab., Letchworth Village, Thiels, N.Y.

Conflicting reports have appeared concerning the ability of lymphocytes from patients with Down's syndrome to respond to phytohemagglutinin (PHA) in vitro. These reports suggest an impairment of delayed-type hypersensitivity in this syndrome. Cell-mediated immune function was assessed in 14 patients (7 males, 7 females) with trisomy 21 using in vivo skin tests and the in vitro techniques of lymphocyte transformation and assay of release of migration inhibition factor (MIF). 12 of the 14 patients gave a delayed-type hypersensitivity response to intradermal monilia extract, 12 of 14 gave response to intradermal streptokinase-streptodornase (SK-SD), and 9 of 14 gave response to intradermal trichophyton extract. There was 100 per cent response to intradermal PHA. The in vitro response of circulating lymphocytes to PHA determined by the rate of incorporation of ^{14}C-tritiated thymidine into DNA was similar in all patients to levels achieved in 5 healthy control subjects. A high spontaneous release of MIF as measured by inhibition of migration of human lymphoid cells in vitro was detected in 11 of the 14 individuals studied. Since cell-mediated immunity appears to restrict the replication of intracellular viruses, impairment of cell-mediated immunity would be expected to be associated with increased humoral antibody production. Serum antibody titers against herpes-like virus (HLV), cytomegalovirus (CMV), and Australia antigen were normal in the 14 patients. These data suggest that there is no significant impairment in the cell-mediated immune responses of patients with trisomy 21.

IMMUNOLOGIC STUDIES OF SCLERODERMA IN CHILDREN. Virgil Hanson (Intr. by Robert Ward) and Helen K. Kornreich. Univ. of So. Calif. Sch. of Med. and Childrens Hospital of Los Angeles, Department of Medicine.

The results of this study suggest a profound stimulus to antibody production in the course of childhood scleroderma, but there is no known study with which to compare these findings. Twenty-one children with focal scleroderma and 7 with systemic scleroderma were studied and the findings compared with those in 23 normal children of the same age and sex. Immunoglobulins, G, M, and A and C'3 were measured by radial immunodiffusion, anti-gammaglobulins by sensitized latex particle and sheep red cell agglutination, and antinuclear antibodies by fluorescent antibody and immunodiffusion methods. Substrates for the fluorescent antibody studies were human buffy coat smears, snap-frozen rat liver sections, and pure nucleohistone, DNA and denatured DNA. The mean levels of IgG, IgM, and IgA were all significantly much higher in the scleroderma than the control groups with no difference between those with focal and systemic scleroderma. The mean level of C'3 in scleroderma did not differ significantly from the normal group. Antihuman gammaglobulins were found in 5 children with titers ranging from 1:40 to 1:40,000 by latex agglutination and antibodies to rabbit gamma globulin in 5 children in titers from 1:32 to 1:1024. No anti-gammaglobulins were present in the control group. Eighty percent of children with scleroderma showed antibody to 1 or more nuclear antigens in the G and M immunoglobulin classes. Only 1 child had antinuclear antibody in the IgA fraction. Two children with systemic scleroderma showed pure antibody to nucleoli and 3 others antibody to the speckled nuclear antigen, but none of the children with systemic scleroderma showed antibody to native or denatured DNA. Seven children with focal scleroderma were found to have antibody to DNA. In the children with focal scleroderma high levels of immunoglobulins and the high titers of anti-gammaglobulins and antinuclear antibodies were associated with severe destructive lesions affecting a single extremity. No evidence of immunodeficiency was detected in the children with scleroderma.

IMMUNOLOGY

Second Session

SOLUBLE COMPLEXES STIMULATE PHAGOCYTOSIS: IN VITRO AND IN VIVO STUDIES. Lauren M. Pachman, Panida Jayanetra, Richard M. Rothberg, Northwestern Univ., Children's Memorial Hosp., Dept. of Ped. and Univ. of Chicago, Wyler Children's Hosp., Dept. of Ped., Chicago, Illinois.

Reduction of nitroblue tetrazolium dye (NBT) accompanies peripheral blood phagocytosis of particulate matter. The finding of increased numbers of NBT positive cells in rheumatoid patients (RA), primarily those with rheumatoid factor (RF), prompted investigation of the role of soluble antigen-antibody complexes in phagocytosis as measured by NBT dye reduction. Following intravenous injection of I^{131} bovine serum albumin (BSA) into six rabbits, the mean onset of immune clearance was 7.6 days (range 6-8.5) and the onset of increased NBT positive cells began at 4-6 days, reaching a maximum of 35% (range 22-47%) at 6.5 days (range 4-9). Preinjection control levels were 2-10%. In vitro studies of phagocytosis of anti-BSA -- BSA complexes by human peripheral blood leukocytes, as measured by ^{14}C-1-glucose → $^{14}CO_2$, demonstrated a 2-3 fold stimulation in the range of slight BSA excess (greater than 4:1). The number of NBT positive cells was not consistently increased. These studies suggest that increased numbers of NBT positive cells in RA patients might be due to phagocytosis of RF and associated proteins. When high titre RF sera was incubated with normal human leukocytes, the maximum number of NBT positive cells were found when the RF titre was 604 units. The mean was 27% versus controls of 0-2%. Increased $^{14}CO_2$ evolution was also seen. It is concluded that soluble complexes stimulate phagocytosis in the range of antigen excess and that NBT positive cells in RA may be due to phagocytosis of RF.

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DEFICIENT SERUM OPSONINS IN SICKLE CELL DISEASE. Richard B. Johnston, Jr., Alan Struth, and Simon L. Newman. Dept. of Pediatrics, U. of Ala. Med. Ctr., Birmingham. (Intr. by Max D. Cooper)

Patients with sickle cell disease (SCD) have been shown to have increased susceptibility to pneumococcal infection and a deficiency in one or more serum factors (opsonins) necessary for phagocytosis of pneumococci. In this study sera from SCD patients and normals were tested for their ability to promote the phagocytosis of pneumococci in the presence of varying amounts of human IgG antibody (Ab). The serum requirements for phagocytosis in this assay have been previously defined as antibody and complement components (C) 1,4,2 and 3. In the presence of optimal amounts of Ab, serum from 28 SCD patients promoted the phagocytosis of pneumococci normally, indicating that levels of C1,4,2 and 3 were normal in these sera. However, if the amount of Ab added to the system was decreased, a point was reached at which the SCD sera promoted phagocytosis 4-50% as well as did the average normal serum. The deficiency did not appear to be related to Ab, since levels of agglutinating and phagocytosis-promoting Ab (tested in the presence of added complement) were equally low in the SCD and normal sera. C3 levels in SCD sera were normal by immunoprecipitation. The ability to enhance phagocytosis could be restored to SCD sera with small amounts of fresh normal serum but not with serum from a patient with hypercatabolic C3 deficiency. The restorative factor in normal serum was found to be a pseudoglobulin, to reside in the 5-6S fraction of gel filtration and in the supernate after 45% $(NH_4)_2SO_4$ precipitation, to be labile at 52° C., and to be removed by incubation with zymosan. A serum protein with these physical-chemical characteristics has been shown to promote phagocytosis in the presence of Ab and C1423. It is presently hypothesized that this protein plays a role in the alternate pathway for direct activation of C3. Thus, in the absence of optimal Ab, a situation which might exist on first encounter with a new pneumococcal serotype, SCD patients may be unable to normally activate and fix the critical opsonin C3 to the bacterial surface by this alternate route of opsonization.

CHEMOTAXIS AND RANDOM MOBILITY. CHARACTERIZATION OF TWO DISTINCT MECHANISMS OF LEUKOCYTE MOVEMENT, THEIR CLINICAL SIGNIFICANCE AND THEIR CORRELATION WITH NEUTROPENIA. Michael E. Miller, Children's Hosp. of Phila., and Charles R. Drew Postgrad. Med. School, Los Angeles, California 90059.

In previous studies from this laboratory, two clinical disorders of leukocyte (PMNS) movement have been partially defined: a) the "Lazy Leukocyte Syndrome" characterized by deficiency of chemotactic activity (C) and random mobility (RM) of PMNS, and b) a familial disorder of chemotaxis characterized by deficient C but normal RM. Further studies now demonstrate that: 1) Deficiencies in C occur separate from those of RM, and C and RM involve different mechanisms of PMN function. Both C and RM are relatively low in normal human neonates. C is deficient but RM normal in children having diabetes mellitus and in several newly reorganized, non-familial disorders as well as in the previously reported familial defect. 2) Responses of PMNS to epinephrine, piromen, hydrocortisone or Rebuck "skin window" show no correlation with C but significant correlation with RM. 3) Temperature, pH, incubation with glycolytic and other metabolic inhibitors effect C and RM differently. 4) Peripheral neutropenia correlates significantly with RM but not with C.

Full characterization of C and RM should lead to further understanding of leukocyte movement in normal and abnormal inflammatory states.

IN VITRO STUDIES OF CELL-MEDIATED IMMUNITY IN MAN. Samuel P. Gotoff and Somsak Lolekha. Dept.of Ped., The Abraham Lincoln Sch.of Med., U. of Ill., Chicago.

We have adapted the macrophage aggregation assay for the study of cell-mediated immunity in man. In the guinea pig, aggregation of peritoneal exudate cells(PEC) correlates with the presence of delayed hypersensitivity but not with humoral antibody. The reaction depends on the synthesis of a factor, MAF, from sensitized lymphocytes which causes aggregation of nonsensitive PEC macrophages. Human peripheral blood lymphocytes ($12x10^6/4$ ml) were cultured with and without antigens for 24 hours in RPMI 1640 media without serum. The supernatant fluids were concentrated five-fold and added to guinea pig PEC ($2\text{-}3 \times 10^6$/ml) in 20% fetal calf serum. Aggregation was observed grossly after incubation for five hours. The lymphocytes were resuspended and cultured for five days, with H^3 thymidine (H^3T) added 24 hours prior to harvesting. Candida albicans, PPD and histoplasmin were used as antigens to compare MAF synthesis, H^3T incorporation and delayed hypersensitivity reactions in 30 subjects. A correlation between all three variables was observed in 80% of the comparisons. False positive aggregation did not occur. Streptolysin O was used in 12 subjects to compare MAF synthesis with H^3T uptake. 11 of the 12 synthesized MAF, and H^3T uptake was observed in all. Patients with Hodgkin's disease and sarcoidosis have impaired MAF synthesis as well as diminished cutaneous reactivity and H^3T incorporation. These results indicate that the MAF assay may be used to measure cell-mediated immune function and to study further the mechanism of delayed hypersensitivity in man.

Human MAF has been partially purified by chromatography and electrophoresis. The MAF was prepared from tonsillar lymphocytes stimulated with tetanus toxoid. After chromatography on Biogel P100, MAF activity appeared in the second fraction which followed the peak of major protein synthesis. Following disc electrophoresis at pH=8.9, activity was found throughout the lower half of the disc indicating considerable heterogeneity. These fractions migrated anodal to and with albumin. (Supported by USPHS grant AM 10318.)

GROWTH INHIBITING AND CYTOTOXIC FACTORS PRODUCED BY HUMAN PERIPHERAL BLOOD LEUKOCYTES IN VITRO. Rudolf F. Eife and Charles S. August (Intr. by William E. Hathaway). Univ. of Colorado Med. Ctr., Dept. of Ped., Denver, Colorado.

Interest in the mediators of cellular immunity (CI) led us to study the cytotoxic and growth inhibiting activity in the cell-free culture medium of stimulated human peripheral blood leukocyte (PBL) cultures. Such activity, called "lymphotoxin" (LT) after Kolb & Granger (PNAS, 61:1250, 1968), is estimated quantitatively in cultures of growing HeLa cells by measuring the release of 3H-thymidine (3H-TdR) from pre-labeled cells, or as decrements in cellular synthesis of protein and DNA. It has been found that exposure of PBL to mitogens such as phytohemagglutinin, allogeneic cells, and soluble antigens (e.g. candida extract) (in order of potency) stimulate the release of LT. Comparative studies have shown that cell free culture medium from such stimulated leukocyte cultures inhibit HeLa cell DNA synthesis (and therefore growth) earlier and to a greater extent than amino acid uptake or release of pre-labeled DNA which are estimates of overall cell viability and monolayer destruction. Furthermore, LT appears to be synthesized and released by lymphocytes rather than PBL which adhere to glass. We have also found that although this process is triggered by mitogens, it is unaffected by mitomycin-C, an inhibitor of DNA synthesis.

In patients, LT production appears to be related to intact CI. Preliminary studies have shown that the PBL of children with primary antibody deficiency syndromes produce LT normally and that the PBL of children with CI defects (e.g. thymic dysplasia, Wiskott-Aldrich syndrome), make LT poorly, if at all.

ATYPICAL CHRONIC GRANULOMATOUS DISEASE OF CHILDHOOD. George H. McCracken,Jr. and Arthur C. Weinberg, Depts. of Ped. and Path., Univ. of Texas Southwestern Med. Sch., Dallas, Texas

A female infant was well until 2 1/4 years of age at which time she developed a progressive bilateral pneumonitis due to Pseudomonas cepacia and died 6 months later. Postmortem examination revealed characteristic histopathologic findings of chronic granulomatous disease of childhood (CGD) limited to the lungs, pigmented lipid histiocytes throughout the reticuloendothelial system, and a 2 gram thymus containing small numbers of lymphocytes, reduced number and size of Hassall's corpuscles and absent corticomedulary delineation. Peripheral lymphoid tissues exhibited various degrees of involution.

Laboratory studies showed normal antibody production and abnormal polymorphonuclear leukocyte (PMN) and lymphocyte function. Leukocyte nitroblue tetrazolium (NBT) reduction progressively decreased over the 4 month period of observation from 43% to 14% and was associated with impaired intracellular killing of P. cepacia, Listeria monocytogenes, Staphylococcus aureus, Salmonella infantis and Candida albicans by patient's PMN. Enterococci were killed normally.

Studies of cell-mediated immunity demonstrated absence of cutaneous delayed hypersensitivity to C. albicans and 10% dinitrochlorobenzene and abnormal lymphocyte transformation with phytohemagglutinin on 2 occasions. A serum inhibitor of lymphocyte transformation could not be demonstrated.

The patient had laboratory and histopathologic evidence of CGD, but her illness was atypical in the following ways: 1) late onset of illness, 2) granulomas limited to the lungs, 3) progressively decreasing leukocyte NBT reduction, and 4) depressed lymphocyte function associated with abnormal thymic histopathology.

IN VITRO STUDIES ON THE ROLE OF CELL MEDIATED IMMUNITY IN HOST RESISTANCE TO VENEZUELAN EQUINE ENCEPHALOMYELITIS (VEE) VIRAL INFECTION IN MICE. William H. Adler and Stanley Rabinowitz, U.S. Army Medical Research Institute of Infectious Diseases

Using in vitro lymphocyte culture methods and selective elimination of either thymic-derived or bone marrow-derived lymphocytes with appropriate antisera, the reactivity to VEE viral antigen was studied. It was found, using tritiated thymidine incorporation as an index of cell stimulation, that spleen cells from vaccine strain VEE (TC-83) immunized mice could be stimulated with gamma-irradiated, inactivated, purified VEE antigen in vitro. The peak in vitro responsiveness to the antigen occurred 7-10 days after immunization and decreased thereafter. This stimulation of the immune spleen cells in vitro with the viral antigen could be inhibited by treatment of the spleen cells with anti-thymocyte sera or anti θ sera in the presence of complement prior to initiating the cell cultures. The stimulation could not be inhibited to any great extent by prior treatment of the cells with anti-mouse γ globulin sera plus complement, although this treatment did decrease the number of viable bone marrow derived lymphoid cells in culture.

These in vitro studies were coupled to in vivo cell transfer experiments which demonstrated that the ability of the cells to be stimulated by viral antigen in vitro was directly correlated with the ability of the immune cells to protect an adoptive nonimmune host from the lethal effects of virulent VEE viral inoculation. The treatment of the immune cells with the antisera and complement, which prevented their in vitro reactivity to antigen, also ablated their protective function.

These studies demonstrate that cell mediated immunity can play a role in protection from the effects of a viral infection and the degree and nature of this immunity can be measured by in vitro culture techniques.

GENETIC STUDIES OF THE ANTIBODY RESPONSE TO TYPE-III PNEUMOCOCCAL POLYSACCHARIDE USING A STRAIN OF MICE WITH HYPOGAMMAGLOBULINEMIA-M. David R. Barthold, Diana F. Amsbaugh, Philip W. Stashak, Richard M. Asofsky and Phillip J. Baker. (intro. by Robert McAllister) Lab. Micro. Immun., NIAID, NIH.

Antibody produced in mice to purified type-III pneumococcal polysaccharide (SSS-III) is entirely of the IgM class. Genetic studies of the antibody response to immunization with SSS-III in very low (CBA/HN) and high (Balb/cAnN) responding strains of mice, including F_1, F_2 and appropriate backcrosses revealed a sex-linked pattern of inheritance for the capacity to respond to SSS-III. Responsiveness to SSS-III appeared to correlate in part with very low levels of IgM. Hypogammaglobulinemia-M was found in the low responding CBA/HN parental strain. Further studies in F_1 and F_2 mice heterozygous for the sex-linked component indicates that there are probably several other independently segregating genes controlling the magnitude of the antibody response to SSS-III. The low responding CBA/HN strain also gave poor antibody responses to immunization with either sheep red blood cells or Brucella antigen. The CBA/HN mice may prove to be a useful model for the study of immune deficiency disease states in man.

IgA BEARING B-LYMPHOCYTES IN PATIENTS WITH DEFICIENCY OF CIRCULATING IgA. A.R. Lawton, S.A. Royal, K.S. Self, and M.D. Cooper. Depts. of Pediatrics and Microbiology, University of Alabama in Birmingham, Birmingham, Ala. 35233

Isolated IgA deficiency, the most commonly encountered immunologic defect, is remarkably heterogeneous with regard to pathogenesis. This phenotype has been described as an autosomal dominant or recessive trait, occurs in deletions of chromosome 18, and is found in patients with ataxia-telangiectasia. It may be acquired as a result of intrauterine infection. In the hope of elucidating the pathogenesis of various types of IgA deficiency, we have determined the percentage of precursor B-lymphocytes having membrane-bound IgA in 14 patients. IgA deficiency was classified as familial (4 cases), associated with ataxia-telangiectasia (1), associated with intrauterine rubella (2) or toxoplasma (1) infection, or sporadic (6). Serum IgA was undetectable in 10 patients and very low (3-16 mg%) in the others, while IgG and IgM levels were normal or increased. Titers of isohemagglutinins were normal, as were responses to S. typhi in 8 patients tested. Cellular immunity was normal in 12 patients and deficient in the child with ataxia-telangiectasia. Three patients had antibodies to a goat serum protein. None had antibodies to IgA. Peripheral blood lymphocytes were isolated and stained with fluorescent antibodies to IgM, IgG, and IgA as previously reported (Lancet ii:791, 1971). IgA bearing lymphocytes were present in all 14 patients; the mean percentage (6.7%) was similar to that found for 29 healthy controls (5.8%). Percentages of IgM and IgG bearing lymphocytes also did not differ substantially from control values. These results suggest that IgA deficiency, whether inherited or acquired, results from failure of precursor B-lymphocytes to differentiate to IgA secreting cells rather than a defective expression of gene(s) for α chain. In thymectomized animals IgA antibody responses are depressed to a much greater degree than are IgM or IgG responses; the pathogenesis of isolated IgA deficiency in some instances may be related to a subtle defect in "helper function" of thymus-dependent lymphocytes.

ANAPHYLAXIS-LIKE REACTIONS TO CORTICOSTEROID THERAPY. Louis M. Mendelson*, Eli O. Meltzer*, and Robert N. Hamburger. University California, San Diego, Department of Pediatrics, La Jolla, California 92037.

Although corticosteroids are very useful in the management of many diseases, especially those involving hypersensitivity, we should not lose sight of the fact that they, like any other drug, can cause an anaphylaxis-like reaction.

We studied a 17 year old male with a history of reactions characterized by the precipitous onset of urticaria, angio-edema, and increased bronchospasm following therapy for status asthmaticus with either Solu-Medrol or Solu-Cortef.

Intravenous challenge with 40mg. of Solu-Medrol and methylprednisolone sodium succinate and oral challenge with 40mg., of methylprednisolone produced dramatic confirmation of his history within two, eleven, and thirty-five minutes respectively. Intravenous challenge with 4mg. of Solu-Medrol and methylprednisolone sodium succinate, and oral challenges with 40mg. of prednisolone and prednisone, and 6mg. of dexamethasone produced no adverse reactions.

Direct skin testing reveals positive immediate reactions to pure methylprednisolone and hydrocortisone, whereas on passive transfer these reactions were negative at four and forty-eight hours. Negative skin test reactions were obtained to Solu-Medrol, Methylprednisolone sodium succinate, methylprednisolone sodium acetate, prednisolone, prednisone, triamcinolone, dexamethasone, Solu-Cortief, hydrocortisone sodium succinate, and cortisone acetate.

Serial measurements during two intravenous challenges which produced anaphylaxis revealed no significant changes in CH_{50}, C1q, C'1 esterase inhibitor, C'2, C'3, C'4, C'5, C'6 and fibrinogen, or the presence of split products.

IMMUNOLOGY

Read by Title

GIARDIASIS AND MALABSORPTION IN THE PRIMARY IMMUNODEFICIENCY SYNDROMES (IDS). Marvin E. Ament, Hans D. Ochs, Starkey D. Davis, Cyrus E. Rubin. Univ. of Washington Sch. of Med., Depts. of Med. and Ped., Seattle.

Gastrointestinal (GI) disorders are frequently encountered in patients with primary IDS, but the incidence and the nature of GI disease in these patients are not known. In an attempt to clarify these points, 36 patients with various primary IDS were systematically studied for the presence of small bowel disease.

GI symptoms were present in 1 of 8 patients with infantile X-linked agammaglobulinemia and in 8 of 18 patients with variable IDS. Ten patients with other forms of IDS were free of GI symptoms. Diarrhea and weight loss were the most common complaints. Of the 9 patients with GI symptoms, 6 had steatorrhea and 5 of 8 had lactose intolerance. Of the 23 asymptomatic patients, 4 had abnormal lactose tolerance tests with diarrhea; none had steatorrhea. A total of 539 small intestinal biopsies from 32 patients was obtained and reviewed blindly. The villus architecture of the biopsies varied from normal to severe flat lesions. The most abnormal biopsies were found in patients with diarrhea and steatorrhea. Bacterial overgrowth in the proximal small bowel with coliforms was present with equal frequency in both asymptomatic and symptomatic patients. Giardia lamblia trophozoites were found in small intestinal biopsies from 8 out of 9 patients with GI symptoms but in only 1 of 26 asymptomatic individuals. Cysts were detected in the stools of 3 symptomatic patients. Eradication of the parasites with metronidazole resulted in disappearance of symptoms, reversal of malabsorption, and return of villus lesions toward normal. The one symptomatic patient who was not infected with G. lamblia did not respond to treatment with metronidazole, broad spectrum antibiotics or a strict gluten-free diet.

Giardiasis was the cause of diarrhea and malabsorption in 8 of 9 symptomatic patients with primary IDS and may be overlooked if only stool examinations are performed. Diarrhea, malabsorption, and intestinal lesions respond to specific therapy for Giardiasis.

HYPERREACTIVITY TO COW'S MILK IN AN INFANT WITH LE AND TART CELL PHENOMENON John A. Anderson, Luis A. Cabal, Lester Weiss, John W. Rebuck, Henry Ford Hospital - Detroit

Positive LE slide tests were found in a 6 month old N/M with recurrent URI's, pulmonary infiltrates, increased IgG, and milk precipitins. ANF was absent in the child and mother. LE and Tart cell phenomenon could not be passively transferred to normal leukocytes. With milk elimination, LE cells disappeared and IgG levels and Tart cells decreased. Coincident with milk challenge, symptoms and pulmonary infiltrates reappeared with an increase in Tart cells. During the LE cell positive period, host response was studied in serial skin windows stimulated with diphtheria-tetanus (DT) or DT plus milk antigens. The DT-milk stimulated window demonstrated a massive accelerated inflammatory response characterized by early appearance at 9 hrs. of lymphocytes, plus immunoblasts (some in mitosis), and plasma cells. At 24 hrs. an LE cell was found. Subsequent milk and DT-milk skin windows again showed an accelerated inflammatory response with eosinophils at 3 hrs. and IgG and IgM forming cells at 12 hrs. Control skin windows were done on a normal infant and adult. Immediate milk skin tests on the patient were negative. An Arthus milk skin test and biopsy were positive. Lymphocyte cultures during the LE positive period demonstrated increased transformation as measured by H^3-Thymidine uptake. During oral milk challenge, C_3 levels as measured by radial diffusion decreased 19% by 6 hrs. The character of the C_3 arc on immunoelectrophoresis was altered. The findings in this patient demonstrate that ingestion of cow's milk can produce qualitative and quantitative overresponse of the host defense systems including an accelerated inflammatory reaction and massive antibody formation. The LE, Tart cell phenomenon appeared to be associated with milk precipitins resulting from this over response. An Arthus reaction involving milk and milk antibodies may be responsible for the pulmonary pathology.

ALLOGRAFT SURVIVAL IN RATS REJECTING CANCER, Kathryn D. Anderson, John R. Lilly, Section of Surgical Research, Research Fndn. of Children's Hosp. of the D. C., George Washington Univ. Sch. of Med., Washington, D. C.

Allograft survival in animals undergoing an anamnestic response to extrinsic tumor antigen stimulation was studied. Fischer rats were immunized to cancer by inoculation of viable methylcholanthrene induced fibrosarcoma cells into the hind leg and amputation of the leg after progressive tumor growth. The animals were then grafted with skin from Marshall (M520) rats who differ from Fischer rats at a major histocompatibility locus. A second tumor inoculum of viable cells were given at the time of allografting.

As controls, eighteen Fischer rats received full thickness skin grafts from M520 rats. 34 Other rats were divided into three groups: Group I (20 rats) were injected with 10^6 viable tumor cells and in two weeks the leg containing growing tumor was amputated. One week later the animals were challenged with 10^4 viable fibrosarcoma cells (which were rejected) and with a full thickness skin graft from a M520 rat. Group II (8 rats) were treated as Group I except a sham inoculum of buffered saline was given instead of tumor cells at the time of skin grafting. Group III (6 rats) received a skin graft in the presence of actively growing tumor.

Mean skin allograft rejection in the control group was 9.3 days (range 7-11 days); in Group I, 11.7 days (range 7-13 days); in Group II, 11.5 days (range 11-12 days); and in Group III 9.5 days (range 9-11 days). The differences between groups are not biologically significant.

The results in this experimental model suggest that tumor antigens and histocompatibility antigens elicit an independent and specific immunological response; that cross-reactivity between histocompatibility antigens and tumor antigens does not occur and that allograft survival is not affected by an ongoing accelerated tumor rejection.

The findings indicate tumor antigen stimulation (immunotherapy) may ultimately be feasible in children having vital organ transplantation for cancer.

SEVERE COMBINED IMMUNODEFICIENCY DISEASE (SCID) AND SKELETAL ABNORMALITIES. Normand Lapointe, Michel Guay, Gilles Perreault, (Intr. by J.R. Ducharme). University of Montreal, Ste-Justine Hospital, Department of Pediatrics, Montreal.

The association of immunodeficiency disease and skeletal abnormalities has been recently described. A 2½ months male infant with SCID and skeletal abnormalities was recently seen. The boy presented, progressively from day 15, with seborrhea, purulent nasal discharges, pulmonary disease, diarrhea, thrombopenia culminating in death at 3½ months of age. Staphylococcus aureus, Pseudomonas, E. Coli were the proeminent pathogens.

Laboratory findings included leucocyte counts between 3 to 9000/MM^3 with 7 to 14% lymphocytes and 12 to 40% eosinophils. Bone-marrow showed no plasmocytes and increased eosinophils. Immunoglubulins: IgG 50 to 115 mgms%, IgM 0, IgA 0 to 15, blood group A and no isohaemagglutinins. Cellular immunity was abnormal. Blastic transformation of lymphocytes by PHA was abnormally low. There was no clinical suspicion of an underlying bony dysplasia. Radiographically, the positive findings were: Short and wide pelvic bones with broad and flat acetabulae with narrow and deep sacrociatic notches. Widening of the metaphyses with decreased density and slight cupping. Flaring of the rib ends. Minimal interstitial infiltration of the lung with absence of thymic shadow and adenoid tissus. The measurements of the long bones and vertebral bodies were normal.

At autopsy a typical thymus of SCID, without lymphocytes, nor hassall's corpuscles was found. Gut-associated lymphocytes were absent.and the lamina propria was depleted of plasmocytes. Lymph node architecture was abnormal, plasmocytes and lymphocytes were absent. An older brother had transient hypogammaglobulinemia of infancy, a younger sister has SCID without skeletal abnormalities, for which she has received a bone-marrow transplantation.

Exacerbation of anaphylactoid purpura following exposure to cold associated with cryoproteinemia. **William R. Griswold and Rawle M. McIntosh. Department of Pediatrics, Columbia University, New York, New York.**

Cryoproteins have been isolated in a variety of disorders and are thought to play a role in the pathogenesis of immunologically mediated tissue injury. Cryoproteins have not been previously reported in anaphylactoid purpura. The present study described characterization of a cryoprotein isolated from a patient who had an exacerbation of anaphylactoid purpura following prolonged overexposure to low temperature.

Cryoprecipitates were isolated as previously described (J. Lab. Clin. Med. 75: 566, 1970). The washed cryoprecipitate was dissolved in 0.05 M barbital buffer pH 8.0. The cryoprotein was tested for serum proteins and fibrinogen by double diffusion in agar gel using monospecific antisera. Immunoglobulin and C_3 levels were determined by radial immunodiffusion. The cryoprecipitate contained IgG, IgM, C1q and fibrinogen.

Our previous studies demonstrating that cold insoluble proteins have biologic properties of antigen-antibody complexes and are of immunopathological significance suggest that the lesions may be immunologically mediated.

DESTRUCTIVE CHORIORETINAL LESIONS IN FAMILIAL CHRONIC GRANULOMATOUS DISEASE - A HYPOTHESIS. Harold W. Lischner, and Lois J. Martyn (Intr. by Angelo M. DiGeorge). Temple Univ. Sch. of Med. and St. Christopher's Hosp. for Children, Philadelphia.

We have described the consistent finding of destructive chorioretinal lesions in familial chronic granulomatous disease (Martyn, L.J., et al, Trans. Am. Ophthal. Soc. 69:84, 1971). The lesions were present in all of six patients followed at this hospital. Progression of these lesions has now been observed in 2 patients during periods of quiescence of other manifestations of the disease. Although it remains possible that some or all of the chorioretinal lesions are the result of septic emboli, this seems unlikely in view of the consistency with which such lesions have been observed in the absence of active ocular inflammation, overt infection elsewhere or evidence of embolization to the brain. The chorioretinal manifestations may rather be related to the pigment-laden histiocytes found in reticuloendothelial tissues of all patients with chronic granulomatous disease. It is postulated that the defect in peroxide production by activated phagocytes which characterizes the disease may extend to the phagocytic pigment epithelial lining cells of the retina which are normally responsible for dissolution of the photosensitive outer segments of the visual rods (Young, R.W.J., Ultrastructure Res. 34:190, 1971). Intracellular accumulation of of lipid residues of these outer segments may be a factor in the development of the chorioretinal lesions. An analagous defect appears to be responsible for an inherited retinal dystrophy in the rat (Herron, W.L., Riegel, B.W. and Rubin, M.L.: Invest. Ophthal. 10:54, 1971). In vitro studies to test this hypothesis are planned. (Aided by USPHS grants RR-75 and HD-3848.)

IMMUNOLOGIC PHENOMENA ASSOCIATED WITH ACUTE SERUM SICKNESS (IMMUNE COMPLEX DISEASE) IN THE HUMAN. William T. Kniker and Nancy C. Pace. University of Texas Medical School, Department of Pediatrics, San Antonio.

Most knowledge of pathogenetic mechanisms in serum sickness (SS) comes from animal studies. In rabbits, typical glomerulitis, arteritis and carditis depend upon the passive deposition of circulating immune complexes, with rapid disappearance of foreign antigen. The opportunity to study such mechanisms in humans was afforded by a recent diphtheria epidemic during which 137 persons who received an average IV dose of 60,000 u (5.0 gm) of horse antitoxin globulin (HAG) were followed. Last year at these meetings it was reported that prophylactic oral antihistamines largely prevented the occurrence of SS in these patients (Ped. Res. 5: 381, 1971).

For several weeks after receiving HAG, sera were periodically collected on each patient and stored at -70°C. Hemolytic complement (C) activity, expressed in CH50 u/ml, was measured by standard techniques. Levels of HAG were determined by serial immunodiffusion using rabbit HAG-antiserum. Heterophile antibody (H.Ab) was measured by hemagglutination methods while presence of globulin aggregates (complexes) was evaluated by latex agglutination inhibition employing a rheumatoid factor reagent. None of 61 children under age 10 exhibited manifestations of SS such as fever, rash, arthralgia, etc. They had little lowering of C, yet as compared to older patients, had the most rapid rate of HAG elimination, highest levels of globulin aggregates, and marked H.Ab response. Of the "adults" 10 years of age or older, 66 did not get SS. Their C was low during the first 1½ weeks, while HAG disappeared more slowly than it did in children, and levels of H.Ab. and globulin aggregates were relatively low. The 10 "adults" who developed SS in the second week were different: markedly low C levels after 1½ weeks; extremely slow elimination of HAG; highest levels of H.Ab and moderate levels of globulin aggregates. It is apparent that persons who develop SS make a different type of response to HAG (persistence of IgM? more reagins?) than those who do not, and that "immune complex disease" in humans differs significantly from that in rabbits.

ALTERATION OF PLASMA C'3 COMPLEMENT COMPONENT FOLLOWING CHALLENGE WITH FOOD ANTIGENS IN THE SENSITIVE PATIENT. Douglas H. Sandberg and Charles W. Bernstein. Dept. of Ped., Univ. of Miami Sch. of Med., Miami, Florida.

Recently Soothill demonstrated a qualitative alteration in plasma C'3 complement (C'3) by immunoelectrophoresis following challenge with milk of some infants sensitive to cow's milk. We have used crossed-immunoelectrophoresis to separate the altered complement fraction (β1A) from C'3 and to measure β1A before and after challenge. Results were correlated with clinical evaluation and symptomatic response to small amounts of allergens. Children without a history of allergy did not have measurable β1A in fasting plasma or after milk ingestion. Other causes of malabsorption were eliminated from consideration by appropriate testing. Sixteen children were given 5 cc cow's milk with measurement of C'3 and β1A before and 90 minutes after challenge. In 10 patients β1A increased following challenge. Nine had detectable circulating β1A in the pre-challenge plasma. In only three patients was challenge followed by onset of diarrhea 2-4 hours following ingestion of 5 cc of milk. Five children had no alteration of C'3 or β1A after challenge although three of these had measurable β1A in pre-challenge plasma. Fifteen of 16 developed symptoms following challenge with larger amounts of milk on two or more occasions with subsidence of symptoms after withdrawal of milk. One of the milk sensitive patients had no response to 100 mg casein but a definite response to 15 mg β-lactoglobulin. This child also had an increased β1A after 3 oz of oatmeal and no change after 3 oz beef. Twelve patients had a strongly positive family history of allergy. Eight had positive scratch tests to cow's milk. All patients improved after removal of cow's milk from the diet, although some patients required removal of other foods as well. In addition, six children with history of wheat intolerance were challenged with one slice of bread. Five of the six patients showed no change in C'3 or β1A after challenge while one patient did show an increase in β1A. This technique appears to be useful for demonstration of sensitivity to specific foods in that group of patients whose allergic reaction involves complement.

CLOSTRIDIAL GAS GANGRENE AND HYPOGAMMAGLOBULINEMIA: Robert H. Schwartz, Eric A. Schenk, Marilyn R. Brown and Robert L. Miller, Department of Pediatrics, Univ. Rochester Sch. of Med., Rochester, New York

A 25 mos. male was diagnosed as having hypogammaglobulinemia (IgG=54; IgA=0; IgM=64 mg%) at age 5 mos. during his first illness of bilateral bronchopneumonia. Neutropenia soon developed and persisted for the next 20 mos. despite gamma globulin and antibiotic therapy for recurrent pneumonia and otitis media attributed to Diplococcus pneumoniae, Hemophilus influenza and hemolytic Streptococcus. Bone marrow revealed maturation arrest at the myelocyte-metamyelocyte level. Delayed skin tests (Monilia, Trichophytin) were positive. He had chronic diarrhea with normal lactose tolerance, D-xylose absorption, stool fat, duodenal enzymes and lack of bacterial and parasitic G.I. pathogens. Gastric and small bowel biopsies were normal except for absence of plasma cells in the lamina propria. These and two rectal biopsies (at 6 cm.) showed decreased IgG, IgA and increased IgM containing cells. Rectal biopsies had microcrypt abscesses.

The terminal illness began 37 days after biopsies. Fever and necrosis of the nasal septum was followed by prostration, and brawny ecchymosis with crepitus in the left flank and thigh. X-rays showed linear collections of gas around the psoas muscle and soft tissues of the left hip. Tissue biopsy was necrotic and Clostridia were found on Gram stain and culture. Post-mortem revealed perforation of the colon (18 cm. from anal orifice) and marked adhesions of the left iliac fossa. Other lymphoid findings were consistant with congenital sex-linked hypogammaglobulinemia.

This case relates gas gangrene due to Clostridium as another bacterial complication of hypogammaglobulinemia. Route of infection was via the gastrointestinal tract. Its development occurred in a setting of abnormal local, systemic and inflammatory immune mechanisms.

INFECTIOUS DISEASE

First Session

ADENINE ARABINOSIDE (ARA-A) TREATMENT OF SEVERE POX AND HERPETIC INFECTIONS OF MAN. Lawrence T. Ch'ien, John W. Benton, Robert A. Buchanan and Charles A. Alford, Univ. of Ala. Sch. of Med., Dept. of Ped., Birmingham, Ala. and Parke-Davis & Co., Ann Arbor, Mich.

Studies in cell culture and animals suggest that adenine arabinoside (Ara-A) might possess important advantages over idoxuridine (IDU) and cytosine arabinoside (Ara-C) for treatment of severe DNA viral infections. These include: equal but more prolonged anti-viral activities, lesser toxicity and immunosuppression and the ability to be given by multiple routes. Because of these properties, permission was granted for limited trials in humans; results of the initial studies are given here.

Ara-A was given by continuous I.V. drip over 12 hours for intervals varying from 5-15 days. Three patients, 3-22 yrs. of age, received 5 mg/Kg for 1 week for treatment of severe progressive vaccinial, Type 1 herpes or Zoster infections. Clinical and virologic improvement occurred promptly within 24 to 48 hours followed by rapid clearance of infection in all.

Three infants, 1-6 months of age, with severe congenital cytomegalovirus infections received 5-15 mg/Kg of Ara-A for intervals varying from 6-14 days; 2 courses were given to 1 infant. During treatment in 2 of these, virus disappeared from throat and urine (pretreatment level of virus 2.5-4 logs) and was suppressed 1000 fold in the other who received a smaller total quantity of drug. In all, virus excretion returned but at lower levels 2 weeks after cessation of therapy. However, striking increases in wt. and ht. growth occurred in the posttreatment period suggesting efficacy of therapy in spite of suboptimal doses for total viral clearance in this type of infection.

Unlike IDU and Ara-C, Ara-A produced no evident toxicity or immunosuppression even with high and prolonged dosages in infants nor did it magnify the immunosuppression produced by leukemia. It, therefore, appears a better candidate drug for treatment of severe pox or hepetic infection in man than the 2 currently available compounds and should receive further control studies.

EXPERIMENTAL ANTIVIRAL CHEMOTHERAPY FOR DISSEMINATED HERPESVIRUS HOMINIS INFECTION IN MARMOSETS. C.T. Cho*, K.K. Feng, D.W. Voth & C. Liu, Dept. of Ped. & Med., Univ. of Kansas Medical Center, Kansas City, Kansas 66103

Marmosets (Oedipomidas oedipus) were inoculated intravenously (I.V.), subcutaneously (S.C.), or intracerebrally (I.C.) with a strain of Herpesvirus hominis (HVH) isolated from the brain of a patient who died of encephalitis. Infected marmosets developed anorexia, diarrhea, constipation, dehydration, hypothermia and, generally, died within 3 weeks as a result of disseminated herpesvirus infection and/or encephalitis. Virological and histopathological features resemble those of fulminating herpesvirus infection in man. Antiviral chemotherapy was started either 4 hours before or 24 hours after virus inoculation. A total dose of 400 mg/kg of Iododeoxyuridine (IDUR) was given daily for 5 to 8 days by I.V. route. The results indicated: 1) IDUR afforded no protection against mortality in all routes of infection tested; 2) in I.C. infected marmosets, the average survival time (AST) was 8 days for controls and 9.5 days for IDUR treated animals. At autopsy, virus was equally distributed in the brain tissues of both treated and untreated animals, however, there was suppressed virus replication in the visceral organs (ie. spleen, lymph nodes, adrenal, kidney, etc.) of the treated animals; 3) in I.V. infected marmosets, AST was 10.5 days for controls and 9.8 days for treated groups. No significant difference in virus titers in organs of treated or untreated groups; 4) in S.C. infected animals, AST was 18 days for controls and 15 days for treated marmosets. There was suppressed virus replication in visceral organs when therapy was initiated 4 hours prior to infection. This study suggests that marmosets may provide a useful non-human primate model for studying experimental antiviral chemotherapy in severe herpesvirus infections. Within the limitations of experimental designs in marmosets, our results demonstrated that IDUR slightly modified the disease process, but gave no protection against mortality and produced no significant prolongation of survival time.

ELEVATED CSF VACCINIA ANTIBODIES IN MULTIPLE SCLEROSIS. C. Henry Kempe. Univ. of Colo. Sch. of Med., Dept. of Ped., Denver, Colo.

Over the past thirty years, we have analyzed over 400 cerebrospinal fluid (CSF) specimens from a large variety of clinical conditions for the presence of neutralizing antibodies against vaccinia virus; the majority of the specimens were from patients suffering from serious complications of smallpox vaccinations including postvaccinia encephalitis. In no instance has neutralizing antibodies been found in patients with vaccinia or its complications regardless of the height of antibody level in the peripheral blood. Among 85 CSF specimens from patients suffering from a variety of serious neurologic disorders (including bacterial meningitides, viral encephalitides, subacute sclerosing panencephalopathy [SSPE], Pick's presenile dementia, Creutzfeld-Jakob disease, amyotrophic lateral sclerosis, and multiple sclerosis) neutralizing antibodies to vaccinia have been found only in patients with multiple sclerosis; of 37 specimens from patients with a clinical diagnosis of multiple sclerosis, 19 had neutralizing antibodies against vaccinia at levels of between 1:8 and 1:256. The 9 patients with SSPE had negative CSF vaccinia antibody titers in the face of high measles antibody titers and high gamma globulin levels.

The finding of antibodies to vaccinia in the CSF of one-half of the diagnosed cases of multiple sclerosis may be of diagnostic or etiologic significance.

GENTAMICIN: A NEW ENZYMOLOGIC ASSAY AND SOME PHARMACOKINETIC PARAMETERS IN CHILDREN, Paul S. Lietman, Arlene A. Forastiere, Alan E. Zuckerman, and Herman M. Risemberg, The Johns Hopkins University School of Medicine, The Johns Hopkins Hospital and The Baltimore City Hospitals, Departments of Pediatrics and Pharmacology and Experimental Therapeutics, Baltimore.

A new micro method for the rapid measurement of gentamicin levels in biologic fluids has been developed. This method is based on the adenylylation of gentamicin catalyzed by an enzyme derived from R factor mediated gentamicin resistant bacteria. The reaction involved is as follows:

Gentamicin + ^{14}C-ATP $\rightleftharpoons$ Gentamicin-^{14}C-adenylylate + PP_i

The gentamicin-^{14}C-adenylylate is tenaciously bound by a phosphocellulose cation exchange resin loaded paper and, after the remaining ^{14}C-ATP is washed out, can be quantified by liquid scintillation counting.

The assay is specific in that it measures only gentamicin and kanamycin and not other antibiotics likely to be used concurrently with gentamicin. It is sensitive in that therapeutic levels (1-10 μg/ml) can be measured in 0.010 ml of plasma, allowing duplicate determinations on the plasma obtained in two micro-hematocrit tubes. The accuracy of the method is excellent when compared with a careful bioassay and the precision is good (S.D. ± 10% of the mean). The assay is conveniently performed and rapid. The reaction time is 30 minutes and the entire reaction can be completed in less than an hour.

The use of this assay has greatly facilitated the determination of some pharmacokinetic parameters of gentamicin in children. Our estimations of the rate of elimination, the rate of absorption from an intramuscular site, and the volume of distribution will be presented and an approach to a rational dosage schedule suggested.

THE RATE OF BACTERIOLOGIC RESPONSE TO ANTIMICROBIAL THERAPY IN NEONATAL MENINGITIS. George H. McCracken, Jr., Dept. of Ped., Univ. of Texas Southwestern Med. Sch., Dallas, Texas.

The rate of bacteriologic response to antimicrobial therapy of 38 infants with neonatal meningitis was studied. Four infants died within 24 hours of the diagnosis. From 1 to 13 followup cultures of cerebrospinal fluid (CSF) were obtained from the remaining 34 infants. Cultures from 14 of 15 infants with meningitis due to gram positive organisms were sterilized promptly. Thirteen of 19 infants (68%) with meningitis due to gram negative pathogens had positive CSF cultures for from 2 to 11 days after initiation of therapy. The first sterile cultures of CSF from these 19 infants were obtained from 1 to 18 days after start of therapy: 50% were sterile after 7 days and 75% were sterile after 11 days.

Clinical improvement appeared to coincide temporally with sterilization of CSF. Fourteen infants were followed for 2 to 3 years; neurological sequellae were observed in 6 of 8 infants with delayed bacteriologic cure and in none of 6 with prompt sterilization of CSF.

The concentrations of antibiotics and the in vitro bactericidal titers of 24 CSF specimens from these infants were determined. There was wide variation in the CSF antibiotic concentrations; the levels were generally highest 1 to 4 hours after parenteral administration and when the degree of meningeal inflammation was greatest. The bactericidal titers in CSF correlated with the CSF antibiotic levels when related to the minimal inhibitory concentrations of the pathogens. Demonstrable bactericidal effect in vitro did not ensure sterility of the CSF cultures.

The time necessary to sterilize the CSF of neonates with meningitis may be an important determinant of satisfactory response to antimicrobial therapy and delayed bacteriologic cure may contribute to the development of neurological sequellae.

A PROSPECTIVE STUDY OF MATERNAL CYTOMEGALOVIRUS AND ITS EFFECT ON THE FETUS. George A. Nankervis, Frederick E. Cox, Mary L. Kumar and Eli Gold, Dept. of Pediatrics, Case Western Reserve Univ. Sch. of Med. at Cleveland Metropolitan General Hospital, Cleveland, Ohio.

Over 1200 young pregnant women who attend the Prenatal Clinic at the Cleveland Metropolitan General Hospital are participating in a prospective study designed to determine the proportion of this group who have or acquire cytomegalovirus (CMV) infection during their pregnancy and the effect of maternal CMV infection on the products of conception. The subjects range in age from 13 to 20 years and 73% of the population is black. Approximately one quarter presented during the first trimester and one half during the second trimester. Nearly 70% had a positive CMV CF titer and 9% excreted CMV in their urine on at least one occasion. Slightly greater than 2% of the total number of babies who have been delivered thus far are congenitally infected with CMV. Most babies born to excreting mothers were free of CMV infection at the time of birth but babies with congenital CMV infection were delivered by mothers who did not have viruria during their pregnancy. Three subjects converted from negative to positive for viruria and CF antibody during the period of gestation. The one who has thus far delivered had a congenitally infected infant. Two of three mothers with infected placentas have delivered congenitally infected infants. All infants born to CMV excretors are evaluated clinically as well as by X-rays and multiple laboratory tests and are seen in follow-up at 1,2,3,6, and 12 months of age. To date none of the congenitally infected infants has presented with clinically apparent CID and no gross congenital malformations have been detected. Hematologic data and liver function tests have not been helpful in identifying the congenitally infected babies and cord IgM levels have not been uniformly elevated. Ten infants have acquired CMV infection after having been negative as neonates, the majority at less than 10 weeks of age.

ANTIBACTERIAL EFFECTIVENESS OF ROUTINE HANDWASHING, Katherine Sprunt, Grace A. Leidy, Winifred Redman Columbia College of Physicians & Surgeons, Dept. Pediatrics, N.Y.C.

The effectiveness of brief handwashing as carried out routinely by nursery personnel was examined using a quantitative technique for assay of total and differential counts of aerobic bacteria removed from both hands with 20 ml broth by a standardized procedure. Nursery routine required pHisoHex in dispensers for personnel and water for infant bathing. Random sampling of the hands of 24 nursery workers on different days (40 samplings) showed that bacteria easily shed by the hands varied little from individual to individual and on repeated testing of a single individual. All shed staphylococci (10^2-10^5/ml); most also shed streptococci (10^1-10^4/ml).Coliforms (rare-10^4/ml) were found in 15 samplings; 10 of these were from individuals who had handled babies just before testing. Removal of organisms apparently acquired from patients was examined using pHisoHex, Betadine Surgical Scrub, Ivory soap, a 70% alcohol-in-cream emulsion and tap water. Hands of 5 nurses were tested before handling a baby (changing dirty diaper or patting butt), immediately thereafter and after a routine handwash with a test substance. Each nurse was tested 2x with each substance. Enteric bacilli were acquired from the infants in 45 of 49 experiments. The washing procedures reduced the number of coliforms > 1 log in 40 of the 45. One test substance was as effective as another in removing coliforms. Staphylococci were apparently acquired from infants (incr. titer > 1 log) in only 7 instances. The increase was borderline; there was no change in titer with handwashing. Streptococci were acquired in 12 instances. Handwashing caused a minimum of a 2 log drop in 4 and complete removal or return to baseline in 7. In general, independent of the wash agent, a routine handwash eliminated infant acquired bacteria in 50% of the samplings and reduced the titers significantly in 90% of the remainder.

DISTRIBUTION AND CHARACTERIZATION OF HEPATITIS ASSOCIATED ANTIGEN (HAA), AND ANTI-HAA ANTIBODY IN HUMAN BODY FLUIDS. Pearay L. Ogra,* Dept. of Peds., Sch. of Med., State Univ. of N.Y. at Buffalo. (Intr. by David T. Karzon).

Routine screening for HAA in 3400 specimens of serum revealed the presence of the antigen in 8 specimens obtained from apparently normal healthy young adolescents, adults with clinical hepatitis and children with anicteric hepatitis who had no history of transfusion or needle contact. The techniques of counter-electrophoresis, and indirect immunofluorescence using smears of peripheral blood, were employed to determine the presence of HAA and anti-HAA antibody in concentrated specimens of serum, nasopharyngeal washings, urine and fecal extracts obtained for several months after the initial detection of HAA in the serum. Highest concentrations of HAA were demonstrable in the serum at the time of initial screening. Subsequently, the titer of HAA declined, and no activity was observed after 2 months. HAA was detected in the nasopharyngeal washings and urine of 5 patients studied. The antigen was recovered for as long as 26-65 days after initial detection. All subjects manifested appreciable quantities of HAA in their fecal extracts, and the antigen persisted in the feces for as long as 4 months. In many subjects the excretion of HAA in the nasopharynx and feces continued for 1-2 months after its disappearance from the serum. Anti-HAA antibody response in the serum was characterized by infrequent appearance of small amounts of γG antibody 2-3 months after the initial detection of antigen in the serum. No antibody activity was detected after 6-7 months. The response in the nasopharynx and urine was characterized by the transient appearance of detectable amounts of γA and small amounts of γG class of antibody. The response in the fecal extracts was characterized by frequent appearance of HAA-anti HAA complexes 2-3 months after initial detection of HAA. Subsequently, appreciable levels of free γA antibody to HAA were detectable for 7-8 months. It is suggested that HAA may replicate extensively in various mucosal surfaces, thus, resulting in continued excretion of the antigen, and the appearance of specific anti-HAA antibody in the external body fluids. These observations may explain the mechanisms underlying the non-parenteral transmission of long incubation hepatitis and HAA.

NEONATAL DEFICIENCY IN ENDOTOXIN INACTIVATION. Eugene Ainbender, Helen D. Zepp and Horace L. Hodes. The Mount Sinai School of Medicine. Dept. of Ped. New York.

A normal humoral defense mechanism exists for the detoxification and inactivation of bacterial endotoxins. Clinical endotoxemia probably results when this mechanism is overloaded. In vitro measurements, in this laboratory, of this endotoxin inactivation system have revealed that the sera of neonates are markedly deficient in this important defense mechanism.

A lysate obtained from the amoebocytes of the horseshoe crab (Limulus polyphemus) will gel when incubated with as little as 1 nanogram of active endotoxin. However, endotoxin that has been detoxified or inactivated does not cause lysate gellation. The ability of a serum to inactivate endotoxin was measured by mixing 0.1 ml of the serum with a known amount of endotoxin and then testing for residual active endotoxin by the Limulus lysate technique.

All sera obtained from 20 normal adults consistently inactivated 100 to 1000 nanograms endotoxin per 0.1 ml of serum. On the other hand none of the sera obtained from 20 normal term infants inactivated more than 10 nanograms of endotoxin per 0.1 ml serum. This same 10 to 100 fold difference was obtained when paired maternal and cord sera were compared. The maternal sera inactivated from 100 to 1000 nanograms of endotoxin whereas the cord sera could inactivate no more than 10 nanograms.

It is evident that the normal term infant can inactivate a small load of endotoxin, but this defense mechanism can be easily overcome by increasing the endotoxin load. In contrast, the adult has at least ten times the capability for endotoxin inactivation per unit of serum.

NURSERY EPIDEMIC CAUSED BY A NON-TYPABLE "GREY" COLONY VARIANT OF STAPHYLOCOCCUS AUREUS, Rajam Subramanyam, Sherwood L. Gorbach and Rosita S. Pildes(Intr. by Ira Rosenthal), Abraham Lincoln Sch. of Med. of Univ. of Illinois Col. of Med. and Cook County Hosp., Depts. of Pediatrics and Medicine, Chicago.

The introduction of hexachlorophene for bathing infants has been considered effective in the prevention of Staph.aureus nursery epidemics;however,sporadic outbreaks still occur.We report the occurrence of an epidemic in the nurseries of Cook County Hospital caused by a non-typable strain of pathogenic Staphylococcus with a previously undescribed colony morphology.The epidemic was controlled by conventional epidemiologic measures.Thirty-two infants, 4 days to 4 weeks of age presented with a variety of lesions including mastitis (5), parotitis (1) and lung abscess (1).All cultures yielded coagulase positive, hemolytic Staph.aureus, resistant to pencillin but sensitive to methicillin. The colonies on blood agar were grey in color and produced intense hemolysis. These distinctive characteristics made it possible to identify the causative pathogen and the carriers.During this period, 998 infants were born at this hospital; approximately 1/3 were cultured. Staph.aureus coagulase positive was cultured in 18% and the grey colony variant was found in 11.4% of the positive cultures.Culture survey was done of all the nursery personnel (83),30% were nasal carriers of coagulase positive Staph.aureus; 44% of these were grey colony variants.In addition to reinforcement of routine nursery techniques which included hexachlorophene bathing of infants, the epidemic was brought under control by 1)the use of nasal antibiotic cream by all nursery personnel and infants, 2)removal of personnel with persistant grey organisms, 3)strict adherence to a cohort system. Bacteriological and clinical surveillance showed the efficacy of these measures. Attempts to further differentiate this strain of Staph.aureus by phage typing, antibiogram, hemolysin production and biochemical reactions proved unsuccessful. Since recent abandonment of hexachlorophene bathing of neonates may result in recrudescence of nursery epidemics, methods of prevention and control of these infections should be re-evaluated.

INFECTIOUS DISEASE

Second Session

PREVENTION OF VARICELLA IN HIGH RISK CHILDREN WITH ZOSTER IMMUNE GLOBULIN. A.A. Gershon and P.A. Brunell. New York Univ. Sch. of Med., Dept. of Pediatrics

Varicella has been prevented in normal children by administration of zoster immune globulin (ZIG), following exposure to the disease. However, a dose of ZIG, adequate to protect a normal child, only modified varicella when given to a child with leukemia. Since it thus appeared that larger quantities of antibody might be required to prevent varicella in children at high risk, an evaluation of ZIG in such patients was undertaken. Eight children, six with leukemia, one with thymic aplasia and one who had received a renal transplant were given ZIG from the same lot within 48 hours after household exposure to varicella. Varicella did not occur in five children while mild disease occurred in three. Two of the three illnesses followed secondary household exposures one month after administration of ZIG. Two of the five children who did not develop varicella also were exposed secondarily. Therefore, this lot of ZIG appeared to have prevented or modified varicella in the eight recipients. In contrast, one child with leukemia was given ZIG from a different lot and developed severe progressive varicella. This second lot of ZIG had been prepared from plasma which had a relatively low titer of antibody to varicella-zoster virus. This observation suggests that different lots of ZIG may vary in potency, and illustrates the need for a laboratory method of standardization of ZIG. It appears that varicella can be prevented or modified in high risk individuals, but that high-potency preparations of ZIG might be required to protect these patients.

SAFETY AND ANTIGENICITY OF TEMPERATURE SENSITIVE (TS) MUTANT RESPIRATORY SYNCYTIAL VIRUS VACCINE IN INFANTS AND CHILDREN. Robert H. Parrott, Hyun Wha Kim, Carl D. Brandt, Robert M. Chanock. Children's Hospital of the District of Columbia, George Washington University School of Medicine and National Institute of Allergy and Infectious Diseases, Bethesda, Maryland.

The consensus is that the most promising approach to immune prophylaxis against respiratory syncytial virus (RSV) disease in infants is to stimulate local respiratory tract antibody with inactivated or attenuated vaccines prior to natural infection. A 26°C adapted RSV vaccine was found to have sufficient residual pathogenicity for young infants that we have initiated safety and antigenicity studies with a different candidate attenuated vaccine, a temperature sensitive mutant of RSV-strain A2 (ts-1 mutant) propagated at 30°C in primary bovine embryonic kidney tissue culture. Before use in children the mutant strain was administered to 13 young adults; no illness occurred although virus was excreted by four men. In our current studies, the ts-1 mutant RS-A2 virus has been administered to 30 infants and children 6 months to 6 years of age and has produced infection in 29 of these individuals as documented by recovery of virus from the throat and/or a significant rise in nasal secretion antibody. Serum and nasal secretion antibody rises occurred more frequently than in the group of infants and children who were infected with the 26°C RS-A2 virus. No illness accompanied ts-1 virus infection in individuals who had prior experience with RSV as evidenced by presence of serum antibody. Infection in infants without prior RSV experience resulted in mild afebrile coryza with no systemic signs. Pending the findings with additional infants in the age range 6 to 12 months we believe that this agent shows sufficient attenuation that it can be considered for administration to infants under the age of 6 months.

These studies supported in part by National Institute of Allergy and Infectious Diseases Grant AI01528, Contract NIH71-2091, and General Clinical Research Center Grant 5 M01 FR00284.

ATTACK RATES FOR HOSPITALIZED CROUP IN CHILDREN IN A MILITARY POPULATION. IMPORTANCE OF A2 INFLUENZA INFECTION. Jerry J. Eller, Vincent A. Fulginiti, Daniel C. Plunket, Otto F. Sieber, Jr., and Gordon Meiklejohn. Univ. of Col. Med. Center, Denver.

From July 1966 until May 1969, 79 infants and children were hospitalized for croup at Fitzsimons General Hospital. Viruses and M. Pneumoniae were determined as etiologic agents in 59 (75%). Identification of agents in order of frequency was as follows: Para 1, RSV, A2 *Flu, Para 2, Para 3, M.P., Adeno, and Flu B. (*An epidemic of A2 Asian influenza occurred in the spring of 1968. An epidemic of A2 Hong Kong influenza occurred during the winter of 1968 and spring of 1969.) Croup associated with A2 influenza was found to be unusually severe in infants and small children. Eleven had illness associated with A2 influenza, 48 had illness associated with other agents. Eight patients with noninfluenzal croup had severe respiratory distress, and 4 required tracheostomies. In contrast, 8 patients with A2 influenzal croup had severe respiratory distress (X^2_C = 11.53, $p < .005$) and 4 required tracheostomies (X^2_C = 3.84, p = .05). Each of 3 infants 6-11 mos. of age with A2 flu infection required a tracheostomy. In all, 5 infants, and 3 2-3 yr. old children had tracheostomies performed. Seventy-five percent of patients with severe distress were 3 years of age and under. Age specific attack rates are expressed as the number hospitalized with croup per year for Para 1 and A2 flu per epidemic year in an average metropolitan city with a total population of 1 million. (P-1) 6-11 mos: 3, 1-3 yrs: 21, 4-12 yrs: 11. (A2F) 6-11 mos: 7, 1-3 yrs: 11, 4-12 yrs: 29. These data suggest that recommendations for immunization of normal infants and children with influenza vaccine should be made.

PNEUMOCYSTIS CARINII PNEUMONITIS. Walter T. Hughes, Ho K. Kim, Sandor Feldman, Robert A. Price and Thomas P. Coburn. (Intr. by Donald Pinkel). Infectious Disease, Pathology and Radiology Services, St. Jude Children's Research Hosp. and Univ. Tenn. Med. Units, Memphis.

Epidemics of *Pneumocystis carinii* pneumonitis (PCP) have been encountered for several decades in European nurseries. In the United States sporadic cases have occurred in recent years, predominantly in the compromised childhood host. Fifty-one children with PCP have been systematically studied at St. Jude Children's Research Hospital. The data permit description of clinical manifestations, therapeutic efficacy of pentamidine isethionate, recurrence rate after therapy, incidence in childhood neoplastic diseases and epidemiological, radiological and pathological aspects of PCP. In each case *P. carinii* was identified by the silver methenamine impregnation method of Grocott from material obtained by percutaneous needle aspiration of the lung or from necropsy specimens.

PCP occurred in 45 (6.5%) of 684 children with leukemia, 1 (1.3%) of 77 with Hodgkin's disease, 3 (3.8%) of 78 neuroblastoma, 1 (3.8%) of 26 with reticulum cell sarcoma and 1 (14.3%) of 7 with Letterer-Siwe disease. The incidence was proportional to the number of patients at risk and was unrelated to the environmental factors investigated, season, age, sex or type of neoplasm. Eighty-five percent of the leukemia patients with PCP were in hematological remission.

The disease presented abruptly with fever, marked tachypnea, flaring of nasal alae, intercostal retractions and frequently with cyanosis. Roentgenograms revealed bilateral diffuse alveolar disease.

Immunoglobulin (Ig) G values were below the normal range in 26%, IgA in 13% and IgM in 13% of the cases. In only 1 patient were values markedly low. Total serum lactic dehydrogenase activity was increased during pneumonitis although isoenzyme fractions were unaffected.

Forty-one patients were treated with pentamidine and 28 (68%) recovered. A second episode of PCP occurred in 4 (14%) of the 28 children from 5 to 12 months after complete clinical recovery. Adverse side-effects attributed to pentamidine included azotemia, hypoglycemia and reactions at injection sites. These were usually reversible. (Supported by Cancer Research Center Grant CA-08480 and General Research Support Grant RR-05584, National Cancer Institute, NIH, and by ALSAC.)

COUNTERCURRENT IMMUNOELECTROPHORESIS IN THE DIAGNOSIS OF SYSTEMIC DISEASES CAUSED BY HEMOPHILUS INFLUENZAE TYPE B. *David L. Ingram and David H. Smith, Department of Pediatrics, Harvard Medical School, Children's Hospital Medical Center, Boston.*

Polyribophosphate (PRP), the capsular antigen of Hemophilus influenzae type b, was detected in a concentration as low as 0.03 ugm/ml in cerebrospinal fluid (CSF), sera, subdural fluid and knee aspirates using type-specific rabbit anti-H. influenzae type b, strain Eagan serum and countercurrent immunoelectrophoresis (C.I.E.). CSF or sera from 10 of 13 children with culture proven H. influenzae type b meningitis had detectable PRP by C.I.E. PRP was detected in the serum and CSF of 2 of the 3 children with H. influenzae type b meningitis who had infected CSF and sterile blood, and in 7 of 10 CSF and 5 of 9 sera from the 10 other children who had infected CSF and blood. Two subdural fluid specimens, one of which was infected, contained detectable PRP. One child with H. influenzae type b pyogenic arthritis had PRP detectable in the infected joint fluid obtained at admission, and at 48 hours when the fluid had become sterile on treatment. PRP was detected in the sterile CSF of 2 of 7 children with partially treated meningitis. With the anti-serum and technique employed, no cross reactions were obtained with culture supernatants or extracts of certain E. coli or pneumococcus types 6, 15, 29 and 35 previously reported to react with anti-H. influenzae type b serum by other methods. Likewise, PRP was not detected in the CSF or sera of 63 other children with meningococcal (4), pseudomonas (2), pneumococcal (2), E. coli (1), streptococcal (1) or aseptic meningitis (12) or fever and normal CSF (41). The detection of PRP by C.I.E. is easily performed in 1 hour, more sensitive than a gram stain and, with properly selected sera, specific for H. influenzae type b.

VACCINATION OF HEALTHY CHILDREN WITH CVI-78 AND CALF LYMPH SMALLPOX VACCINE

John M. Neff, Wendell C. Speers, Richard B. Wesley, Joel Goldstein, Frederick L. Ruben & Bernard Lourie (Intr. by David H. Carver)

JohnsHopkins, Dept. of Peds., Baltimore

Primary smallpox vaccinations were performed on healthy children comparing an attenuated chick embryonic tissue vaccine, CVI-78, to standard calf lymph vaccine of a similar C.A.M. Titer, $10^{8.0}$ pfu/ml. Fifty-four children received primary vaccination with CVI-78 vaccine and 52 with standard calf lymph. CVI-78 vaccination resulted in a less severe clinical response and a lower percentage of dermal and serological conversion. Only 65% of those vaccinated with CVI-78 developed a typical Jennerian vesicle as compared to 94% with standard vaccine, and only 16% of the CVI-78 vaccinees developed post-vaccination neutralizing antibodies as compared to 89% of the calf lymph vaccinees. Twenty-six of the CVI-78 vaccinees, and 22 of the calf lymph vaccinees received revaccination with standard calf lymph vaccine five to nine months after primary vaccination. Following revaccination, 96% of the original CVI-78 vaccinees and 73% of the calf lymph vaccinees developed vesicular dermal reactions. Those who had failed to demonstrate either a dermal or a serological reaction to primary vaccination, developed a typical primary like Jennerian vesicle on revaccination. This was observed in 5 of the 26 CVI-78 subjects and in 1 of the 22 standard calf lymph subjects. Serologically following revaccination all children had positive HI titers, but only 65% of the original CVI-78 vaccinees had positive neutralizing antibodies as compared to 100% of the calf lymph vaccinees. These results raise the question whether CVI-78 vaccine is a reasonable alternative to standard calf lymph vaccination.

CIRCULATING FIBRIN IN MENINGOCOCCEMIA. C. Thomas Kisker and Ruth Rush (Intr. by Beatrice C. Lampkin). Dept. Ped., Univ. Cincinnati and Children's Hosp. Research Fndn., Cincinnati.

Six patients with meningococcemia were studied and measurement of circulating fibrin (CF) done with a technique based on the ability of fibrin stabilizing factor to incorporate ^{14}C glycine ethyl ester into fibrinogen after the alpha peptide of fibrinogen has been hydrolized by thrombin (J. Clin. Invest. 50:2235, 1971). The method detects fibrinogen altered by thrombin but is insensitive to fibrinogen digested by plasmin. CF initially was found in all 6 patients studied, indicating the presence of disseminated intravascular coagulation (DIC). Other coagulation tests including the prothrombin time and partial thromboplastin time were not invariably abnormal. Hypotension was also an inconstant initial finding and platelets were initially adequate in 5 of 6 patients. All 6 patients were treated with antibiotics and heparin was begun coincident with obtaining the initial sample for measurement of CF. Three or more measurements of CF were obtained in 3 patients. The half life of CF in these patients ranged from 8 to 10 hours. The levels of CF as measured by ^{14}C glycine ethyl ester incorporation decreased with time in a single exponential manner. When the levels of CF in subsequent samples were plotted against time on a semi-log graph, a straight line through these values intercepted the value of the original sample. Thus the production of CF ceased prior to or at the time heparin therapy was begun. Although CF was no longer detected in any patient after 15 hours of heparin therapy, death occurred in 2 patients. The results of these studies indicate that prolonged heparin therapy is unnecessary in the treatment of meningococcemia and in fact heparin may not be the critical factor in abolishing DIC. Furthermore the control of DIC does not insure survival of the patient.

UNEXPECTED HIGH FREQUENCY OF ANTIBODY TO M. PNEUMONIAE IN YOUNG CHILDREN

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M. pneumoniae disease occurs with greatest frequency in individuals 5-15 years of age. In order to help explain this and other anomalous features of the epidemiology of M. pneumoniae infection two highly sensitive methods of antibody assay were developed. In comparative studies the new complement dependent mycoplasmacidal (MC) and radioimmunoprecipitation (RIP) techniques were found to be considerably more sensitive than the standard methods for measurement of antibody in human sera. Using the MC and RIP techniques antibody reactive with M. pneumoniae was found with an unexpectedly high frequency in young children 1-5 years of age; in contrast 7-12 month old infants were relatively free of detectable antibody. In addition, analysis of sera from a prospective study indicated that almost all adults who developed M. pneumoniae pneumonia possessed MC and RIP antibody prior to exposure to the organism. These findings suggest that prior sensitization to M. pneumoniae may play a role in the pathogenesis of disease caused by this organism.

INFECTIOUS DISEASE

Read by Title

DIMINISHED CYTOMEGALOVIRUS (CMV) EXCRETION IN CONGENITALLY INFECTED INFANTS TREATED WITH ADENINE ARABINOSIDE (ARA-A). Joseph V. Baublis. Univ. of Michigan, Dept. of Pediatrics, Ann Arbor.

Congenital infection with CMV is associated with disease which varies in extent of organ involvement and severity. Those infants most severly affected by their infection die or may survive with brain damage. The consequences of subclinical infection of the newborn with CMV are still uncertain. These characteristics of the disease have lead us to study the effect of treatment on certain infants with symptomatic CMV infections. Ara-A has been employed in this clinical trial because its toxicity and antiviral effect compares most favorably with other drugs which are active in-vitro against CMV.

Four courses of Ara-A have been administered to three infected infants. The amount of virus recoverable from a throat swab as well as the amount of virus in the urine diminished as much as two logs consequent to the administration of the drug, and in one case became undetectable. The duration of this apparent antiviral effect was transient. Clinical improvement was observed during the course of therapy in two of the three infants. No significant toxicity has been observed at doses of Ara-A up to 10 mg. per kg. per twenty-four hours administered for as long as twenty-one days. Resistance to Ara-A of virus strains isolated from a patient did not appear to increase during therapy. These preliminary results suggest that control of cytomegalovirus infection with drugs of relatively low toxicity is an attainable goal. Additional in-vitro and in-vivo studies employing adenine arabinoside are in progress.

TRANSIENT BACTEREMIA DURING DENTAL MANIPULATION. Frederic A. Berry, Catherine M. Russell, Sandra Yarbrough, Nelson Yarbrough, Martha A. Carpenter, and J. Owen Hendley. (Intr. by William G. Thurman). Univ. of Virginia Sch. of Med., Dept. of Pediatrics, Charlottesville, Va.

There is little information concerning bacteremia during dental manipulation in pediatric patients. Current recommendations on antibiotic prophylaxis during dental procedures in children with heart disease are based primarily on adult studies. In a recent study (Am. J. Dis. Child., 121:286, 1971) bacteremia was not observed in children following dental cleansing. The authors suggested that conclusions drawn from the studies in adults may not apply to children. In the current investigation pediatric patients ages 4-11 with moderate to severe dental pathology were screened for bacteremia during restoration and/or extraction of carious teeth under general anesthesia. Blood cultures were obtained before nasotracheal intubation, after intubation, after restoration of carious teeth but before extraction, following extraction of teeth, and in the immediate postoperative period.

Results of cultures in 20 patients studied to date are as follows:

	Intubation		After	After	
	Before	After	Restoration	Extraction	Post-op
Positive/Tested	0/11	3/20	1/7	11/17	4/20
% Positive	0	15%	14%	65%	20%

Seventy percent had at least one positive blood culture during the study period. No cultures were positive prior to intubation; two thirds were positive following extraction. Nineteen organisms were isolated; alpha strep (7), Corynebacterium sp. (4), anerobic diphtheroids (4), Brevibacterium sp. (3), and Hemophilus parainfluenzae (1).

Transient bacteremia was seen to occur during dental surgery, particularly dental extraction, in children as in adults. The use of antibiotic prophylaxis in children with heart disease undergoing dental manipulation should be continued.

MULTIPLICITY ASSOCIATED INTERFERENCE OBSERVED IN RESPIRATORY SYNCYTIAL VIRUS INFECTIONS OF HEp-2 CELLS

Marc O. Beem and Mary W. Treuhaft, Pritzker School of Medicine in the Division of Biological Sciences of the University of Chicago, Department of Pediatrics, Chicago

In attempting to produce large quantities of high titered Respiratory Syncytial (RS) virus, it was found that undiluted passage of the laboratory strain in HEp-2 cells resulted in unexpectedly low yields of infectious virus. This was found to be due to a multiplicity associated interference: infections at a multiplicity of infection (moi) of 7.0 yielded 0.2 plaque forming units (pfu) per cell, while infections at moi of 0.02 yielded 25 pfu/cell. This interfering activity has been found to be readily sedimentable (30,000 rpm X 15 min., SW 50L rotor), acid and ether labile, and neutralizable by immune ferret serum raised to infection with RS virus. It is postulated that this interfering activity is due to a defective virus particle similar to those described for influenza, Sendai and vessicular stomatitis viruses. These defective virus particles contain an incomplete genome and can be replicated (perhaps "preferentially") only in cells which have been coinfected with a second virion having a complete genome. The morphology and sedimentation characteristics of the interfering particle as compared to the plaque forming particle, the circumstances, in vivo and vitro, under which such defective particles arise and the prevalence of this phenomenon are under investigation.

TOTAL SERUM LIPIDS IN INFECTIOUS DISEASE. J. Dennis Pollack, Albert S. Klainer, and Henry G. Cramblett. The Ohio State Univ., Col. of Med., The Columbus Children's Hosp. and Univ. Hosps., Dept. Med. Microbiology, Ped., and Med., Columbus.

Over 400 sera were obtained from fasting patients hospitalized with various infectious diseases. Total lipids were determined gravimetrically after extraction with chloroform-methanol. Non-lipid contaminants were removed from organic extracts (without washing) by G-25 Sephadex column chromatography using organic eluting solvents as described by Rouser et al. In normal sera, the lipid range was relatively narrow: 614 ± 36 mg% (mean ± standard error of mean). The value with specimens from familial hyperlipidemia (Type IV and V), used as controls, was appropriately elevated: 2408 ± 665 mg%. Specimens from seven groups of patients diagnosed with 1) apparent viral infections, 2) pyelonephritis, 3) meningitis, 4) pneumonias, 5) infectious mononucleosis, 6) cellulitis, and 7) lower UTI, showed no statistically significant difference compared to normals. In contrast, sera from Australia antigen positive (756 ± 25 mg%) and negative (725 ± 25 mg%) hepatitis were elevated compared to normals ($P < 0.010$ and $P < 0.025$), or compared to infectious mononucleosis ($P < 0.001$ and $P < 0.025$). Fasting total serum lipid levels may be useful in the differential diagnosis of hepatitis and infectious mononucleosis. In cases of severe gram-negative infection (other than urinary tract infection), a highly significant ($P < 0.002$) depression was found (408 ± 32 mg%) and represents a hypolipidemia. These data were correlated with the levels of both serum triglycerides and total cholesterol, and also with the lipid "fingerprint" revealed by a four-directional thin-layer chromatographic screening procedure.

HEPATITIS ASSOCIATED ANTIGEN AND DOWN'S SYNDROME: EFFECT OF INSTITUTIONALIZATION. Lawrence F. Cohen, Philip M. Schmidt, Lawrence J. Dangelo and David J. Lang. Duke Univ. Med. Ctr., Dept. of Ped., Durham, North Carolina.

Investigations of Hepatitis Associated Antigen (HAA) have demonstrated a correlation with long incubation hepatitis, lepromatous leprosy, leukemia and Down's syndrome (DS). Three studies employing the micro-Ochterlony technique have found an increased prevalence of HAA in DS patients relative to other mentally retarded institutionalized patients, and to non-institutionalized DS children. Many of the non-institutionalized DS children tested were considerably younger than the institutionalized DS patients, making it difficult to evaluate the relative prevalence of HAA in these groups.

In the present study the prevalence of HAA was determined among 124 institutionalized patients with DS and compared with that in 52 non-DS institutionalized patients and 40 DS children who had always lived at home. Forty-seven percent of the non-institutionalized DS children were more than 10 years of age. The institutional groups were matched for age, sex, and duration of institutionalization. Sera were tested for HAA by immunoosmoelectrophoresis and for cytomegalovirus (CMV) antibody by complement fixation (CF).

Among the institutionalized DS children, 12 (10%) were positive for HAA. The presence of HAA correlated with age and duration of residence in the institution. In contrast none of the non-DS institutionalized children nor any of the DS individuals living at home were HAA positive. The prevalence of CMV-CF antibody was comparable in both DS groups.

These data confirm that HAA carriage in DS patients is correlated with institutionalization. In addition once infected the DS patient is more likely to be HAA positive than non-DS individuals housed in the same environment, suggesting that DS predisposes to persistent HAA carriage. The similar prevalence of CMV antibody in the groups tested indicates a comparable degree of exposure to a different virus but one also frequently transmitted in residential homes and institutions. The mechanism by which DS predisposes to HAA persistence remains unclear although it has been demonstrated that DS patients may possess a subtle defect in cellular immune function.

THE SCALDED SKIN SYNDROME: RELATIONSHIP TO PHAGE GROUP II STAPHYLOCOCCI. Adnan S. Dajani, Univ. of Minnesota Med. Sch., Department of Pediatrics, Minneapolis.

Twelve infants and children with the scalded skin syndrome were investigated, 11 of whom were infected with phage group II staphylococci. Only 2 neonates were in the group; both developed staphylococcal septicemia and died. The remaining 10 patients recovered. Focal infection was manifest as conjunctivitis (8 cases) more commonly than impetigo (3 cases). Conjunctivitis was a prominent feature of children over one year of age. Cultures of bullae, when present, were uniformly sterile. The frequent recovery of phage group II staphylococci from conjunctival cultures in these patients prompted the survey for staphylococci in an inpatient population. Phage group II strains were commonly recovered from superficial body sites (eyes, nose, skin), but not from deep infections.

The relationship of a staphylococcal bacteriocin (SB) previously described from this laboratory, to the exfoliative toxin (ET) responsible for the dermatologic manifestations of the scalded skin syndrome was investigated. SB is liberated best in tryptic soy broth with constant shaking, is heat stable and active at pH 4.0. In contrast, ET production in liquid media requires yeast extract and a 10% CO_2 atmosphere, ET is less heat stable and is inactivated at pH 4.0. Furthermore, whereas representative strains of all phage types in group II (3A, 3C, 55 and 71) produce an experimental disease in newborn mice closely resembling the human syndrome, only strains of phage type 71 are capable of producing the SB. Purified SB fails to produce disease in the animal model.

These data extend previous reports about the pathogenic role of phage group II staphylococci in the scalded skin syndrome and indicate that the SB and ET are 2 distinct products of this group of staphylococci with different biological activities.

DISSOCIATION OF LYMPHOCYTE FUNCTIONS IN CHILDREN WITH CHRONIC VIRAL INFECTIONS. Rudolf F. Eife and Charles S. August (Intr. by William E. Hathaway) Univ. of Colorado Med. Ctr., Dept. of Ped., Denver, Colo.

It has been reported that human peripheral blood leukocytes (PBL) stimulated in vitro by the mitogen phytohemagglutinin (PHA) not only undergo blast cell transformation but also release into their culture medium a substance(s) which is cytotoxic for growing HeLa cells (Green et al. J. Immunol. 105:48, 1970). This substance, called "lymphotoxin" (LT) after Kolb & Granger (PNAS 61:1250, 1968), is presumed to represent one of the lymphocyte-released mediators of cellular immunity. In normal individuals, the production and release of LT correlates directly with the extent of blast cell transformation.

In the course of studies of PHA-induced blast cell transformation and LT production in children with a variety of chronic inflammatory states, six patients were found with chronic viral infections whose PBL transformed normally but were defective in their production of LT. Blast cell transformation by lymphocytes was estimated as incorporation of 3H-thymidine (3H-TdR). Lymphotoxin activity was measured as the decrement of 3H-TdR uptake by target HeLa cells grown in the presence of cell-free culture medium of PHA stimulated leukocyte cultures and expressed as percent of unstimulated controls.

The patients, whose diagnoses included apthous stomatitis, viral encephalitis, SSPE, congenital rubella, and acquired cytomegalovirus infection, all showed normal lymphocyte blast cell transformation. However, as compared to normal controls (60-90% reduction in HeLa cell 3H-TdR uptake) their PBL released markedly reduced amounts of LT (15-44% reduction in HeLa cell 3H-TdR uptake). Our data indicate that in these patients, lymphocyte transformation or activation was dissociated from the production and/or release of at least one mediator of cellular immunity. Whether this lymphocyte dysfunction underlies the prolonged viral infection or whether the virus infection interferes in some way with lymphocyte function remains to be established.

THE ASSOCIATION OF VIRAL AND MYCOPLASMA INFECTIONS WITH LOWER RESPIRATORY TRACT DISEASE IN PATIENTS WITH CYSTIC FIBROSIS. Adamadia Deforest, Lourdes Laraya-Cunsay, James E. Gregory, Jay Satz, and Nancy N. Huang. St. Christopher's Hosp. Children, Temple Univ. Sch. Medicine, Dept. of Pediatrics and Penna. State Dept. of Health, Philadelphia, Pennsylvania.

Viral infections of the respiratory tract may play an important role in the exacerbations of lower respiratory tract disease seen so frequently in patients with cystic fibrosis (CF). Between January 1970 and December 1971 we studied a total of 126 cases of acute respiratory infection in patients with CF showing some clinical evidence of deterioration or increased severity of their pulmonary disease. Bronchial secretions, as well as acute and convalescent serum specimens were collected from patients in whom a viral infection was suspected. Bronchial secretions from 14 patients yielded the following agents: echovirus type 16 in 3; echovirus type 9 in 1; and influenza A2/Hong Kong in 1. No viruses were isolated from the remaining 9 specimens. A four-fold or greater rise in complement-fixing or hemagglutination-inhibition antibody titer was observed in 42 paired sera against the following agents: influenza A2/Japan in 8; influenza A2/Hong Kong in 6; adenovirus in 6; parainfluenza type 3 in 5; respiratory syncytial virus in 4; Mycoplasma pneumoniae in 4; measles virus in 3 (2 of these patients had previously received measles vaccine); parainfluenza type 1 in 2; and one case each of influenza A, influenza B, varicella, and rubella. There were 6 instances of a double viral infection, occurring in 6 different patients over the two-year period of the study. All of the above infections preceded or accompanied acute exacerbations of lower respiratory tract disease in these patients with CF. One patient with evidence of influenza A2/Hong Kong infection expired. We conclude that although the incidence of respiratory virus and mycoplasma infections may not be higher in patients with CF, the consequences of these infections appear to be more serious than in healthy children. (Supported in part by a Center Grant from the National Cystic Fibrosis Research Foundation).

HONG KONG INFLUENZA VIRUS CELL-FIXING ANTIBODY. Jerry J. Eller, Richard W. Newcomb, and Kenneth J. Moran. Univ. of Texas Med. Sch., San Antonio, and Children's Asthma Research Institute and Hospital, Denver (Intr. by W.T. Kniker)

The purpose of the present study was to determine if an immunoglobulin or other substance in secretions and sera from atopic patients, as a result of natural influenza infection or intranasal immunization with influenza vaccine, is capable of fixing in vitro to primary rhesus monkey kidney (MK) epithelial cells and preventing infection by a subsequent homologous virus challenge. One tube of rhesus MK cell culture was used for each nasal secretion or serum sample or for each fraction. The tube was inoculated with 0.5 ml of material and 0.5 ml of medium and incubated for 3 hrs. at 37°C. Tubes were carefully washed 3 times with fresh medium. Each tube was then challenged with about 100 TCID50 influenza virus and incubated at 33°C for 4 days. Supernatant fluids were removed and assayed for infectivity and compared with infectivity obtained in virus control tubes. Six nasal washes obtained after natural infection and 7 after intranasal immunization were active in preventing growth of influenza virus. Vaccinia virus was not inhibited. Activity was lost after all immunoglobulins were removed, or after 3 adsorptions with MK cells. Cell-fixing activity did not correlate with conventional neutralizing tests measuring IgA antibody. Myeloma IgE failed to block activity. Only IgG Sephadex and DEAE fractions of sera were active. Activity was lost when a serum was adsorbed with anti-IgG, but not anti-IgA or IgE, and was restored with IgG eluate. The cell-fixing antibody is in the IgG fraction of active sera. Other evidence suggests that activity is present in exocrine IgG but not IgA or IgE. The presence and protection afforded by these antibodies are not detectable in conventional neutralization or other serologic tests. Antibody already attached to epithelial cells may be more effective in neutralizing virus than freely circulating antibody. Such antibodies may be protective, as we have demonstrated in this study, or react with antigens in vivo resulting in tissue damage.

A COMPARISON OF THE ANTIBODY RESPONSE TO TRIVALENT ORAL POLIOVIRUS VACCINE IN BREAST-FED AND BOTTLE-FED INFANTS. Adamadia Deforest, Pamela B. Parker, John H. DiLiberti, H. Taylor Yates, Jr., Maarten Sibinga, and David S. Smith (Intr. by Victor C. Vaughan, III). St. Christopher's Hosp. for Children and Temple Univ. Sch. Medicine, Dept. of Pediatrics, Philadelphia, Pennsylvania.

It has been suggested in the past that infants receiving oral poliovirus vaccine (OPV) not be breast-fed during the period 6 hours before and 6 hours after vaccine administration because antibody in breast milk can neutralize some of the vaccine virus. We compared serum neutralizing antibody titers to all 3 types of poliovirus in 25 breast-fed and 25 bottle-fed infants. Sera were collected between 7-15 months of age. All infants were from the same communities and the same socio-economic background. All but 4 had received a full series of 3 doses of trivalent OPV at approximately 2,4, and 6 months of age. No effort was made to supplant breast-feeding at the time of vaccine administration. Neutralizing antibody titers were determined against 10-100 tissue culture doses of poliovirus types 1,2, and 3. Serum-virus mixtures were incubated 1 hour at 37 degrees C. prior to inoculation into Vero monkey kidney cells. Geometric mean antibody titers to poliovirus type 1 were: breast-fed 1:74; bottle-fed 1:69; to poliovirus type 2: breast-fed 1:128; bottle-fed 1:91; and to poliovirus type 3: breast-fed 1:34; bottle-fed 1:28. Two infants in the breast-fed group and 2 in the bottle-fed group lacked detectable antibody to one or more types of poliovirus at a 1:8 serum dilution, the lowest dilution tested. One of these infants (breast-fed) had received only 2 doses of OPV. Neutralizing titers in the remaining 46 infants against all 3 types of poliovirus ranged from 1:8 to 1:1024. There were no significant differences in antibody responses to OPV in the two groups. We conclude that breast-feeding, even when continued for a prolonged interval of time (up to 15 months in this study), does not interfere with the antibody response of infants to OPV, if the vaccine is administered under the above conditions, starting at approximately 2 months of age. (Supported in part by Grant RR-5624 from USPHS).

CARBON MONOXIDE PRODUCTION FROM HEMOGLOBIN BY BACTERIA. Rolf R. Engel, John M. Matsen, and Samuel Schwartz. Univ. of Minnesota Hosp., Minneapolis (Intr. by William Krivit).

CO formation from heme compounds by bacteria was investigated to compare microbial hemoglobin catabolism with the heme oxygenase reaction of mammalian tissues. Alpha, beta and non-hemolytic bacteria were incubated aerobically and anaerobically with the following substrates: erythrocytes, hemoglobin, myoglobin, cytochrome C, hematin, iron hematoporphyrin, copper hematoporphyrin, protoporphyrin and bilirubin. After 18 hours at 36°C the evolved CO was measured by gas chromatography. Under aerobic conditions non-hemolytic Streptococcus mitis did not evolve CO from any of the substrates, whereas both alpha hemolytic Streptococcus mitis and beta hemolytic Bacillus cereus formed CO from all of the heme compounds tested. These hemolytic bacteria did not produce CO when the iron of heme was replaced by copper or removed as in copper hematoporphyrin and in protoporphyrin. None of these bacteria formed CO anaerobically.

The finding that CO was formed the most rapidly from cytochrome C prompted further studies which suggest that hemolytic bacteria may derive a survival advantage from this reaction and that animals may also produce CO during cytochrome C catabolism.

Since vitamin B_{12} is also a metallic tetrapyrrole the same bacteria were tested for CO production from hydroxocobalamin. Both the alpha and beta hemolytic strains generated CO from vitamin B_{12} aerobically, whereas anaerobic incubations or non-hemolytic bacteria did not evolve CO. Apsorption spectra of the incubation mixture confirmed that CO production was always coupled with substrate destruction. These studies of heme catabolism provide new information on interactions between host and hemolytic bacteria and catabolism of cytochrome C and vitamin B_{12}.

BENZATHINE PENICILLIN PROPHYLAXIS OF STREPTOCOCCAL IMPETIGO. Patricia Ferrieri, Adnan S. Dajani, and Lewis W. Wannamaker. Univ. of Minnesota Med. School, Department of Pediatrics, Minneapolis.

Little information exists on the efficacy of antibiotic prophylaxis against streptococcal skin infections in populations at high risk. A controlled double-blind study of parenteral benzathine penicillin (Bicillin) was conducted during the summer of 1971 in 78 children from 18 families on the Red Lake Indian Reservation. Bicillin (600,000 units to children 6 years or younger and 1.2 million units to children 7 years or older) or a saline placebo was given (1st study period), followed 6 weeks later by the reverse of the 1st injection (2nd study period). Of the 78 children 11 received no injections and acted as internal controls. Serial cultures of nose, throat, normal skin sites and skin lesions, if present, were taken and processed for group A streptococci.

Prevalence and incidence of lesions was reduced significantly in children following Bicillin. The frequency of lesions in the two study periods following Bicillin was 15.6 and 24.1% compared to 56.7 and 60% after placebo. Mean interval between Bicillin injection and development of lesions was 7 weeks, but 18% of children broke through within 5 weeks. Throughout the study lesions were more frequent in younger children. 14 of the younger children exhibited lesions within 6 weeks following Bicillin compared to 2 in the older age group ($P < 0.001$). At 2, 4 and 6 weeks after Bicillin administration there was a higher percentage of children with positive normal skin sites than with lesions. At 2 weeks, when no lesions were present 6.8% of children had normal skin sites yielding streptococci.

It appears that Bicillin exerted a beneficial effect in decreasing skin lesions in these children. 38% fewer children developed lesions following Bicillin. Duration of protection varied and was less in younger children. This latter observation may reflect an influence of age or inadequacy of dosage and requires further study. Streptococcal recovery from normal skin within a few weeks of Bicillin administration may be due to persistence of organisms or reacquisition, although lesions did not develop until later.

A COMMUNITY SEROSURVEY DESIGNED TO ESTIMATE IMMUNE STATUS OF SELECTED POPULATIONS. Alfred Fevrier and Eli Gold, Dept. of Pediatrics, Case Western Reserve Univ. Sch. of Med. at Cleveland Metropolitan General Hospital, Cleveland, Ohio and the Nat. Communicable Disease Ctr., Atlanta, Ga.

The occurrence of small outbreaks of diphtheria, poliomyelitis or measles among lower socioeconomic groups throughout the U.S. raised the question of the immune status of young children residing in Cuyahoga County, Ohio. A serosurvey modeled after one conducted in that community ten years previously was carried out with the support of the Academy of Medicine of Cleveland, NCDC and others. Samples of blood were collected from randomly selected children aged 1-4 years, living in three central city and one suburban census tracts. The survey teams which included members of the community determined the usual source of immunization for the family and also obtained demographic information. Nearly half the families living in the suburban census tract refused to permit blood collection but the cooperation in other areas was good. The serological data indicated that the children living in the inner city were not as well immunized as children of comparable age group residing in the suburbs. The percentage of children aged 1-4 years susceptible to rubella, for example, ranged from 72% in a inner city largely Spanish speaking census tract, to 62% in a predominantly Appalachian white neighborhood, to 58% in the tract inhabited largely by blacks to 35% in the middle class suburb.

The existing immunization facilities in Cleveland are differentially utilized by various portions of the population. Rather than curtail the community immunization program to conserve spending, it may be more prudent to adopt approaches which may lead to the immunization of a larger portion of inner city children.

CYTOMEGALOVIRUS (CMV) SYNDROME POST-RENAL TRANSPLANTATION IN CHILDREN. Richard N. Fine, Carl M. Grushkin, Mohammad Malekzadeh and Harry T.Wright, Jr. Dept. of Pediatrics, Univ. So. Calif. Sch. of Med., Div. Renal Dis. and Virology, Childrens Hospital of Los Angeles, Los Angeles.

Nine renal allograft recipients, aged 3-15 years, developed prolonged fever (> 38°C for 8 to 19 days) and hematologic abnormalities during the initial 3 post-transplant (P-T) months (21 to 64 P-T days). The hematologic abnormalities included leucopenia (< 4000/mm3) in 8 recipients, lymphocytosis (> 45%) in 6, hemolytic anemia in 7 and thrombocytopenia (< 100,000/mm3) in 4. In addition, pulmonary symptoms ("transplant lung") occurred in 3 patients and hepatic dysfunction in 2 during the clinical course. CMV viremia was documented during the clinical illness in 6 patients, 3 of whom demonstrated a significant rise in the CMV complement-fixation (C-F) titer. Cytomegalovirurla during the febrile period in conjunction with a rise in the C-F antibody titer implicated CMV in 1 patient, and transient virurla either prior to or after the clinical illness in the remaining 2 patients. Virus isolation from bone marrow specimens in 3 patients and from lung tissue in 2 of 3 patients with "transplant lung" were additional confirmatory evidence. Spontaneous remission occurred in 5 recipients, 1 patient remitted coincident with cytosine arabinoside therapy and all 3 patients with "transplant lung" died. An elevated C-F titer in transfused blood administered to 2 patients during hemodialysis who subsequently developed the syndrome suggested that the transfused blood may be the vehicle of CMV transmission in these patients.

DIFFERENTIAL ATTACK RATES OF BACTERIAL MENINGITIS David W. Fraser, Charles P. Darby, Robert E. Koehler, Cecil F. Jacobs, Roger A. Feldman (Intr. by John B. Robbins), Center for Disease Control, Atlanta, and Med. Univ. of South Carolina and Charleston County Health Ctr., Charleston, South Carolina

Strategy for vaccine delivery and differential diagnosis rest upon knowledge of relative risk of disease in various population groups. With the recent development of vaccines against Neisseria meningitidis and Hemophilus influenzae, such knowledge is acutely needed.

In Charleston County, South Carolina, from January 1961 to June 1971, the peak incidence rates of meningitis due to H. influenzae, N. meningitidis, and Streptococcus pneumoniae were each in 6-7 month olds. H. influenzae was the most common cause of bacterial meningitis. The incidence of meningitis of each type was greater in blacks than in whites - the difference being 2 1/2-fold for N. meningitidis, 4-fold for H. influenzae, and 6-fold for S. pneumoniae.

However, in a population in which the economic status of whites differs so strikingly from that of blacks, it is important to distinguish the effects of economic levels from those of race. For S. pneumoniae meningitis, blacks had higher rates than whites regardless of family income and housing crowdedness. In contrast, for meningitis due to H. influenzae and N. meningitidis, race-specific attack rates were similar when blacks and whites of similar level of median income and crowding were compared. For blacks there was a 6-fold difference in the incidence of H. influenzae meningitis between the poorest and richest areas of the county. A similar though less striking correlation was shown for N. meningitidis meningitis.

Extrapolating these rates to the United States as a whole, one could estimate that 5,000 H. influenzae, 4,000 N. meningitidis, and 2,000 S. pneumoniae meningitis cases occur each year.

To be most effective, vaccines against H. influenzae and N. meningitidis would have to be given to infants less than 6 months of age in areas of low socioeconomic status.

MENINGOCOCCI IN VAGINITIS. JAMES E. GREGORY and ELLEN ABRAMSON (Int. by Nancy N. Huang) Dept. of Ped., Temple Univ. Sch. of Med.; St. Christopher's Hosp. for Children, Phila., Pa.

The presence of Neisseria meningitidis in the vagina has not been well documented. This is probably due to the rare occurrence of this organism in this anatomic site. N. meningitidis, when present in humans, can usually be recovered from the blood, cerebrospinal fluid, the nasopharynx, and petechiae of the skin. A 5-year-old Negro girl was brought by her mother to the Emergency Clinic of St. Christopher's Hospital with a 24-hour history of a white vaginal discharge and itching with considerable excoriation externally in the vulvar area. Her condition was diagnosed as vaginitis. A vaginal culture yielded N. meningitidis; a throat and nasopharyngeal culture were both negative for this organism. This was a self-limiting case of vaginitis, in that symptoms subsided without antibiotic or chemotherapy. Daily lukewarm baths with a mild soap was suggested to the mother initially.

The recovery of N. meningitidis in this case represents, in addition to a rare isolate, the possibility that the meningococcus was the etiologic agent in a case of vaginitis. The association of this organism with vaginitis had not been previously reported.

ANTIGENIC ANALYSIS OF ECHOVIRUSES 1 AND 8. Ralph E. Haynes, Lester F. Harris, Henry G. Cramblett, Robert M. Conant, and George R. Jenkins. The Ohio State Univ., Col. of Med., The Columbus Children's Hosp., Dept. Ped., and Med. Microbiology, Columbus, and Sepulveda VA Hosp., Dept. Surgical Services, Sepulveda, and NIH, Bethesda.

A number of investigators have documented a relationship between echovirus types 1 and 8. The extent of cross reactivity has varied from that of strong one-way neutralization, suggesting a prime relationship, to minor reciprocal neutralization. This study extends both the neutralization and gel precipitation studies of others utilizing prototype strains of echovirus 1 and 8. In addition, strains of each virus isolated from patients with various diseases have been studied intensively to quantitate any intratypic variations between prototype and the so-called wild strains. Neutralization studies revealed that 4 patient isolates and prototype echovirus 1 and 8 were neutralized by either type 1 or type 8 antisera, but not by both. Eight of 12 isolates were neutralized without serum preference. These relationships were further studied with serum dilution endpoints of prototype and other hyperimmune sera prepared in this laboratory. Studies of plaque morphology using 12 wild strains and the prototype strains failed to reveal differences, all strains studied produced heterogeneous plaques 4 to 10 mm in diameter. Double diffusion gel precipitation studies with prototype and isolate strains of echovirus 1 and 8 convincingly supported their antigenic relationship. All strains shared a common antigen. In addition, some strains possessed a second antigen which related them more closely to one or the other of the prototype strains. A third distinct antigen is implied in the reaction observed between a wild strain and prototype strain antisera. Neither the prototype nor isolate strain demonstrates the classical prime relationship described for echovirus type 6. Rather the antigenic variation is more similar to that described for echovirus types 4 and 9. For this reason the diagnostic laboratory should consider the use of both prototype variant strain antisera in attempting to identify virus from clinical material.

CHANGING INCIDENCE OF HEMOPHILUS INFLUENZAE MENINGITIS. Ralph E. Haynes, Edward W. P. Smith, Jr., and Henry G. Cramblett. The Ohio State Univ., Col. of Med., The Columbus Children's Hosp., Dept. Ped., and Med. Microbiology, Columbus.

Numerous investigators have documented the increase in meningitis caused by Hemophilus influenzae. Some reports relate this to a proportionate increase in the number of hospital admissions, while in others it is clearly unrelated. At Columbus Children's Hospital (CCH) the incidence of H. influenzae meningitis has been studied during the following periods of time--A (1942-1950), B (1951-1959), and C (1960-1968). The number of patients with influenzal meningitis was 74, 171, and 369 in Periods A, B, and C respectively. The number of hospital admissions was 32,046 in Period A, 72,103 in Period B, and 119,296 in Period C. The increase in influenzal meningitis is roughly proportional to the increase in hospital admissions during each period. Since the factors controlling hospital admissions are so variable, it seemed that this method of comparing incidence was unreliable. Almost all children with bacterial meningitis in Franklin Co., Ohio, are hospitalized at the CCH. The number of patients with influenzal meningitis from Franklin Co. treated at CCH therefore represents the approximate actual number of cases. Since 95% of the cases of H. influenzae meningitis occur in children under 5 years of age, each child under 5 is presumed to be a potential candidate for this disease. The number of children under age 5 in Franklin Co. represents 95% of the population at risk. The incidence can then be stated as number of cases per 100,000 population at risk. The chance that any child in Franklin Co. under age 5 would acquire H. influenzae meningitis was 2 times greater in Period C than in Period A. The incidence of D.pneumoniae or N. meningitidis meningitis has not increased. The increase of influenzal meningitis and the associated significant morbidity and mortality indicate the desirability of developing methods of prevention. In evaluation of preventive measures the proposed method of determining incidence allows direct comparisons in widely separated geographic areas during specific time periods.

A BACTERIOLOGICAL STUDY OF UNHEATED CENTRIFUGAL VAPORIZERS AND HUMIDIFIERS IN AMBULATORY CHILDREN. Charles J. Hyman, Edward L. Charnock, Martin Wand and John V. Bennett. Intr. by Richard Michaels. From Dept. of Ped., U.S.A.F. Hosp., Mt. Home, Id. & Bact. Dis. Branch, Ctr. for Dis. Control, Atlanta, Ga.

Inhalation therapy apparatus contaminated with gram-negative bacteria have been causally implicated in the pathogenesis of respiratory infections in hospitalized patients with altered host defenses. Since gram-negative pneumonias may occur, although rarely, in young patients without serious underlying disease and since "cool air" vaporizers are being used with increasing frequency in pediatric practice, a prospective study was undertaken to determine the infection hazards of this type of apparatus. 177 "healthy" children between 3 months and 16 years of age who did not have a "cool air" vaporizer served as a control group. 170 similar children who were exposed to the above type of vaporizer for a minimum of 8 hours per day for a 3 month period were the study group. During the second and third months of the study each child had a nasopharyngeal culture taken and those in the study group had cultures taken from their vaporizer and its effluent. All cultures were plated directly on McConkey media. 82% of the vaporizers and 50% of the effluents were contaminated with 32 gram-negative organisms which included Pseudomonas, Nonfermenter, Mima, Herellea, Erwinia, Enterobacter, Alkaligenes, and Klebsella. Gram-negative colonization of the nasopharynx occured in 4.8% of the control group and 6.7% of the study group. Adjusting this figure to include only those nasopharyngeal cultures which had similar organisms growing from either the vaporizer or the effluent reduced the rate of colonization to 1.8%. An unexpected finding was the presence of 11 isolates of Salmonella species cultured from the apparatus. None of the exposed children became colonized with Salmonella nor were there any episodes of bacterial diarrhea. None of the children had nasopharyngeal cultures which were positive during both phases of the study and there was no evidence of gram-negative respiratory infection. Although the unheated centrifugal vaporizer may be a cesspool, it does not seem to represent an infection hazard in relatively healthy children.

PNEUMOCOCCAL SEROTYPES AND ANTIBODY RESPONSES IN OTITIS MEDIA IN CHILDREN. Virgil M. Howie, John H. Ploussard, Huntsville, Ala.; Robt. Austrian, U. of Pa., Philadelphia; Arthur J. Ammann, U. of Cal., San Francisco; and Richard B. Johnston, Jr., U. of Ala., Birmingham (Intr. by Hugh C. Dillon)

The natural immune response to pneumococcal otitis media has not been previously reported. Capsular polysaccharides from pneumococci are presently under study as vaccines. Knowledge of the character of the natural immune response to localized infection by pneumococci should serve as a basis for comparison of the response to these vaccines, and knowledge of the serotypes infecting children should aid selection of vaccine types. In this study, pneumococci were obtained by culture of exudate aspirated from the middle ear cavity in 300 episodes of acute otitis media in a pediatric practice. Although 25 different serotypes of pneumococci were identified, three serotypes (14, 19, 23) accounted for 52% of all infections, and nine other serotypes (1,3,4,6,7,8,11,12,18), an additional 38% of all infections. Type-specific antibody levels were measured in acute and 9 to 21-day convalescent sera by radioimmunoassay (RIA), indirect hemagglutination (HA), and indirect fluorescent antibody (IFA) techniques. Preliminary results with the RIA technique, which measures the primary binding of type-specific antibody of any immunoglobulin (Ig) class, gave evidence of an antibody response in about a quarter of those infected. The HA test, which reflects primarily the response of antibodies in the IgM class, showed a significant rise in titer in 60% of the convalescent sera tested. Results of the IFA assay, which measures antibody in IgG, IgM and IgA classes, correlated well with those of the HA test. When acute and convalescent sera were tested for HA antibody activity against each of the seven most common serotypes, there were small responses to serotypes other than that infecting the patient in some instances, the significance of which requires further investigation.

CLINICAL EXPERIENCES AND RAPID DIAGNOSIS OF HERPESVIRUS HOMINIS ENCEPHALITIS. C. Liu*, R. Llanes-Rodas, D.W. Voth, L. Muangmanee, & C.T. Cho, Univ. of Kansas Medical Center, Depts of Ped. & Med., Kansas City, Kansas 66103

We have reviewed our clinical and laboratory experiences on 13 patients with encephalitis caused by Herpesvirus hominis. In 7 patients diagnosis was confirmed by positive immunofluorescent (FA) staining of herpesviral antigen and virus isolation in brains obtained from biopsy and/or autopsy. Etiologic diagnosis for 6 survivors was considered probably as only serologic evidence of high anti-herpes neutralization and FA antibody titers was available.

Major clinical manifestations in these 13 patients were headache, fever, confusion and seizures. Presence of RBC in CSF in 9/13 patients additional to pleocytosis was considered helpful in diagnosis. Abnormal EEG was seen in 9/9 patients studied and positive brain scan indicating a temporal lobe lesion was present in 5/5 patients.

Among 7 patients in whom brain tissues were available for examination, diagnosis of herpesviral infection in all 7 of them was first established by direct FA staining. In 2 recent cases, positive diagnosis was made by FA technic within 2 hours after the brain biopsy was obtained and IDUR therapy was initiated. The first patient began receiving IDUR on the 6th day of her illness. She died despite IDUR therapy but there was a decrease of virus content in the brain at autopsy. The second patient made a definite clinical recovery after receiving 24 gm. of IDUR began on 4th day of illness. She died suddenly from a massive pulmonary embolism 12 days after completion of IDUR but postmortem brain was negative for viral antigen and virus isolation.

Herpesviral encephalitis has a high mortality and morbidity and specific therapy with IDUR or cytosine arabinoside has been reported to be beneficial. Our data warrant the suggestion that if an encephalitic patient with presence of RBC in CSF and a positive brain scan in the temporal lobe, a brain biopsy should be performed and examined by FA staining and virus isolation. If FA result is positive, therapy should be started without delay.

THE EBV INFECTION IN THE NEONATAL PERIOD AND IN CHILDHOOD. Jean H. Joncas, Jocelyne Boucher, Claudette Filion, Antoine Eid. (Intr. by Jacques R. Ducharme). Inst. of Microbiology and the Department of Microbiology and of Ped. of the University of Montreal and Ste Justine Hosp., Montreal, Canada.

The present study was undertaken in an attempt to characterize EBV associated syndromes in early life and find out if EBV infection in these age groups results in the occurrence of infectious mononucleosis in older children and young adults from the same family. The sera of 92 infants and children admitted to Ste Justine Hospital from birth to age 10 were screened for EBV antibodies and their titer determined by indirect IF. Heparinized blood from an additionnal group of 20 newborns prior to and following exchange transfusion was collected for leukocyte culture. Sera from these newborns and their mothers were taken at birth and follow-up sera from the whole group taken at 3 months intervals thereafter. 63/92 sera were EBV negative and 29/92 were EBV positive. A 3 year old child with a pharyngitis, a rash and heterophil agglutinins had an EBV antibody titer of 1/20 on admission and a titer of 1/160 3 months later with no other illness during this period. Two cases of encephalitis were found to have serum EBV antibody titers of 1/160 and 1/320 and a CSF titer of 1/5. One of the two cases, had characteristic heterophil agglutinins in his serum. Control CSF-EBV antibody titers in 28 cases of meningo-encephalopathies were negative despite high serum EBV antibody titers. Both cases underwent complete recoveriesdespite extremely stormy clinical courses. The prospective follow-up of the other cases and their families is otherwise so far negative. One permanent (EBV positive by immunofluorescence and electron microscopy) lymphoblastoid cell line with a female karyotype was obtained from the post exchange blood sample of a female newborn infant after transfusion of fresh blood from an EBV positive male donor. The EBV antibody titer of the infant was 1/5 at birth and negative at the age of 3 months while the mother's titer was 1/20. Infection of this newborn's leukocytes therefore probably occurred in vitro but not in vivo. The association of encephalitis with EBV infections deserves further studies.

ROUTINE ELECTIVE TRACHEOTOMY IN H. INFLUENZAE, TYPE B, EPIGLOTTITIS. Carmi Z. Margolis, David L. Ingram and Jerome H. Meyer. (Intr. by C. D. Cook) Yale University School of Medicine, Dept. of Pediatrics, New Haven.

Acute epiglottitis, usually caused by H. influenzae, Type B, may be associated with mortality rates as high as 50% in cases not tracheotomized. At Yale-New Haven Hospital during a 6 year period when tracheotomies were not routinely performed, 2 of 23 children died and severe morbidity from hypoxia occurred in one other. A protocol involving routine tracheotomy was instituted for the management of children with acute epiglottitis considered due to H. Influenzae. The protocol provided for rapid mobilization of pediatricians, otolaryngologists and anesthesiologists in every case of suspected epiglottitis. Direct visualization of the epiglottis was performed on every suspected case and tracheotomy was subsequently performed on every definite case of epiglottitis. During 18 months, in fourteen successive cases, there were no deaths or residual morbidity from the disease, or lasting detrimental effects from tracheotomy. Mean time from onset of symptoms to tracheotomy was 8 hours, 10 minutes. Mean time from the entrance into the emergency room until tracheotomy was performed was 50 minutes (range 5 to 165 minutes). Tracheotomies were removed within four days, and all patients were home within one week. Thirteen children had positive cultures for H. influenzae, Type B, from the epiglottis and/or blood. Four of these had fourfold rises in antibody titers against H. influenzae in acute and convalescent sera, and five others had very high titers in convalescent sera. One case had negative cultures and no change in antibody titer. In our experience definite inflammatory epiglottitis is almost always due to H. influenzae. Routine tracheotomy may occasionally be done unnecessarily, but appears to reduce the expected high mortality and is associated with low morbidity from the procedure itself.

ASYMPTOMATIC ACQUISITION OF GROUP A STREPTOCOCCUS IN THE THROAT. Arthur A. Mauceri, Eugene Sanders, Patsy R. Page, Elia M. Ayoub, Depts. Med. and Ped., College of Med., Univ. of Florida, Gainesville.

A prospective study to define the pattern of acquisition of group A streptococcal pharyngeal infection in a closed population was conducted during the winter and spring of 1970-1971. Weekly throat cultures were performed on 55 children, ages 6-13 years, housed in one cottage at a training center for the retarded. All cultures positive for β-hemolytic streptococci were processed for serological group identification. Group A strains were then typed by the M-precipitation and T-agglutination techniques. Upon isolation of a group A streptococcus from an individual, acute and convalescent sera were obtained for streptococcal antibody studies, antistreptolysin O (ASO) and anti-deoxyribonuclease B (anti-DNAse B). Initial cultures revealed the presence of a variety of non M-typable, T-typable group A streptococci in about 10 per cent of the study population. However, during the period of observation, pharyngeal acquisition of a group A, type M-11:T-11 strain occured in the population under study. The incidence of positive pharyngeal cultures for this strain peaked over three weeks and eventually was recovered from 43 of the 55 (78%) patients. The source of the outbreak was traced to a newly admitted patient who was asymptomatic but had a positive culture for this strain on admission. Of interest is that only one of the 43 patients who acquired this organism developed clinical symptoms and that only four patients showed a significant rise in their streptococcal antibodies (ASO/anti-DNAse B). No difference was observed in the geometric means of titers for the acute and convalescent sera obtained from these patients. There were no acute or late complications noted in this group during the one year of follow-up observation. These data suggest that pharyngeal acquisition of group A streptococcus, even in epidemic proportions in a closed population, need not be associated with symptomatic infection or antibody response.

THE RELATION BETWEEN CERVICAL AND PERINATAL CYTOMEGALOVIRUS (CMV) INFECTIONS. David W. Reynolds, Sergio Stagno and Charles A. Alford, Univ. of Ala. Sch. of Med., Ped. Dept., Birmingham, Alabama.

To better define the role of silent cervical CMV infection in the production of infection in utero or early infancy, virologic and serologic studies were serially performed in 470 pregnant women and, where pertinent, in their offspring. Like others, we have found a high rate of cervical infection which increased with advancing gestational age. The rates are 1/94 (1%) in 1st trimester, 14/241 (6%) in 2nd trimester, and 21/142 (15%) near delivery. This increase could not be related to C-F antibody changes suggesting reactivation of cervical infection rather than primary acquisition. Moreover, virus could not be recovered from throat or WBC's of women with cervical infection even though urinary excretion was demonstrated in half.

Of 14 late cervical excretors who have delivered, none of their infants shed virus at birth; placentae and amniotic fluid specimens obtained during pregnancy were also negative. However, 5 of 6 infants who have been followed closely for at least 3 months have begun to excrete virus from throat and urine between 3-12 (average 8) weeks after delivery while none of our control group have done so. The other 8 are still to young to exclude early acquisition of infection.

The data indicates that cervical CMV infection in pregnancy is very prevalent and can, like Type 2 herpes infections, be associated with a significant rate of infection of the fetus either in late gestation or, more likely, during delivery. Because of its prevalence, it is important to better understand the true significance of this type of silent infection of early infancy.

TISSUE CULTURE DIAGNOSIS OF DISSEMINATED HISTOPLASMOSIS. HOPE H. PUNNETT, SUMALEE THOVICHIT, J. LAWRENCE NAIMAN, JAMES B. AREY, Depts. of Ped., Path., Temple Univ. Sch. of Med., St. Christopher's Hosp. for Child., Phila., Pa.

Human cells, grown in tissue culture, provide an optimum medium for the identification of Histoplasma capsulatum when neither histologic section nor microbiologic cultures yield positive findings. An eight week old female with fever, hepatosplenomegaly, pancytopenia and active bone marrow, evaluated for possible histoplasmosis, had negative findings on blood and urine cultures, bone marrow smears (x2) and skin test. Splenectomy was performed at 12 weeks of age. Histologic sections suggested a reticuloendotheliosis. No organisms were identified in sections stained with PAS and methenanine silver, and even after the diagnosis was established few organisms could be positively identified after prolonged search.

Tissue cultures of skin and spleen were established. Spleen cultures contained bizarre cells filled with haloed bodies which stained positively with PAS. The intracellular yeasts could not be cultured from medium or sections of spleen. Skin cultures were normal. A third bone marrow aspiration, prior to definitive tissue culture identification, finally revealed Histoplasma on smear and culture. The child responded to therapy (amphotericin B and sulfonamide) and has maintained normal growth and development.

Cultured human cells promote rapid growth of Histoplasma. A tissue explant with no histologically detectable organisms acts as an enrichment culture, the yeast proliferating within dividing fibroblasts. This observation, first made by Randall and Hackney (Am. J. Path. 29:861) in 1953 has not been exploited for diagnostic purposes. Tissue culture of the first marrow aspirate might have averted our patient's splenectomy. Marrow cultures should become part of the investigation of suspected fungal septicemia.

ZOSTER IMMUNE GLOBULIN: PRODUCTION AND USAGE. Avron H. Ross, S. Wayne Klein, Linda Rodriguez, Edathil K. S. Narayanan, Barbara McKennett, Anita Kaminer and Karen Redmond. Nassau County Medical Center, Department of Pediatrics, East Meadow, New York. (Intr. by P. J. Collipp).

A program for the production of zoster immune globulin (ZIG) to meet community needs and to refine criteria for usage was launched on 7/1/70 in Nassau and Suffolk Counties, Long Island, N.Y. 2 months were required to assemble equipment, train 2 medical technicians and 1 medical secretary to perform plasmaphereses, varicella-zoster complement-fixation (V-Z CF), and to launch a convalescent herpes zoster donor recruitment campaign. 32 liters of plasma with a minimum CF titer of 1:64 were then collected in 10 months. 20 liters (30 plasmaphereses) with titers of 1:64 to 1:512, with a median and mode of 1:128, yielded 340 ml., or 11.3 ml. per donation, of 10% gamma globulin solution of ZIG. 14 months after program onset ZIG was ready for the 1971-72 V-Z season. Also, 8 units of zoster immune plasma (ZIP) were used for critically ill V-Z patients. ZIG requests from 9/2/71 to 1/14/72 were honored for 46 V-Z exposed moderate to high risk patients: 26 household, 2 school, 4 in-patients (2 children's ward exposures), 14 newborn (1 nursery exposure by ill house officer). 68 ml. of ZIG, 2.3 liters of ZIP were used. Age range from 5 days old to 41 years. Doses of ZIG were 0.025, 0.05 (modifying), 0.10, 0.20 (preventive) ml./kg.; totals from .03 to 4.0 ml., given 1-8 days after exposure. 5 patients are still under observation; 34 developed no disease (none in newborns or hospitalized patients); 7 contracted varicella with 1, 2, 2, 4 and 7 pox when ZIG given 1-4 days after exposure, 43 and 60 pox given 7 days after. Sibling controls of the 7 had 405, 725, 823 pox. 3 of 5 modified varicella cases tested had V-Z CF rise to 1:8 to 1:16. Early data confirm the high efficacy of ZIG in modification, and suggest effectiveness up to 7 days after exposure, immune response, possible non-infectiousness of modified varicella, usefulness in curbing in-hospital spread. Current community needs are being met for prevention, modification and possible treatment.

NBT TEST IN STREPTOCOCCAL PHARYNGITIS. John E. Randall, Gerald L. Mandell, Vito Perriello, J. Owen Hendley. Univ. of Virginia Sch. of Med., Charlottesville, Virginia. (Intr. by William G. Thurman)

The Nitro Blue Tetrazolium (NBT) reduction test as developed by Park et al (Lancet ii:532, 1968) has shown promise in differentiating between bacterial and non-bacterial causes of fever in hospitalized patients. The current study was designed to determine whether the NBT Test would be useful in outpatients in predicting whether pharyngitis was of bacterial origin. The test was modified to employ capillary blood obtained by finger stick rather than venous blood; children in a private group practice were studied. Patients with clinical pharyngitis without otitis media or pneumonia were studied prior to treatment. A throat culture for B-hemolytic streptococcus and an NBT test were performed on each patient.

Results with 30 patients studied to date are as follows:

NBT Positive Neutrophils (%)	Controls	Pharyngitis	
	No.	B-strep Neg.	B-strep Pos.
0-9	12	16	5
10-19	0	2	2
20-29	0	1	1
≥ 30	0	1	2
Total	12	20	10

Mean percentages of NBT positive cells in controls, B-strep negative and B-strep positive pharyngitis were 2%, 8% and 13% respectively. Although 80% of the patients with B-strep Negative pharyngitis had a normal (0-9%) NBT value, 50% of the B-strep positive patients were also in the normal range. The NBT test appeared to be of little value in differentiating between streptococcal and non-streptococcal pharyngitis in these ambulatory patients.

FACTORS AFFECTING CIRCADIAN PERIODICITY OF SUSCEPTIBILITY OF MICE TO PNEUMOCOCCAL INFECTION. Penelope G. Shackelford, Ralph D. Feigin, and Virginia V. Weldon. Washington Univ. Sch. of Med., St. Louis Children's Hosp., Dept. of Ped., St. Louis, Missouri

The present studies were undertaken to elucidate factors which might affect the previously reported periodicity of mortality following pneumococcal challenge of mice. Groups of mice conditioned for 21 days in an animal chamber lighted from 1800 to 0600 hours daily were challenged with pneumococci every four hours beginning at 0800 hours and terminating 24 hours later. Longest survival followed 1600 hour challenge (75.74 ± 37.08 hours) and shortest survival followed 0400 hour inoculation (47.43 ± 19.67 hours). This represented a 12 hour phase shift in survival pattern compared to that seen following challenge of animals conditioned in a chamber lighted from 0600 to 1800 hours. Conditioning for 10 days in a chamber lighted from 1800 to 0600 hours altered the periodicity of mortality but not produce a full 12 hour phase shift. Survival pattern was also altered by conditioning animals in continuous light or continuous dark, but periodicity of mortality was not abolished. Activity and feeding patterns of mice were dissociated from the light-dark cycle and this failed to change the light synchronized mortality periodicity pattern. Penicillin prolonged the survival of animals challenged with pneumococci at every inoculation time, but did not alter mortality periodicity. Animals were sacrificed at 6 and 12 hours following each challenge time and circulating corticosterone levels measured. Steroid levels were significantly increased at 6 hours only in animals challenged at 0400 hours. All animals sacrificed 12 hours after injection had increased circulating corticosterone compared to controls but maximum values followed 0400 hour challenge. The pattern and magnitude of bacteremia following 10^1 or 10^6 pneumococci injected at 0400 and 1600 hours was independent of challenge time. Periodicity of mortality depends upon exogenous variables and endogenous host factors but appears to be independent of bacteriologic events or antibacterial therapy.

THE RAPID DIAGNOSIS OF ENTEROVIRAL MENINGITIS USING THE INDIRECT IMMUNOFLUORESCENT TECHNIQUE. Larry H. Taber, Radmila R. Mirkovic, Sharon S. Ellis, Martha D. Yow, Winnie B. Stephenson, and J. L. Melnick, Department of Pediatrics and Virology and Epidemiology, Baylor College of Medicine, Houston, Texas. (Introduced by Mary Ann South)

A rapid method of diagnosis for enteroviral meningitis has long been needed. Sommerville reported in 1966 that indirect immunofluorescence (IF) could be employed for detecting enteroviral antigens in the leukocytes in the cerebrospinal fluid (CSF). This work has been extended during the past year when 50 children with the clinical syndrome of enteroviral meningitis were studied employing conventional tissue culture methods of virus isolation and IF staining of leukocytes from the cerebrospinal fluid. The cells were concentrated by centrifugation and smears fixed with acetone. The reagents employed in the staining process were the Lim-Benyesh-Melnick enteroviral equine antiserum pools and commercial antihorse globulin conjugated with fluorescin. Enteroviruses (13 different serotypes of echoviruses and coxsackieviruses) were isolated from the CSF in 16 patients and were diagnosed by IF technique in 11 of the 16. The sensitivity of the IF technique was demonstrated by results in an additional 17 patients. In these 17 children enteroviruses were not isolated from the C.S.F. but were isolated from throat or rectal swabs. In 14 of the latter 17 patients, IF and type-specific diagnosis of viral meningitis was made on direct examination of the leukocytes from the CSF and the same enterovirus type was isolated from throat or rectal swabs in tissue culture. This technique promises to be a valuable and sensitive method of rapidly establishing a specific diagnosis in enteroviral meningitis.

INCREASED ACTIVITY OF NBT REDUCTION BY POLYMORPHONUCLEAR LEUKOCYTES IN PHARYNGITIS DUE TO BETA HEMOLYTIC STREPTOCOCCUS.

L. Douglas Wilkerson and Owen C. Grush, introduced by R. W. Blumberg. Department of Pediatrics, Emory University School of Medicine, and Grady Memorial Hospital, Atlanta.

A preliminary study was performed to test the ability of Nitro-Blue Tetrazolium dye reduction by polymorphonuclear leukocytes to distinguish between pharyngitis or tonsillitis due to beta hemolytic streptococcus and that due to other causes. Only throat cultures producing 10 or more colonies of Group A beta hemolytic streptococcus were considered positive; all others were considered negative. acute and two-week convalescent sera were obtained from patients with negative cultures for serological changes associated with streptococcal and viral infections.

Previously established healthy controls in this laboratory range from 1 to 10% activity of NBT dye reduction. 16 of 17 patients with negative cultures had activity of NBT in the range of 1 to 10%, or the same as healthy controls. These negative cultures include non-beta hemolytic streptococci, various other bacteria, and also represent viral infection, in some cases indicated by serology. 4 of 5 patients with pharyngitis and positive cultures had activity of NBT dye reduction of 11% or greater. Preliminary results indicate that this test may be of clinical use in rapid recognition of pharyngitis due to Group A beta hemolytic streptococcus.

In patients and controls the increasing activity of NBT reduction over a series of dilutions increasing concentrations of heparin was demonstrated. Thus, even healthy controls could be demonstrated to have increased NBT reduction by sufficiently increasing concentration of heparin. This suggests the necessity of very strict technical control.

POLYPEPTIDES OF RESPIRATORY SYNCYTIAL VIRUS

Mary W. Treuhaft and Marc O. Beem, Pritzker School of Medicine in the Division of Biological Sciences of the University of Chicago, Department of Pediatrics, Chicago

Respiratory syncytial (RS) virus grown in HEp-2 cells in the presence of ^{3}H-amino acids was purified and then analyzed by SDS-polyacrylamide gel electrophoresis for component polypeptides. Gels were analyzed for proteins staining with coomassie blue and for radioactive proteins. The stained and radioactive protein profiles were interpreted to indicate RS is composed of 7 polypeptides ranging in molecular weight from 26,500 to 90,000.

Intracellular proteins synthesized by HEp-2 cells during the last 12 hours of a 48 hour growth period were examined by the same method for infected and control cells. In contrast to control cells, infected cells displayed considerable restriction of the number of newly synthesized proteins associated with mitochondrial and microsomal subcellular fractions. The majority of the newly synthesized proteins associated with mitochondrial and microsomal fractions of infected cells displayed identical electrophoretic mobilities to virion polypeptides. However, the profile of newly synthesized proteins associated with soluble fraction of infected cells was very similar to that of the soluble fraction of control cells and was apparently unrelated to viral synthesis.

THE PATHOPHYSIOLOGY OF VIRAL INDUCED FETAL GROWTH RETARDATION. Terry Yamauchi, Joseph W. St. Geme, Jr., and William Oh. UCLA Sch. of Med., Harbor Gen. Hosp., Dept. of Ped., Torrance, Calif.

Placental insufficiency resulting from uterine vessel ligation causes fetal growth retardation (FGR). In the avian species it has been demonstrated previously that embryonic mumps virus infection produces FGR. This model presents a unique opportunity to study the direct effect of virus on the embryo in the absence of a placenta. It was important to determine whether viral induced FGR was the result of decreased cell number or decreased cell size.

The weight, RNA and protein (a reflection of cell size) and DNA (a reflection of cell number) content were determined for the organs of 8 infected and 19 control hatchling chicks. The weight, RNA and protein content of the liver, kidney, heart, and spleen from infected and control groups were similar. However, the weight, RNA and protein content of the brain and carcass of infected chicks were significantly less than control chicks ($p<0.05$).

Organs from infected and control chick fetuses were removed at 12 and 20 days of incubation and cultivated in vitro. The rates of cell replication were similar, consistent with the observation that there was no difference in the DNA content of comparable organs from infected and control chicks. Replicate cell cultures of normal fetal organs were infected with mumps virus and long-pulsed with isotopically labelled precursors of cellular DNA, RNA and protein. There was no difference in the DNA, RNA and protein metabolism of the infected and non-infected cultures, suggesting the possibility of an indirect effect of virus on the alteration of cellular growth.

Organs were assayed for virus and the heart yielded the highest titers of virus throughout incubation, consistent with the development of myocarditis previously reported. We speculate that altered cardiac function results in systemic hypoperfusion of peripheral tissues, the brain and carcass, with consequent diminution of cell size rather than cell number.

AGAR GEL PRECIPITIN TEST FOR THE RAPID DIAGNOSIS OF VARICELLA-ZOSTER INFECTION. S.A. Uduman, A.A. Gershon, and P.A. Brunell. New York Univ. Sch. of Med., Dept. of Pediatrics

An agar gel precipitin test was evaluated for rapid laboratory differentiation between varicella-zoster (V-Z) infections and other vesicular eruptions. Vesicular fluids and scabs were obtained at intervals from patients with V-Z infections, and gel precipitin tests were performed along with attempts at virus isolation. A double diffusion precipitin technique with positive control V-Z antigen and zoster immune serum was used. In a prospective study of 50 patients, 30 with clinical varicella and 20 with clinical zoster, gel tests were performed on 117 occasions. Of 71 vesicular fluids tested, 67 were positive for V-Z antigen. Negative reactions occurred only late in the course of illness, and vesicular fluid obtained previously had been positive for V-Z antigen. Positive reactions were obtained as late as 14 days after the onset of varicella and up to 20 days after the onset of zoster. Virus was isolated from vesicular fluid on only 6 of 60 occasions during the first 5 days after the onset of rash. Results of gel precipitin tests were available within 24 hours, much earlier than virus isolation and/or serologic confirmation. Atypical chickenpox which had been misdiagnosed clinically as generalized herpes simplex, disseminated vaccinia, and erythema multiformae was correctly identified as varicella by the gel precipitin test. The gel precipitin test is a specific and sensitive test for the diagnosis of V-Z infections.

METABOLISM

First Session

PYRUVATE CARBOXYLASE: TWO FORMS IN HUMAN LIVER. E. Delvin, J.L. Neal and C.R.Scriver. McGill University-Montreal Children's Hospital Research Institute, Montreal 108, Canada.

Recent work on mammalian liver has revealed two fractions of pyruvate carboxylase (EC 6.4.1.1) whose apparent Km values for pyruvate are about 0.4 and 4.0 mM. Nine samples of human liver were obtained, six at operation and three not later than six hours after death. The enzyme was assayed by a modified Utter and Keech method on the mitochondrial enriched fraction. When the pyruvate concentration was varied between 0.1 mM and 10 mM, pyruvate carboxylase exhibited two values for the Km-pyruvate similar to those obtained for other mammalian livers. Upon computer resolution, the first component had a Km value of 0.4 mM and accomodated 80% of the pyruvate conversion to oxaloacetate at the usual intracellular concentration of pyruvate. The second component had a Km value of 3.7 mM. Stimulation of the high-Km component and inhibition of the low-Km component by 6.0 mM glutamate was observed. Further evidence for two forms of pyruvate carboxylase activity in human liver was found in a child with a congenital disorder of gluconeogenesis, and with plasma accumulation of pyruvate, lactate and alanine up to 10 x normal. A deficiency of the low-Km component of liver pyruvate carboxylase was found; the normal high-Km fraction was retained. These findings indicate molecular and genetic heterogeneity of an important enzyme serving gluconeogenesis in man.

THE ULTRASTRUCTURE AND LIPID COMPOSITION OF CULTURED SKIN FIBROBLASTS IN CHOLESTEROL ESTER STORAGE DISEASE. John C. Partin and William K. Schubert. The Children's Hospital Research Foundation, Cincinnati, Ohio 45229.

Cultured skin fibroblasts were obtained over a period of 3 years from a boy with cholesterol ester storage disease (Am. J. Med. 44:538, 1968). Cultures grown in McCoy's 5a with 30% fetal calf serum consistently demonstrated crystalline inclusions through passage 15. Such inclusions were not seen in unaffected members of his family or in cultures from 20 other individuals. The inclusions resembled liquid crystal profiles found in liver of the same patient. They were semilunar or angular electron lucent images immersed in an electron dense material contained in membrane bounded structures, probably lysosomes. As in liver, angular profiles are found in dilated vesicles of smooth endoplasmic reticulum. Lipid analysis by gas chromatography (sample size: 250 mgm wet wt., 4-8 mgm lipid) showed:

	mgm per mgm Kjeldahl nitrogen	
	Patient	Normals
Total Lipid	1.992	1.822
Cholesterol	.200	.183
Cholesterol Ester	.332	.073
Free Fatty Acid	.012	.021
Triglyceride	.145	.227
Total Phospholipid	1.179	1.004

As in the liver, the skin fibroblasts lack acid hydrolase activity against cholesteryl oleate and tripalmitin (Method: Hayase and Tapple, J. Bio. Chem. 245:169, 1970). These data show that the skin fibroblasts in cholesterol ester storage disease share both the ultrastructural and biochemical lesion with the liver parenchyma. *Unexplained are the clinical and ultrastructural* dissimilarity of cholesterol ester storage disease and Wolman's disease, both of which exhibit deficient acid hydrolase activity.

(Supported by Grants RR-123 and RR 05535)

METHYLMALONYL-COA RACEMASE DEFECT: ANOTHER CAUSE OF METHYLMALONIC ACIDURIA. Ellen S. Kang, Philip J. Snodgrass and Park S. Gerald, Harvard Med. Sch., Child. Hosp. Med. Center, Dept. of Ped., and Peter Bent Brigham Hosp., Dept. of Med., Boston, Mass.

A newborn infant with metabolic acidosis, coma and hyperammonemia, treated with 4 exchange transfusions, antibiotics and maintenance of fluid, electrolyte and caloric needs did not clinically improve despite normalization of blood ammonia levels. Gastrointestinal hemorrhage developed without a further rise in the blood ammonia level. Studies on physiological fluids, fibroblasts cultured from skin and liver obtained at autopsy at 11 days of age indicated the presence of large amounts of methylmalonic acid in the blood and urine. The conversion of C^{14} labelled propionate, methylmalonate and succinate to $C^{14}O_2$ by intact fibroblasts indicate a block between methylmalonate and succinate metabolism. The concentration of Vitamin B_{12} co-factor for the isomerase enzyme, 5'deoxyadenosylcobalamin (DBCC), was low normal and methylmalonate metabolism was not enhanced by excess amounts of DBCC in vitro. Tritiated methylmalonyl-CoA was converted to labelled succinate on incubation with homogenates of liver and fibroblasts indicating intact isomerase activity. In the liver, this conversion was 50% of normal, consistent with the proportion of the (b) or L form of methylmalonyl-CoA present in the chemically synthesized compound. The specific assay for racemase activity; namely, the ability to convert the (a) or D form of the thioester to the (b) or L form by incorporation of a proton (H^3) from the surrounding media (H_3^3O) by the liver homogenate indicates this enzymatic activity was deficient. The activities of the urea cycle enzymes were low but none were rate-limiting. To our knowledge, this is the first description of defective methylmalonyl-CoA racemase activity. This disorder should be considered in the differential diagnosis of methylmalonic aciduria along with defective isomerase activity.

THE MOLECULAR BASIS FOR ACHONDROPLASIA IN THE RABBIT. Gerald J. Bargman, Bruce Mackler, Thomas H. Shepard. University of Washington School of Medicine, Department of Pediatrics, Seattle, Wash.

A strain of rabbits (ac) having a type of achondroplasia inherited as an autosomal recessive, shows morphological and clinical changes closely resembling the human form of achondroplasia. Biochemical studies of mitochondria isolated from cells of the affected animals demonstrate that they are partially deficient in their ability to generate ATP from oxidative metabolism and lack one phosphorylation site (site 3 in the region of cytochrome oxidase) with both succinate and DPN linked substrates. The preparations oxidize succinate and DPNH at normal rates and possess normal amounts of mitochondrial ATPase (coupling factor I) and, therefore, appear to be defective in their ability to generate high energy bonds at site 3 during aerobic metabolism. Tissue culture cells from achondroplastic humans are now under study to determine if they also have defective oxidative energy metabolism.

The above findings suggest that the syndrome of achondroplasia may be a result of defective oxidative-energy formation and represent the first biochemical description of a genetically determined phosphorylation deficiency in a mammalian system.

Hypophosphatemic Rickets Secondary to a Benign Reparative Granuloma of the Radius. James A. Pollack, John D. Crawford, Harvard Med. Sch., Massachusetts Gen. Hosp., Children's Service, Boston.

A nine-year-old boy presented with a history of waddling gait, generalized muscle weakness, and diminishing growth velocity progressive over the prior 16 months. X-rays demonstrated active rickets and a lytic lesion of the distal right radius. Bone structure in films taken prior to age 7 was normal. Serum calcium (9.6 mg%), phosphorus (1.7 mg%) and alkaline phosphatase (31.6 BU) suggested a diagnosis of hypophosphatemic rickets, but no family members had hypophosphatemia. Generalized aminoaciduria and glucosuria were absent, but urinary glycine excretion was increased to 280 mg/24 hours. Renal glomerular function was normal. Serum immunoreactive parathyroid hormone levels were normal and suppressed with induced hypercalcemia. Chemical improvement and radiological healing were not obtained on vitamin D in doses to 200,000 u/day, but occurred promptly, with complete symptomatic relief, when oral phosphate, 1250 mg daily, was added. The lytic radial lesion, initially untouched because of its benign radiologic appearance and its proximity to the epiphyseal center, responded to therapy with increasing sclerosis. Nonetheless, even after three years of medical therapy, continuing activity was indicated by an exacerbation of chemical rickets when vitamin D, but not phosphate, was discontinued. When the patient was 12 years old, the lesion was excised, therapy being discontinued on the day of surgery. Gross and microscopic examination of the tissue revealed only benign, active and sclerotic, reparative granulation tissue. By the 4th postoperative day, the renal clearance of phosphate had returned to normal with a decline in the phosphate-creatinine clearance ratio from 0.38 to 0.12. The urinary excretion of glycine returned to normal slowly over 3 weeks. The patient is now six months post operation without clinical or biochemical evidence of recurrent disease. Our data suggest that acquired hypophosphatemic rickets with phosphaturia and muscle weakness was induced by the elaboration of an unidentified, humoral substance, immunoreactively dissimilar to human parathyroid hormone.

CORRECTION OF IMPAIRED CHEMOTAXIS OF POLYMORPHONUCLEAR LEUKOCYTES (PMNs) FROM PATIENTS WITH DIABETES MELLITUS BY INCUBATION WITH TRIVALENT CHROMIUM IN VITRO. K. Michael Hambidge, Benjamin Martinez, Julia A. Jones, Constance E. Boyle, William E. Hathaway and Donough O'Brien, Dept. of Pediatrics, Univ. of Colorado Medical Center, Denver.

Diabetic PMNs have defective chemotaxis, which can be corrected by incubation with insulin in vitro, but is not correlated with plasma insulin levels and is not attributable to a simple deficiency of circulating insulin (A.G. Mowat and J. Baum, N.E.J.M., 284:621, 1971). The essential trace nutrient chromium (Cr) facilitates the peripheral action of insulin (W. Mertz, Physio. Rev., 49:163, 1969). The maximal effect of insulin on Cr deficient tissues in vitro is achieved only with the addition of Cr^{+++} to the medium or, alternatively, with higher concentrations of insulin than are required by tissues which are not Cr depleted. The insulin-enhancing effect of Cr^{+++} is observed only on tissues which are Cr deficient.

The aim of this study was to determine if diabetics whose PMNs exhibited defective chemotaxis were Cr deficient, by determining if the impairment of chemotaxis could be corrected by incubation with Cr^{+++} in vitro. The techniques for measuring chemotaxis, for incubation with insulin and for calculation of chemotactic index (CI) were reported by Baum, et al (J. Lab. Clin. Med., 77:501, 1971); PMNs were also incubated with 25ppb Cr^{+++} (chromic chloride), 0.25ml per 0.5ml of cell suspension for 3 hrs. Results were as follows: The mean CI for Controls (10) = 473 ± 28 (1S.D.) and for juvenile insulin-dependent diabetics (JDMs) (10) = 293 ± 55. Following incubation of PMNs of 2 JDMs with Cr^{+++}, the CI increased from 325 to 426 and from 312 to 466; similarly in 2 gestational diabetics the CI increased from 330 to 463 and from 335 to 487. If Cr was not added to the incubation medium, 100 μu/ml insulin was required to achieve a normal CI. The observed effect of Cr without added insulin suggests that adequate insulin was present from the original plasma. It is concluded that the defective chemotaxis in these patients resulted from chromium deficiency.

HORMONAL MODIFICATION OF AMINO ACID TRANSPORT IN CULTURED HEPATOMA CELLS. William L. Risser and Thomas D. Gelehrter, (Intr. by Charles D. Cook) Yale Univ. Sch. of Med., Depts. Ped. and Med., Div. of Med. Genetics, New Haven.

HTC cells, an established line of rat hepatoma cells in tissue culture, provide a simple in vitro system in which to study hormonal effects on hepatic protein metabolism. Dexamethasone (10^{-7}M) induces a 5 to 10-fold increase in the rate of synthesis of tyrosine aminotransferase (TAT) in these cells without increasing total protein synthesis. Insulin (4 μg/ml) produces a further 2-fold rise in TAT activity and a modest increase in amino acid incorporation into total protein. In order to assess the role of amino acid transport in these hormonal effects we have investigated the transport of α-aminoisobutyric acid (AIB), a non-metabolized amino acid analogue.

HTC cells, in suspension culture in a serum-free medium containing essential amino acids and glucose, actively transport AIB by an energy-dependent, saturable process with a K_m =0.45 mM and V_{max} =0.95 mMoles/ml/min. After 150 minutes incubation, the intracellular concentration of AIB is 18 times the extracellular concentration. After 20 hours incubation with dexamethasone, at which time TAT has been fully induced for several hours, the V_{max} of AIB transport is reduced to 0.19 mMoles/ml/min without any significant change in K_m. Under these conditions, insulin increases AIB uptake, restoring V_{max} to 0.75 mMoles/ml/min, again without changing K_m. This effect is observed within two hours after addition of insulin, at which time its effects on TAT are maximal. Significantly, insulin does not affect AIB transport in cells not previously treated with dexamethasone. These results suggest that dexamethasone reduces the capacity for transport of AIB in HTC cells without altering the affinity of the carrier system for substrate. Insulin can restore this capacity but has no effect in untreated cells.

CORRECTION OF THE α-GALACTOSIDASE DEFICIENCY IN FIBROBLASTS FROM PATIENTS WITH FABRY'S DISEASE. R. Matalon, G. Dawson and Y. -T. Li (Intr. by: Albert Dorfman) University of Chicago, Chicago, Ill. 60637 and Tulane University, Covington, La. 70433

Fabry's disease is an X-linked recessive disorder of glycosphingolipid metabolism, usually manifested in the second decade of life. Fibroblasts cultured from patients with Fabry's disease show α-galactosidase deficiency and accumulation of galactosyl-galactosyl-glucosylceramide (GL-3). Turnover studies with U-^{14}C-D-glucose confirm that GL-3 is not catabolized by these fibroblasts. In vitro studies have shown that the terminal galactose residue of GL-3 is liberated by preparations of α-galactosidase from plant sources. Since α-galactosidase from the fig has been isolated in a highly active and stable form, the possibility of replacement enzyme therapy in tissue culture was investigated with such a preparation. Fabry fibroblasts (approximately 20 x 10^6 cells) were labelled with U-^{14}C-D-glucose for 48 hours and incubated for 24 hours with 4 units of α-galactosidase (1 unit hydrolyses 1 millimole of galactose per minute at 37°). The cells were harvested and compared to Fabry cells which had been labelled with ^{14}C-glucose but not treated with the enzyme. α-Galactosidase activity in enzyme-treated Fabry cells rose to the normal range, while untreated Fabry cells had little if any activity. In contrast to untreated Fabry cells which contained large amounts of labelled GL-3, only small amounts of labelled GL-3 were present in α-galactosidase-treated cells. In treated cells, ^{14}C-label was found primarily as glucosyl-ceramide, a catabolite of GL-3. These studies show unequivocally that exogenous enzyme can be taken up by cells, incorporated into lysosomes and remain active. (Supported by USPHS grants HD-04583, AM-05996, and I RO1 NS 09626).

PROPIONYL-CoA CARBOXYLASE DEFICIENCY (PROPIONICACIDEMIA): ANOTHER CAUSE OF HYPERAMMONEMIA. Richard D. Landes, Gordon B. Avery, Frank A. Walker and Y. Edward Hsia, Children's Hosp. of D.C., Dept. of Ped., George Washington Univ., Washington, D.C., The Milwaukee Children's Hosp., Dept. of Ped., Milwaukee, Wisc., and Yale Univ. School of Med., Dept. of Med. and Ped., New Haven, Conn.

Although hyperglycinemia, leukopenia, thrombocytopenia, hypogammaglobulinemia and ketoacidosis are well known complications of propionicacidemia, hyperammonemia, hitherto, has not been recognized as a major complication of this disorder.

A 2 year old girl who experienced several episodes of vomiting, constipation, lethargy, coma, ketoacidosis, seizures, leukopenia and thrombocytopenia was found to have associated hyperammonemia up to 300 μg% (normal 80 μg%). Evaluation for protein intolerance and hyperammonemia showed hyperglycinemia (7.4 mg%; normal 1.7±0.63 mg%), hyperalanemia (9.6 mg%; normal 2.8±0.63 mg%), and hyperglutaminemia (16.7 mg%; normal 10.8±0.5 mg%). Hepatic assays of the five enzymes of the urea cycle revealed moderately depressed activity of several of the enzymes but no specific deficiency. Studies with her leukocytes and skin fibroblast cultures revealed marked propionyl CoA carboxylase deficiency. A protein intake of more than 1.5 gm/Kg/day produced symptoms along with pronounced hyperglycinemia and moderate hyperammonemia (100–150 μg%).

A boy with all the classical features of propionicacidemia, whose sister died in infancy of a similar metabolic disorder, was also found to have hyperammonemia precipitated by protein, infections or constipation. Despite correction of associated ketoacidosis, hyperammonemia and lethargy persisted for several days.

Prompt recognition of propionicacidemia is imperative and should be considered in the differential diagnosis of hyperammonemia. Early recognition along with careful protein restriction may circumvent many of the serious consequences which otherwise follow.

DEFECTIVE ISOLEUCINE METABOLISM AS A CAUSE OF THE "KETOTIC HYPERGLYCINEMIA" SYNDROME. Richard E. Hillman, Ralph D. Feigin, Stanley M. Tenenbaum and James P. Keating. Washington University School of Medicine, St. Louis Children's Hospital, Department of Pediatrics, St. Louis, Missouri.

Inherited defects of propionyl CoA carboxylase and methylmalonyl CoA isomerase have been demonstrated in patients with the "ketotic hyperglycinemia" syndrome. The case described here presented in the early weeks of life with severe ketosis, long chain ketonuria and ketoaciduria, hyperammonemia, sustained hyperglycinemia, neutropenia, and thrombocytopenia. Propionic and methylmalonic acid metabolism in white cells and cultured fibroblasts are normal, but isoleucine conversion to CO_2 is only 40% or less of the control values. The conversion of isoleucine to ketoacids and butanone was demonstrated in cultured fibroblasts suggesting that the metabolic block occurs at a β-ketothiolase reaction which normally cleaves α-methylacetoacetyl CoA to acetyl CoA and propionic CoA. The defect in this child is further evidence that isoleucine degradation is analogous to fatty acid oxidation. This case also demonstrates that the hyperglycinemia and other findings in this syndrome are secondary to products of isoleucine metabolism rather than to propionic acid or methylmalonic acid.

METABOLISM

Second Session

CYSTATHIONINURIA ASSOCIATED WITH NEUROBLASTOMA. Paul Wong, Ira M. Rosenthal, and Ralph Kathan. Chicago Medical School, Abraham Lincoln School of Medicine of the University of Illinois College of Medicine, Mount Sinai Hospital, University of Illinois Hospital, Departments of Pediatrics, Chicago.

The presence of cystathioninuria was first noted in 6 cases of functional neural tumors by Gjessing. Von Studnitz later demonstrated cystathioninuria in 14 of 20 children with neuroblastoma with increased catecholamine production. No correlation was found between cystathioninuria and metastasis as previously suggested. Greater frequency of cystathioninuria was found in the younger children. We have examined the urines of 26 children with neuroblastoma. Cystathioninuria was determined by column chromatography and VMA, metanephrine (MN) and normetanephrine (NMN), and norepinephrine (N) and epinephrine (E) by standard methods. Multiple determinations have been done on many of the patients for cystathionine, VMA, NM and N&E. A total of 76 urines have been analyzed to date. In 20 of the 26 cases both VMA and cystathionine excretions were elevated. In 2 cases VMA was elevated and cystathionine was normal. In 3 cases VMA excretion was normal and cystathionine was elevated. In one case VMA and cystathionine were normal. Similar correlations have been made for NM and N&E excretion and cystathionine. Little correlation was found between the excess excretion of VMA and of cystathionine. Cystathioninuria is found in most cases of neuroblastoma including some with normal excretion of VMA and other catecholamine degradation products. It may be useful to follow cystathionine excretion in studying the response to therapy of patients with neuroblastoma.

COLLAGEN METABOLISM IN FIBROBLASTS FROM PATIENTS WITH OSTEOGENESIS IMPERFECTA. David M. Brown, Univ. of Minnesota College of Medicine, Departments of Ped. & Lab. Med., Minneapolis, Minnesota

Fibroblasts produce several forms of collagen molecules which are similar to collagen found in other tissues. The rates of production of collagen and the nature of its cross-linkage as produced by fibroblasts from patients with osteogenesis imperfecta (o.i.f.) in tissue culture monolayer and from control subjects (c.f.) were compared. Fibroblasts were pulsed with ^{3}H-proline on day 12 and the cells and media harvested on day 15. The ratio of ^{3}H-hydroxyproline (HYDROX)/proline (PRO) X 100 of o.i.f. ranged from 1.8 to 4.0, mean = 2.6 whereas c.f. had values of 4.5-17.2 mean = 11.9 (5 experiments). HYDROX/PRO X 100 ratio of the dialyzed incubation media (representing macromolecules) of o.i.f. was 4.3, 6.8 and 8.6 while this ratio in c.f. was 9.8 and 11.0. No differences in this ratio were found in non-dialyzed media. Cross-linkage of collagen can be measured indirectly by the tendency for less cross-linked collagen to be more easily extracted by neutral salt and weak acid solutions. Sequential extraction of the cells and insoluble material with buffered 0.5 M NaCl and 0.5 M HOAc followed by dialysis of the extracts yielded a larger proportion of the total collagen (^{3}H-HYDROX) of the o.i.f. monolayer within the soluble fractions than in the insoluble pellet as compared with c.f. The soluble (NaCl and HOAc) fractions of o.i.f. contained 42 - 78.6% (range), mean = 56.1%, of total HYDROX whereas c.f. contained 13.9 - 26.3% (range), mean = 21.9% of total HYDROX. Total protein content of o.i.f. and c.f. did not differ. These studies suggest that o.i.f. have qualitative and quantitative defects in collagen synthesis.
(Research supported in part by grants from the N.I.H. AM-13756 and the Minnesota Arthritis Foundation).

A HYPERKALEMIC, SALT-WASTING SYNDROME IN INFANCY. Amin Y. Barakat, Zoe L. Papadopoulou and Gilbert P. August. (Intr. by Wellington Hung). Children's Hospital, Washington, D. C.

The response to treatment and subsequent course of a 6-day old female with hyponatremia and hyperkalemia appear to distinguish her from previously described patients with pseudohypoaldosteronism. Initial electrolytes were: Na, 117 mEq/L; K, 9.0 mEq/L; chloride, 87 mEq/L; and CO_2, 12 mEq/L. The external genitalia were normal. Treatment was started with saline and desoxycorticosterone acetate (DOCA). Due to EKG changes of hyperkalemia, Kayexelate was given. Hyponatremia responded but hyperkalemia required repeated doses of Kayexelate in spite of 2.3 g of oral NaCl and as much as 5 mg of DOCA daily. Urinary excretion of aldosterone was 36 and 33 ug/24 hours (normal: 0.4-2.5). Pregnanetriol, 17-ketosteroids and creatinine clearance were normal. Treatment with 5.3 g/day of oral NaCl maintained her serum Na and resulted in weight gain, but hyperkalemia still required Kayexelate every other day. The urinary aldosterone was now 64 ug/24 hours. On the 28th day she became anoretic, vomited and the serum K rose to 10.8 mEq/L and she died. At autopsy, the kidneys and adrenals were normal. The inability to control the hyperkalemia distinguishes this patient from others with pseudohypoaldosteronism. This contention is supported by the known ability of animals and patients with aldosterone insufficiency to be treated only with NaCl. The action of aldosterone appears to be dependent upon its binding to a cellular receptor protein and then the induction of protein synthesis. Subsequently, the availability of high energy phosphate compounds may be required for the function of the membrane Na-K pump. Such a fundamental defect in membrane transport may exist in our patient rather than just a renal tubular unresponsiveness to aldosterone which is implied in pseudohypoaldosteronism.

FAMILIAL IDIOPATHIC LACTIC ACIDOSIS -- PETITE MUTANT DISEASE IN MAN? Anna Binkiewicz, Robert L. Jungas, Hilel Hochman and Boris Senior. Pediatric Endocrine-Metabolic Service, Tufts-New England Medical Center Hospitals and Dept. of Biological Chemistry, Harvard Medical School, Boston.

We have studied 2 siblings, aged 6 and 4 years respectively, with severe physical and mental retardation who persistently exhibit concentrations of lactate disproportionately elevated in relation to the concomitant levels of pyruvate. The concentrations of lactate were 30-40 mg. per cent vs. 10 mg. per cent in normal children. Pyruvate concentrations were 0.9-1.0 mg. per cent vs. 0.85 mg. per cent. The lactate:pyruvate ratios were several fold the normal ratio $\pm$ 10 -- indicating an excess of lactate. Hepatomegaly, hypoglycemia, organic aciduria and aminoaciduria were absent.

The equation: Lactate = Pyruvate x K $\frac{[NADH_2]}{[NAD]}$ emphasizes that elevated levels of lactate may result from decreased oxidation of $NADH_2$ as well as from increased levels of pyruvate. Oxidation of pyruvate (Pyruvate-1-^{14}C) by white cells was normal. Lactate administered intravenously was disposed of abnormally slowly. The increased formation of $NADH_2$ by the administration of ethanol resulted in further elevation of the lactate. No such effect was seen in controls.

The results are compatible with an impaired oxidation of $NADH_2$ rather than an accumulation of pyruvate, which implies decreased effectiveness of the mitochondrial respiratory chain, a disorder which may be the human counterpart of the petite mutant mitochondrial disorder of yeast.

HYPERGLYCINEMIA: IN VIVO COMPARISON OF NON-KETOTIC AND KETOTIC (PROPIONIC ACIDEMIC) FORMS. II. VALINE RESPONSE IN NON-KETOTIC HYPERGLYCINEMIA. Harvey L. Levy, Robert N. Nishimura, Arline M. Erickson, and Stanislawa E. Janowska; Harvard Med. Sch., Dept. of Neuro., Mass. Gen. Hosp. Boston, Mass.; E.K.S. Center for Men. Ret., Waltham, Mass.

In at least two types of ketotic hyperglycinemia (propionic acidemia and methylmalonic acidemia) the basic metabolic defects seem to have been established as deficiencies in propionyl-CoA carboxylase activity in the former and methylmalonyl-CoA isomerase in the latter. However, in non-ketotic hyperglycinemia the basic defect is unknown. Data indicating reduced conversion of glycine to serine is not conclusive and this reduction could be a secondary phenomenon.

We have compared an 18-month-old male with unequivocal evidence of non-ketotic hyperglycinemia with a 13-month-old female who has propionic acidemia. In response to oral loading with L-valine (200 mg/kg) the infant with non-ketotic hyperglycinemia became somnolent in 40 minutes and semi-comatose in one hour. He remained in this state for 6 hours. During this time there was no acidosis, ketosis, hyperammonemia or hypoglycemia. Blood glycine concentrations rose above his baseline levels (3.87 to 11.40 mg/100 ml.). Concentrations of valine and the short-chain fatty acids showed a normal response. In contrast the infant with propionic acidemia remained clinically unchanged for the first 30 hours after the L-valine ingestion whereupon she became profoundly acidotic and ketotic. Two months later the infant with non-ketotic hyperglycinemia was given L-valine 50mg/kg orally and within 40 minutes he became severely ataxic and within 90 minutes developed somnolence, lasting for 3 hours. Again no biochemical findings explanatory of the clinical state were noted in blood, urine and CSF.

This severe and rapid response to L-valine in non-ketotic hyperglycinemia was in contrast to the unchanged clinical state following loading doses of L-glycine, L-isoleucine, and L-leucine and indicates that in this disorder there may be a defect in valine metabolism.

VITAMIN D DEPENDENCY WITH DIBASIC AMINOACIDURIA ASSOCIATED WITH ANTICONVULSANT THERAPY. Myron Genel, Peter H. Berman, Grant Morrow and Alfred M. Bongiovanni. Depts. of Peds., Yale Univ. Sch. of Med., New Haven, and Univ. of Penna. Sch. of Med., Philadelphia; Children's Hosp. of Philadelphia.

Vitamin D dependency has been delineated as an inherited disorder with hypocalcemic, hypophosphatemic rickets and generalized aminoaciduria responsive to therapy of about 100 times daily maintenance. A similar constellation has been recently associated with anticonvulsant therapy via a mechanism not delineated but ascribed to altered Vitamin D metabolism by drug induced hepatic enzymes. A girl with psychomotor retardation and a mixed type convulsive disorder poorly controlled on high doses of phenobarbital and mysoline presented at 18 months with hypocalcemic rickets (Ca=8.3-9.0 mg%; P=2.0-3.5 mg%; alk p'tase = 20-35 B.U.) unresponsive to a 100,000 U IM dose of Vitamin D. At 20 months a predominately dibasic aminoaciduria was found: lysine 426 mg/24 hrs., cystine 42 mg/24hrs. and ornithine 19 mg/24 hrs. Lysine clearance was 38.5 ml/min/1.73 m^2 or 34% of GFR. Arginine was also slightly increased and threonine, serine and glycine moderately increased. Plasma amino acids were normal. Phosphate excretion was not significantly altered (TRP=84-89%) but serum P was low. Serum phenobarbital was 8 mg%. Sephadex LH-20 liquid-gel partition chromatography of plasma after injection of tritiated Vitamin D$_3$ demonstrated an abnormal metabolism of the vitamin with rapid conversion of 25-hydroxycholecalciferol as well as to an unidentified more polar metabolite and very rapid disappearance of ^{3}H-cholecalciferol. 1,25 dihydroxycholecalciferol was not detected. After 5 months therapy with moderate doses of dihydrotachysterol (0.3-0.4 mg/day), healing of rickets occurred and aminoaciduria disappeared. This case represents the first demonstration of an abnormality in Vitamin D metabolism in a patient on anticonvulsant therapy. The predominately dibasic aminoaciduria is presumed to reflect a genetic predisposition amplified under the influence of compensatory hyperparathyroidism.

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KETOTIC HYPOGLYCEMIA: A SYNDROME OF GLUCONEOGENIC SUBSTRATE DEFICIENCY. Mary A. Micka, Glenn T. Peake, R. Philip Eaton, S. Scott Obenshain. (Intr. by Edward A. Mortimer, Jr.) Univ. of New Mexico Sch. of Med., Bernalillo County Med. Ctr. Departments of Ped. and Med., Albuquerque.

Preliminary observations by Pagliara, et al., 1971, suggested that a deficiency of the gluconeogenic substrate, alanine, was the underlying defect in ketotic hypoglycemia, described by Colle and Ulstrom in 1964. Two children with this syndrome, characterized by episodic fasting hypoglycemia with ketonuria and glucagon unresponsiveness, were studied. During a 16-hour fast both had a dramatic fall in serum glucose to 21 mg% and 15 mg%. When they were hypoglycemic, serum alanine concentration determined by amino acid analyzer technique was only 1.7 mg% and 1.3 mg%. Serum alanine concentration in normal fasted children was found to range from 1.9 mg% to 3.6 mg% by our method. Both children had undetectable serum insulin and had high concentrations of endogenous glucagon when they were hypoglycemic and failed to raise their serum glucose following 1.0 mg intravenous (IV) glucagon. However, the oral administration of 12.0 g alanine resulted in a rise in glucose of 51 mg% and 25 mg% within 1 hour. Serum alanine rose to 2.8 mg% within 1 hour following oral alanine. After a 10-hour fast in one patient serum alanine was 2.7 mg% and he was euglycemic at the time. Treatment for 3 days with 300 mg/M^2 cortisone acetate prevented hypoglycemia during a subsequent 16-hour fast (lowest glucose 84 and 77 mg%) and both patients had a greater than 50% rise in glucose after 1.0 mg of IV glucagon. Importantly, following cortisone treatment the fasting serum alanine concentrations were 4.1 mg% and 4.0 mg%.

These data support the concept that alanine deficiency is characteristic of the syndrome of ketotic hypoglycemia and that no other abnormality of hepatic glucose homeostasis need be postulated. Serum alanine determinations must be added as an important criterion for the diagnosis of ketotic hypoglycemia, and treatment must be directed toward preventing depletion of endogenous alanine.

A NEW FORM OF HOMOCYSTINURIA DUE TO $N^{5,10}$-METHYLENETETRAHYDROFOLATE REDUCTASE DEFICIENCY. Vivian E. Shih, Maria Z. Salam, S.Harvey Mudd, B. William Uhlendorf, Raymond D. Adams, Harvard Med. Sch., Dept. of Neuro.; Mass. Gen. Hosp., Joseph P. Kennedy, Jr. Memorial Lab., Neuro. Serv., Boston; N.I.M.H. and N.I.H., Bethesda.

Several causes of excessive homocystine excretion are now known. Among these cystathionine synthase deficiency is most common. A derangement of B_{12} metabolism which impairs the methylation of homocysteine to methionine also results in homocystinuria, in this instance, accompanied by a low or low normal plasma methionine rather than increased plasma methionine in cystathionine synthase deficiency. N^5-methyltetrahydrofolate-homocysteine methyltransferase, the enzyme which catalyzes homocysteine methylation uses a B_{12} derivative as coenzyme and N^5-methyltetrahydrofolate as substrate. We have studied a previously unrecognized folate metabolic error in which amino acid abnormalities were similar to those in the derangement of B_{12} metabolism. The patient is a 16-year-old boy with proximal muscle weakness, waddling gait, and episodes of flinging movements of the upper extremities. Serum folate level was 2.8 mug/ml (N: 6-15+). Serum B_{12} concentration was normal and methylmalonic aciduria was absent. Sixty-five percent of the sulfur of L-methionine (0.5 mmoles/Kg) was converted to inorganic sulfate within 24 hours, a much greater portion than would have occurred in cystathionine synthase deficiency (<10%). $N^{5,10}$-methyletetrahydrofolate reductase activity in cultured fibroblasts was 9% and 28% of the mean control values when assayed with and without added flavin-adenine dinucleotide (FAD) ($p<0.02$ in each case). The activities of N^5-methyltetrahydrofolate-homocysteine methyltransferase and cystathionine synthase were normal. No biochemical response to B_{12} therapy; folic acid therapy greatly reduced homocystinuria. Clinical improvement, however, was not evident.

Two siblings with similar biochemical findings are described in an abstract submitted by Dr. John M. Freeman et al.

STARVATION IN THE OFFSPRING OF HIGH-FAT DIET RATS: A MODEL FOR HYPOGLYCEMIA IN INFANTS OF DIABETIC MOTHERS. *Raul A. Wapnir, J. Tyson Tildon and Marvin Cornblath. Univ. of Maryland Sch. of Med., Dept. of Ped., Baltimore, Maryland & Rosewood State Hosp., Owings Mills, Maryland 21117.*

To determine if prenatal exposure to elevated ketone levels could account for the asymptomatic hypoglycemia in infants of diabetic mothers, ketonuria was produced in pregnant rats by feeding them a 45% fat diet for eight (8) days prior to delivery and the effect of starvation measured in the newborn pups. Twelve hours after birth the blood glucose levels of fed and fasted pups from ketotic dams (KD) were essentially the same. In contrast, the glucose levels in fasted pups from dams fed a control diet (CD) was significantly less than that of their fed litter mates (Δ = 32 mg%). Liver glycogen was also significantly higher in fasted pups (KD) than that in control fasted pups (CD) (1.29 versus 0.4 mg/mg DNA). After 24 hours, blood levels of glycine and glutamine in fasted pups (KD) were also significantly higher than the values in fasted controls (CD). However, at the end of the same period the brain glycogen in the fasted pups (KD) was significantly less than that in the fasted controls (0.072 versus 0.20 mg/mg DNA). These data suggest that pups from KD become less hypoglycemic and withstand the stress of short-termed starvation better than their controls. However, the striking difference in the brain glycogen after 24 hours suggest that continued stress of starvation appears to reverse the protective mechanism and is associated with dramatic changes in the pups from ketotic dams.(Supported in part by NIH Grant, HD-03959-03 and The John A. Hartford Foundation.)

AUTOREGULATION OF GLUCOSE PRODUCTION BY THE ISOLATED PERFUSED HUMAN LIVER. P.A.J. Adam, M. Kekomaki, E.-L. Rahiala, and A.L. Schwartz. Case Western Reserve Univ. Schl. Med. at Cleveland Metropolitan General Hospital and University of Helsinki, Department of Pediatrics.

Thirty-one isolated human fetal livers (13-19 weeks gestation) were perfused for 3 hrs with intermixed tracer glucose-6-H^3 plus one of lactate-3-C^{14}(10mM), alanine-U-C^{14}(10mM) or tracer glucose-6-C^{14}. Glucose production and utilization were measured by the rates of dilution and disappearance of glucose-H^3; and recycling or gluconeogenesis by the incorporation of C^{14} into glucose-1-C^{14}. When glucose was not added in chemical amounts, its concentration in the perfusate rose rapidly during the initial 5 minutes, and more slowly thereafter, reflecting a rapid initial net production rate (1.2±0.3 μmoles/gm.min. Mean ± S.D.) followed by less rapid glucose production (0.4±0.1 μmoles/gm.min) approximating its rate of utilization. When the initial glucose concentration was 2.8 mM (50mg%) a steady state was maintained with rapid exchange of glucose between unlabeled hepatic glycogen and labeled glucose in the medium (0.9±0.3 μmoles/gm.min). The rates of gluconeogenesis and of glucose-C^{14} recycling were negligible. Cyclic AMP release into the perfusate (p moles/gm) was inversely proportional to the liver weight, and was not affected by perfusion with pharmacological amounts of glucagon or insulin. These hormones did not alter glucose production. Perfusion with glucagon plus caffeine raised the cAMP production rate 50-fold, but did not modify hepatic glucose production. Perfusion with cAMP plus caffeine likewise did not affect hepatic glucose production. Only the largest liver (7.7 gm) perfused with glucagon responded with a markedly enhanced glucose production rate, even though its production of cyclic AMP was not increased: Conclusion: the early human fetal liver can respond rapidly to glucose privation by secreting glucose at rates equal to neonatal glucose production. The major determinant of glucose secretion appears to be the plasma glucose concentration rather than pancreatic hormones.

MONITORING DIABETIC CONTROL IN THE HOME: A NEW APPROACH. L. Baker, A. Blumenthal, R. Kaye. Children's Hospital of Philadelphia.

Recent studies showing a biochemical link between chronic hyperglycemia and diabetic complications create a need for the question of control in diabetes to be reexamined. A major problem has been the definition of control. Definitions which use blood glucose levels have been plagued by the problem of what isolated measurements of glucose (once a week, once a month, etc.) can tell about the intervening times.

A method for monitoring glucose in the home situation has been devised. It involves finger puncture, collection of approximately 0.05 ml of blood in a heparinized capillary tube, discarding the sedimented red blood cells and sealing the tube containing the plasma. These tubes are labeled and kept in the home freezer until brought in at the next visit. The specimens are analyzed in duplicate on a Beckman Glucose Analyzer. Glucose levels in plasma collected in this manner are stable over a wide range (50 - 400 mg%) and over a long time period (2 months).

Preliminary trials with juvenile diabetic volunteers indicate:

1) It is a technique easily learned and acceptable to many patients;

2) The ability to do frequent plasma glucoses in the home gives a better profile of exactly what is happening, and this allows for more meaningful attempts at the definition of 'control'; and

3) This technique has immediate therapeutic implications and can be used in long term prospective studies.

METABOLISM

Read by Title

TREATMENT OF FAMILIAL DYSAUTONOMIA WITH URECHOLINE. Felicia Axelrod, Melvin Becker, Nancy Branom, Richard Nachtigall, and Joseph Dancis, New York University School of Medicine, New York University Medical Center, Departments of Pediatrics, Radiology and Medicine, New York.

Children with familial dysautonomia manifest deficiencies in the sensory and autonomic nervous systems. Previous investigations have demonstrated that I.V. methacholine (mecholyl^R) will correct some of these deficiencies, suggesting that cholinergic agents could be effective for treatment. Bethanechol (urecholine^R) was selected for trial because its major action is muscarinic. This feature indicated the possibility of useful therapeutic effects with minimal risk of adverse reactions.

Six children were treated. All had abnormal cine-esophagrams and 4 had severe G.I. symptoms including vomiting crises, retching and gastric distension. All had reduced to absent tear flow as measured by Shirmer test. Following treatment with urecholine, the cine-esophagrams were improved, at times dramatically. There was a reduction or elimination of G.I. symptoms in 3 of 4 cases. One child with urinary incontinence and poor urinary stream had prompt relief. Two patients with nocturnal enuresis were cured. Tear flow was increased to normal, the amount of increase being dose related. However, contrary to the experience with methacholine, there was no improvement in sensory defects (i.e. return of knee jerks, taste or normal histamine response) indicating a difference in the range of action of the two drugs.

Urecholine is useful in the treatment of familial dysautonomia.

HYPOKETONEMIA IN VON GIERKE'S DISEASE (GLUCOSE-6-PHOSPHATASE DEFICIENCY) GLYCOGEN STORAGE DISEASE (GSD) TYPE I. Anna Binkiewicz, Abdollah Sadeghi-Nejad and Boris Senior. Pediatric Endocrine-Metabolic Service, Tufts-New England Medical Center Hospitals, Boston.

Ketones are formed by the liver from free fatty acids (FFA) released from adipose stores when glucose and insulin are in short supply. The patient with GSD Type I characteristically manifests hypoglycemia, hypoinsulinemia and high levels of FFA and should, therefore, be particularly prone to develop high levels of ketones. Such a tendency has been repeatedly stressed in the literature.

We examined how readily patients with the 3 major varieties of liver glycogenoses became ketonemic. Patients lacking either "phosphorylase" Type VI or amylo-1,6-glucosidase, Type III, activities did manifest marked ketonemia but, unexpectedly, the 5 patients with GSD Type I developed significantly lower levels of serum betahyroxybutyrate (BOHB) than 8 age matched control children ($p<0.001$). This occurred despite similar levels of FFA and of glucose and concentrations of insulin which if anything were lower. Since the lower levels of BOHB could have resulted from either decreased formation or more rapid utilization, we determined the disappearance rate of intravenously administered BOHB (15 gm/m^2 as a 10% solution) in 3 patients with GSD Type I and in 8 control children. The half time for the disappearance of BOHB was found to be 280 minutes in the patients and significantly shorter, 93 minutes, in the control group ($p<0.01$) indicating decreased formation of BOHB in GSD Type I.

The implications are (1) that acidosis if present in GSD Type I results from lactate and not ketones, (2) that apart from FFA and insulin, the flow of intrahepatic metabolites can modulate ketone production and (3) ketones do not seem to comprise a major alternate fuel to glucose in these patients.

REMISSION IN IDIOPATHIC HYPOGLYCEMIA OF INFANCY (IHI): FACT OR FICTION? L. Baker. Children's Hospital of Philadelphia.

IHI is described as a disease whose natural history includes a spontaneous remission. To investigate this further, 4 children with documented IHI were restudied. All had had the leucine sensitive variety of IHI and had required vigorous treatment (which included steroids, zinc glucagon, surgery and diazoxide). All were currently in remission, defined as being completely symptom-free while on no medications.

Three of the 4 developed hypoglycemia (plasma glucose less than 40) upon fasting (18, 22 and 24 hours) with evidence of relative hyperinsulinism, while the 4th child fasted 36 hours without hypoglycemia. Leucine tolerance tests were still abnormal in these 3 patients, with a decrease of plasma glucose of greater than 20 mg%, despite no actual hypoglycemia. Oral GTT were also abnormal in these patients, with peak values greater than 160, and a rapid decline by 5 hours, although not to hypoglycemic levels.

These data would indicate: 1) The remission of IHI is a quantitative one in most cases; 2) The basic disease defect would appear to involve insulin release. It can be unmasked by prolonged fasting which provides a negative stimulus for insulin release and requires the 'turn-off' of insulin.

These data also support the concept that hyperinsulinism is a common causative factor in IHI, and should logically be split away from this larger 'wastebasket' diagnostic entity.

FETAL GLUCOSE AND O_2 UPTAKES IN FED AND STARVED SHEEP. Robert D. Boyd, Frank H. Morriss, Jr., Giacomo Meschia, Edgar L. Makowski, and Frederick C. Battaglia. Division of Perinatal Medicine, University of Colorado Medical Center, Denver.

It is known that severe and prolonged maternal undernutrition can reduce the birthweight of fetal lambs. Our studies were aimed at determining umbilical O_2 and glucose uptakes ($\dot{Q}O_2$, $\dot{Q}_G$) and the placental clearance of glucose (C_G) in late gestation and to observe the effects of acute maternal starvation on these variables. C_G was estimated as the ratio of $\dot{Q}_G$ over the glucose concentration difference between maternal and umbilical arteries. In chronic, unstressed sheep preparations, fetuses were studied repeatedly for up to 21 days. In each study, umbilical blood flows, glucose and O_2 contents in umbilical arterial and venous and maternal arterial blood were determined on 5-7 samples. In the fed group, $\dot{Q}O_2$ increased significantly with time ($\sim$ 2%/day), but there was no significant growth of $\dot{Q}_G$ or C_G. Hence, the glucose/oxygen quotient decreased from $\sim$ 0.7 at 120 days to $\sim$ 0.3 at 140 days gestation. The constancy of C_G with age is in contrast to the previously observed growth of urea and antipyrine clearances. In the starved group, the $\dot{Q}_G$ per kg of fetal body weight was lower than in the fed group (2.7 vs. 6.4 mg/min.kg respectively) and there was no appreciable growth of $\dot{Q}O_2$. The efficiency of placental glucose transfer, as measured by the glucose clearance, was not increased by starvation.

These studies provide the first demonstration that placental glucose transfer does not grow in proportion to fetal O_2 consumption and that maternal starvation over a comparatively short time span has a demonstrable effect upon both glucose and O_2 utilization by the fetus.

MECHANISM OF ACIDOSIS COMPLICATING TOTAL INTRAVENOUS ALIMENTATION WITH CASEIN HYDROLYSATE AND SYNTHETIC AMINO ACID INFUSIONS. James C.M. Chan, Morris J. Asch, Stanley Lin and Daniel M. Hays (Introduced by Maurice D. Kogut) University of Southern California School of Medicine and Childrens Hospital of Los Angeles, Departments of Pediatrics and Surgery, Los Angeles.

Five premature infants aged 1 to 2 weeks and one 10 year old child receiving continuous total intravenous alimentation for extended periods were studied before, during and after the development of metabolic acidosis (Base excess -9 to -17 mEq/L). The hypothesis that this acidosis was secondary to the excessive H^+ intake from the casein hydrolysate or the amino acid solutions employed was studied.

The net acid excretion consisting of the sum of urinary titratable acid plus ammonium minus bicarbonate and the net acid input consisting of the estimated endogenous acid production plus the exogenous acid intake from the infusate were calculated. In the 5 cases studied, metabolic acidosis developed whenever the net acid input exceeded the net acid excretion and recovery occurred whenever the nitrogen source in the infusate was discontinued or continued with a half-strength solution, allowing the net acid excretion to approximate and/or exceed the net acid input. In the premature infants, maximal net acid excretion in response to the exogenous acid load was achieved slowly in comparison with the 10 year old child (9 days vs. 4 days). The correction of the more severe metabolic acidosis with bicarbonate infusion was effective and was not complicated by electrolyte disturbances.

EFFECT OF GLUCAGON AND NUTRITIONAL STATE ON PLASMA AMINO ACIDS IN THE NEWBORN. E.Colle, A.Papageorgiou, S.H.Reisner, D.Schiff, C.R.Scriver & L.Stern. McGill University-Montreal Children's Hospital Research Institute, Montreal 108, Canada.

Four groups of infants were studied: 13 normal full-term infants on the day of birth (FT-1); 6 similar infants on the 3rd day of life (FT-3); 6 infants of diabetic mothers on the day of birth (IDM-1); 7 full-term, small for gestational age infants on the day of birth (SGA-1). Peripheral venous blood was drawn, before and 30 min. after intravenous glucagon infusion (300µg/kg). The plasma was processed immediately to avoid artifacts and analyzed with±3% error by elution chromatography on ion exchange resin. Glucagon produced the expected hypoaminoacidemic effect only in group FT-3, lowering all amino acids and particularly the four amino acids, alanine, glutamine, glycine and proline, which are glucogenic and extracted by splanchnic tissues. Glucagon did not lower alanine and proline in group FT-1. The initial plasma amino acid levels of IDM-1 infants were normal but glucagon had no hypoaminoacidemic effect in the presence of excess circulating insulin. SGA-1 infants had significantly lower initial plasma levels of the four glucogenic amino acids, when compared to group FT-1; the glucagon response, particularly for glutamine and glycine was also impaired in SGA-1 infants. These findings suggest that blood glucose instability on the day of birth may, in part, reflect impaired splanchnic utilization of glucogenic amino acids. Starvation and insulin levels further modulate the gluconeogenic potential of plasma amino acids in the newborn. Intravenous alimentation with alanine for purposes of gluconeogenesis is contraindicated on the day of birth.

A METHOD FOR ESTIMATING TOTAL BODY AND PLASMA PROTEIN FLUX IN THE RAT. Cyril Chantler, Julie Keitges and Malcolm A. Holliday. Univ. of California, San Francisco and San Francisco General Hospital, Dept. of Ped., San Francisco; Guy's Hospital, Dept. of Ped., London.

The capacity to measure nitrogen turnover in the whole body and in different organ systems is valuable in developing an understanding of the influence of disease and diet upon body metabolism--particularly in calorie-protein deficiency and in uremia. Waterlow and Stephen (Clinical Science 33:489, 1967) described a method which provided useful data but their analytical techniques using ^{14}C-lysine were difficult and had some inherent errors. The present study was designed to investigate the use of ^{14}C-leucine as the tracer and to compare the results obtained previously with ^{14}C-lysine.

Female rats weighing 100-170 g were infused intravenously for 5-6 hours with ^{14}C-leucine at a rate of 0.038 µCi min^{-1}. Specific activity of free and protein bound leucine in plasma was measured at 2 hourly intervals during the infusion. Protein was precipitated with ice cold acetone; the amino acids of supernatant and hydrolyzed protein were separated using high voltage electrophoresis and the radioactivity and total leucine content determined. The coefficient of variation for this method of measuring specific activity in plasma was ± 6.7%. The specific activity of free leucine was constant after 3 hours of infusion and from the 5 hour value the total leucine flux was calculated. As the specific activity of plasma protein increased linearly with time, the incorporation rate of leucine into protein and the renewal rate of plasma protein could be derived. The mean total leucine flux in 4 rats was 82 µ moles 100 g^{-1} hr^{-1} (S.D. 13.34). Renewal rate of plasma protein averaged 62% day^{-1}. The leucine flux is equivalent to a total protein turnover of about 30 g kg BWt^{-1} day^{-1}. These results are similar to those obtained with ^{14}C-lysine. Further development will allow measurement of tissue protein turnover in liver, muscle, and gut in rats under various experimental conditions, including rats with poor growth secondary to chronic uremia.

ABNORMAL GLUCOSE TOLERANCE IN ACHONDROPLASIA. Platon J. Collipp, Raj K. Sharma, Joseph T. Thomas, Vaddanahally T. Maddaiah, and Shang Y. Chen. Nassau County Medical Center, East Meadow, New York.

Oral glucose tolerance tests in 20 children with achondroplasia showed glucose intolerance in 16. They were between four months and twelve years of age. None had diabetes mellitus. Elevated free fatty acids and slightly elevated serum cholesterol concentrations were also found. Significantly low fasting serum growth hormone levels were found and 4 of 8 children had a normal increase in growth hormone soon after sleep. Insulin levels were normal. The children were between 4 and 6 standard deviations below the mean in height, and between 1 and 3 standard deviations in weight. Similar metabolic changes were observed in children with cartilage hair hypoplasia and diastrophic dwarfism who were 8 standard deviations below the mean in height. These data suggest the presence of a defect in peripheral glucose utilization in achondroplasia.

FLAT RESPONSES TO ORAL GLUCOSE LOADING IN CHILDREN. Harold S. Cole, Dept. of Pediatrics, New York Medical College, New York, New York. Introduced by Edward Wasserman.

In a study of 109 children from one and one-half to twelve years of age by means of oral glucose tolerance test, 28 (25.7%) demonstrated a low response to glucose. Low responders were those individuals who had an increment blood sugar of less than 40 mg. per 100 ml. from the fasting value. All children in this investigation had negative family histories of diabetes and all were in good health at the time of testing. Samples of capillary blood were taken at fasting and 15,30,60,90,120, and 180 minutes after oral glucose administration. These were analyzed for blood sugar and serum immunoreactive insulin. If the 15 minute testing period were excluded, 39 children would be low responders. Both normal and low response groups revealed no significant differences in insulin output. The 15 minute testing period was of value since a significant number of children attained peak blood sugars at this time.

No positive or negative correlations were evident between the normal and low response groups with respect to peak serum insulin and peak blood sugar values during oral glucose tolerance testing.

A low or "flat" response to glucose is probably a variant of the normal.

REGULATION OF HEPATIC CHOLESTEROL BIOSYNTHESIS BY DIETARY CHOLESTEROL. ISOLATION OF A MITOCHONDRIAL INHIBITOR. V. N. Darakjian, M. J. Arslanian, and A. K. Khachadurian. American Univ. of Beirut Dept. of Biochemistry, and Northwestern Univ. Med. Sch., Children's Mem. Hosp., Chicago. (Intr. by H. L. Nadler)

Previous studies in our laboratories have shown the absence of feedback inhibition of hepatic cholesterol biosynthesis by dietary cholesterol in children homozygous for familial hypercholesterolemia (The Lancet 11: 778, 1969). Present studies were aimed at elucidating the mechanism of this feedback in rats. Male Sprague-Dawley rats weighing 150-250 g. were fed a rat chow containing 15% corn oil and 2% cholesterol for 2 weeks. Liver mitochondria were isolated by differential centrifugation and an extract prepared by sonification for 15 min. followed by centrifugation at 43.00 x g for 5 hrs. at 0°C. Mitochondrial extracts from cholesterol-fed rats (CFR) inhibited the incorporation of acetate and to a lesser extent of mevalonate into the non-saponifiable and digitonin-precipitable fractions by normal liver homogenates. The inhibitor was non-dialyzable, heat labile, and pepsin-sensitive. The inhibitory activity was dose dependent and apparent within 5 minutes of incubation. It could be precipitated by ammonium sulfate but fractionation of the crude extract was not successful. The inhibitor was present only in CFR and could be isolated from liver mitochondria within 24 hours of feeding high cholesterol diet. Mitochondrial extracts from CFR as well as control rats also contained a dialyzable, heat stable inhibitor, which accounted for 15-20% of the total inhibitory activity in the crude extract from CFR. Preliminary studies show the presence of similar inhibitors in serum. The role of mitochondrial inhibitors in the regulation of hepatic cholesterol synthesis in the human and in familial hypercholesterolemia is at present under study.

DEFICIENCY OF HEXOSAMINIDASE-A IN SERUM: NEW INTERPRETATIONS. E. Delvin, C. Clow, R. Gold, H. Goldman, J. Neal, A. Pottier and C. Scriver. McGill University-Montreal Children's Hospital Research Institute, Montreal 108, Canada.

Tay-Sachs disease is a fatal autosomal recessive trait with an expected carrier rate of 1/30 in Ashkenazi Jews. No treatment is yet available for homozygotes. O'Brien et al showed that deficiency of serum Hexosaminidase-A, a glycoprotein, in carriers and affected homozygotes could be identified in the presence of Hexosaminidase-B by a method capitalizing on the heat instability of the former. A modification of this heat inactivation method (60C x 5 min.) is being applied to screen the Montreal Jewish population (110,000 Ashkenazi) to provide prospective genetic counseling to about 1200 fertile carriers and 40 possible fertile couples where both partners could be carriers. The program also provides prenatal diagnosis when a fetus is at high risk. Assignment of the presumptive genotype for the counselee is based on a probability derived from plotting "Hexosaminidase-A" activity in serum in relation to the residual activity after heating ("Hexosaminidase-B"), utilizing the statistical methods of Pearson and Everitt which consider a bivariable normal surface defined by the correlation coefficients and the standard deviations from the mean on the x and y axes for non-Jewish and heterozygous populations, the latter defined by using obligate Tay-Sachs heterozygotes. When this approach is used, it becomes evident that the amount of Hexosaminidase-B in serum of heterozygotes (and homozygotes) exceeds that predicted for a simple partial deficiency of Hexosaminidase-A. The finding infers that Hexosaminidase-A is not the primary mutant gene product, and that Tay-Sachs disease may be a deficiency in conversion of Hexosaminidase-B to A.

HOST FUEL INTERRELATIONSHIPS DURING INFECTION
Robert H. Fiser, Joseph C. Denniston, and William R. Beisel, Dept. of Pediatrics, Harbor Gen. Hosp., UCLA Sch. of Med., Torrance, Calif. and U.S.A. Med. Res. Inst. of Infect. Dis., Frederick, Md., (Intr. by D.A. Fisher)

Widespread alterations in host lipid and carbohydrate metabolism occur during infectious illnesses. To explore the mechanisms responsible for these changes, lipid and carbohydrate metabolism was studied in pubescent rhesus monkeys during Diplococcus pneumoniae or Salmonella typhimurium septicemia or experimental endotoxemia. 3H-palmitic acid was employed to assess free fatty acid (FFA) metabolism in fasted and glucose-loaded states; in other monkeys Triton WR 1339 was used to block triglyceride-FFA (TGFA) uptake by peripheral tissues. Kinetic data were subjected to multicompartmental computer analysis.

Plasma triglyceride concentrations were increased during each infection and endotoxemia, when compared to findings in control monkeys. FFA levels were increased during the gram-positive infection and during endotoxemia but were decreased during gram-negative infection. The disappearance rate of 3H-palmitic acid and its incorporation into the triglyceride fraction was increased during septic states in both fasted and glucose-loaded monkeys. Endotoxemia produced similar changes during fasting, but after intravenous glucose, endotoxemia was accompanied by prolonged hyperglycemia, decreased disappearance rate of FFA and decreased incorporation into TGFA.

The rate at which TGFA accumulated in plasma after Triton blockade of peripheral uptake was employed as an estimate of triglyceride synthesis. After Triton administration, hypertriglyceridemia was markedly exaggerated in the infected and endotoxemic monkeys in comparison to the findings in control groups.

These studies suggest that 1) lipids are the principle fuel supply of the host during infection; 2) newly synthesized TGFA are of quantitative importance in meeting these requirements; 3) rates of TGFA synthesis are increased during bacterial infection and endotoxemia; and 4) changes in plasma concentrations of lipids result from organism- or toxin-specific effects on peripheral tissue metabolism that involve altered FFA uptake, its utilization, or both.

A USEFUL APPROACH TO ELUCIDATING THE HURLER SYNDROME DEFECT.
Ralph J. Germinario, Arthur Kahlenberg and Leonard Pinsky. Lady Davis Institute, Jewish General Hospital, and Departments of Experimental Medicine, Pediatrics, and Biology, McGill University, Montreal.

Despite recent progress in understanding the glycosaminoglycan (GAG) storage disorders, the precise nature of the various metabolic defects remain to be defined. In a strain of Hurler (Hur) cells obtained from E. Neufeld, we have used a double-label technique to measure concomitantly the incorporation of (2-^{3}H)-D-glucose and $^{35}SO_4$ into the hyaluronic acid (HA) and sulfated (S) GAG fractions of the cells during 8 hour pulse and 12 hour chase periods of incubation in Eagle's minimal essential medium. Previous studies of this type (PNAS 56: 1310, 1966; J. Exp. Med. 124: 1181, 1966) did not separate total cell GAG into HA and S fractions, and used acetate rather than glucose. In the present study after 4 hours of exposure to the labels the amount of ^{3}H-glucose incorporation into the HA fraction was increased 2-30 fold in the Hur compared to control cells. Incorporation of $^{35}SO_4$ per mg DNA into the S-GAG of the mutant cells was 3-10 fold higher than that of control cells. This was not accompanied by a parallel increase in ^{3}H-glucose incorporation. Therefore the molar ratio of $^{35}SO_4$ to ^{3}H-glucose was elevated 1.5 to 3.0 fold in Hur compared to control cells. In the chase period, the S-GAG fraction of control cells lost radioactivity from $^{35}SO_4$ but not from ^{3}H-glucose. The Hur cells lost both at the same rate. This indicates that in normal cells, but not in Hur cells, the degradative process for S-GAG permits salvage of the ^{3}H radioactivity originally present in glucose. We believe that this approach may provide an incisive means of investigating the mechanism of action of the Hurler corrective factor.

RESPONSIVENESS OF CONGENITAL METHYLMALONIC ACIDURIA TO DERIVATIVES OF VITAMIN B-12. Stephen I. Goodman, Anthony J. Keyser, S. Harvey Mudd, Joseph D. Schulman, Harry Turse and John Lewy. From the Department of Pediatrics, University of Colorado Medical Center, Denver, National Inst. of Mental Health, Bethesda, and Departments of Pediatrics and Obstetrics and Gynecology, New York Hospital-Cornell Medical Center, New York City.

Three patients with congenital methylmalonic aciduria (MMA) were evaluated for responsiveness to hydroxycobalamin and cyanocobalamin. Deoxyadenosylcobalamin, the specific coenzyme for methylmalonyl-CoA: CoA carbonylmutase (E.C. 5.4.99.2) was evaluated in two of the three patients.

Single courses of (a) 0.5 mg hydroxycobalamin, (b) 1 mg x 5 days hydroxycobalamin, and (c) 1 mg x 5 days cyanocobalamin were given parenterally to one patient with associated homocystinuria, presumably due to defective synthesis of coenzyme for homocysteine remethylation. (a) produced little response, if any. (b) produced a decrease in daily methylmalonate excretion from pretreatment levels of 1055-1449 mg to values of 7-82 mg over the five week interval following completion of therapy. (c) also produced a response, but the lowest daily methylmalonate excretion observed was 127 mg.

The two remaining patients did not have homocystinuria detectable by ion-exchange chromatography and did not respond clinically or biochemically to massive doses of any of the three B-12 derivatives, continuing to excrete methylmalonate in direct relation to protein intake.

If these results are typical of patterns of responsiveness, they suggest that hydroxycobalamin is effective in certain cases of congenital MMA, that it is more effective in this regard than cyanocobalamin, and that it might thus be indicated in the critically ill patient whose responsiveness is untested. The presence of homocystinuria increases the probability of responsiveness, and this is consistent with present understanding of the biochemical basis of this form of congenital MMA. Lack of response to hydroxycobalamin implies the likelihood of non-responsiveness to other B-12 derivatives.

GLYCOGEN STORAGE DISEASE DUE TO GLUCOSE-6-PHOSPHATASE (G6Pase) DEFICIENCY: TREATMENT WITH CLOFIBRATE. Harry L. Greene, Robert H. Herman, Fred B. Stifel, and O. David Taunton. (intr. by H. Peter Chase) U.S. Army Medical Research and Nutrition Laboratory, Denver, Colorado 80240.

A 6 year old girl with G6Pase deficiency had complications of chronic lactic acidosis (65-82 mg/100 ml), hypertriglyceridemia (3,420-4,150 mg/100 ml), osteoporosis and retarded linear growth and weight gain. Glucagon (0.02 mg/kg) caused hyperpyrexia (99° to 103°), decreased blood pH to 7.17 and increased lactate to 148 mg/100 ml but no increase in glucose. We postulated that the secondary complications might be due to an accumulation of glucose-6-phosphate with an excessive rate of glycolysis. Since clofibrate (Atromid$^{(R)}$) causes a decrease in adenyl cyclase and certain glycolytic enzymes in rat liver and human intestine it might decrease the rate of glycolysis and therefore be of therapeutic benefit. During 9 months of clofibrate therapy (2 gm/da), she had appropriate weight gain and linear growth. Serum TA decreased to 800-1420 mg/100 ml, lactate to 24-31 mg/100 ml. After glucagon there was no change in blood pH and the lactate increased to only 81 mg/100 ml. Hepatic enzyme activity changes were as follows: G6Pase - unchanged; fructose-1,6-P_2 aldolase and fructose-1-P aldolase - decreased 60%; pyruvate kinase - unchanged; fructose-1,6-diphosphatase - increased 50%. Hepatic glycogen content decreased from 8.6% to 5.9%. Hepatic cyclic-AMP concentrations before and after glucagon infusions further support the hypothesis that one mechanism of action of clofibrate is to decrease the rate of glycolysis. Clofibrate may be of benefit in the therapy of some patients with G6Pase deficiency.

INCREASED STOOL MERCURY EXCRETION IN THE RAT PRODUCED BY SPIRONOLACTONE PRETREATMENT. J. E. Haddow & P. Marshall, Department of Pediatrics, Boston University School of Medicine, Boston, Massachusetts.

400 micrograms of $HgCl_2$ injected intravenously ordinarily kills a 110 gm. rat. Selye has shown that a similar animal, given 10 mg. spironolactone orally twice daily for three days prior to the $HgCl_2$ injection, does not die. We investigated the fate of $HgCl_2$ injected into control (C) rats and into those pretreated with spironolactone (S) by adding $^{203}HgCl_2$ to the lethal intravenous $HgCl_2$ injection and placing animals in metabolic cages. 11 animals served as controls while 10 were given spironolactone for three days. The table summarizes significant results.

	PERCENT TOTAL INJECTED COUNTS			
	KIDNEYS (24 hr)	URINE (0-4hr)	URINE (4-24hr)	STOOL (0-24hr)
(C) Mean	20.97	3.90	2.65	4.55
SEM	0.88	.56	.60	.69
(S) Mean	13.14	0.77	5.39	24.44
SEM	1.15	.249	.27	2.76

The most striking finding was a five fold increase in stool mercury excretion during the first 24 hours and this might well explain why spironolactone pretreated animals survive. More work is indicated to discover how spironolactone produces this dramatic change.

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COMPARISON OF EFFECTIVENESS OF DIHYDROTACHYSTEROL AND CHOLECALCIFEROL IN INCREASING INTESTINAL TRANSPORT OF CALCIUM IN NEPHRECTOMIZED RAT. Harold E. Harrison and Helen C. Harrison. Johns Hopkins Univ.Sch. of Med., Dept. of Ped. and Baltimore City Hosp., Baltimore, Md.

Dihydrotachysterol$_2$ (DHT), one of the steroids produced by ultraviolet irradiation of ergosterol, is more potent than calciferol in increasing the serum calcium concentration of hypoparathyroid subjects. It is also effective in overcoming the calcium malabsorption of patients with renal insufficiency. Its antirachitic effectiveness in vitamin D depleted humans or rats is much less than that of calciferol, however. Our experimental studies provide an answer to the latter phenomenon. Calciferol is known to be metabolized in the liver to 25 OH calciferol and then in the kidney to 1,25 diOH-calciferol. We have determined the activity of cholecalciferol and DHT in vitamin D deficient, sham operated and nephrectomized rats using in vitro transport of calcium and phosphate by everted intestinal loops as the index. Cholecalciferol is at least ten times more potent in the intact than in the nephrectomized rat indicating the much greater activity of the 1,25 diOH derivative. The activity of DHT, however, on calcium and phosphate transport by the intestine is the same in intact and nephrectomized rats showing that the kidney does not metabolize and activate dihydrotachysterol in the same manner as it does calciferol. This accounts for the lesser antirachitic activity of DHT in the intact vitamin D deficient subject. It also suggests that DHT may be the preferable steroid in the prevention or treatment of calcium malabsorption of the patient with renal insufficiency since its calcium transport activity is not dependent on metabolizing kidney tissue and will therefore be less variable than that of calciferol in the patient with progressive renal disease.

DECREASED RELEASE OF BETA GLUCURONIDASE FROM LYSOSOMES IN MUCOPOLYSACCHARIDOSES. TRANSIENT NORMALIZATION AFTER TREATMENT OF PATIENTS WITH PLASMA INFUSIONS. C. Thomas Kisker, Meinhard Robinow, Emanuel Kauder and Esther Ohlinger. Dept. Pediatrics, Univ. Cincinnati, Children's Hosp. Research Fndn., Cincinnati, and The Children's Hosp. Med. Ctr., Dayton, Ohio.

In mucopolysaccharide disorders (MPS) the release of betaglucuronidase (BG) from intact polymorpholeukocyte (PMN) lysosomes is resistant to osmotic stress. A standardized technique for measuring the release of BG from PMN lysosomes under osmotic stress has been developed and the normal range established. PMN lysosomes are incubated with an excess of phenophthaline glucuronide (PG) and increasing sucrose at concentrations not affecting BG activity. The percent of BG released at each sucrose concentration is calculated by comparing the amount of hydrolysis of PG occurring during incubation at each sucrose concentration with that which occurs when BG is totally released. The BG released from PMN lysosomes was measured before and after plasma transfusion in two patients with Hurler's disease and one with Sanfilippo's disease. Before plasma infusion, decreased BG release was present in all 3 patients; after infusion, BG release was normal. BG release returned to abnormal levels 4 weeks following transfusion in the one patient tested serially. Clinical improvement in corneal clouding, joint mobility, and skin turgor was evident in the patients with Hurler's disease and laboratory improvement on the alkaline phosphatase level, liver scan, and mucopolysaccharide excretion was evident in the patient with Sanfilippo's disease. The results indicate that the transfusion of normal plasma can benefit some patients with MPS disorders and that the effect may in part be due to intracellular changes. The technique for measuring BG release from lysosomes under osmotic stress provides an in vitro method of testing "corrective" factors in plasma, measuring the duration of their effect, and correlating the intracellular changes with clinical improvement.

DEFECTIVE GLUCONEOGENESIS IN MAPLE SYRUP URINE DISEASE (MSUD). Morey W. Haymond, Irene E. Karl, Ralph D. Feigin, Darryl C. DeVivo and Anthony S. Pagliara. Washington Univ. School of Medicine, St. Louis Children's Hospital, Department of Pediatrics, St. Louis, Missouri

A 3-month old retarded female with MSUD (plasma leucine 3.5, isoleucine 0.5, valine 0.6 mM), fasting hypoglycemia (26 mg%), and ketonemia was studied prior to and during dietary therapy. Plasma insulin was always < 5μU/ml. I.V. glucagon and oral fructose resulted in a normal glycemic response (Δ 78 and Δ 30 mg% respectively) without hyperlacticacidemia. Prior to therapy, plasma gluconeogenic amino acids (GNG-AA) were markedly depressed except for glutamate which was 100-150 μM (Normal 30-70 μM). Plasma alanine (ALA) was 50 μM (Normal 350 μM) and was the lowest GNG-AA. Following a 9 hour fast, I.V. ALA (250 mg/kg) resulted in a fall in blood glucose (46 to 30 mg%). With therapy, branched chain AA fell to normal with a concomitant increase in GNG-AA except glutamate which remained unchanged. At this time ALA infusion (250 mg/kg) after a 9 hour fast resulted in a modest glycemic response (42 to 52 mg%). ALA disappearance with infusion was not altered by therapy. Both ALA infusions produced a sustained rise in glutamine and a slight increase in glutamate, pyruvate and lactate. The sustained rise in glutamine is not found in normal subjects.

Conclusion: Hypoglycemia was not due to hyperinsulinism, defective glycogenolysis or inhibited gluconeogenesis from the level of the triose phosphates. GNG-AA substrate limitation could account for the fasting hypoglycemia, however alanine infusion resulted in no glycemic response when her branched chain AA were elevated. Alanine infusion resulted in a normal transient rise in lactate, pyruvate and glutamate implying transamination in the liver. The absent lactate and pyruvate accumulation is evidence against a GNG enzyme abnormality above the level of pyruvate. The sustained rise in glutamine may reflect an abnormal pooling of GNG-AA decreasing substrate availability for gluconeogenesis which was partially corrected after therapy.

TRANSIENT CHILDHOOD OSTEOPOROSIS OF UNKNOWN CAUSE. Sang Whay Kooh, William A. Cumming and Donald Fraser. University of Toronto, Depts. Paed. and Radiol. and The Hosp. for Sick Children, Res. Inst., Toronto, Canada.

We observed 11 children with generalized osteoporosis of unknown cause. All improved, and most have recovered completely. Symptoms began between 19 months and 12 years of age. Half of the patients were under 6. Sexes were affected equally. No family incidence or evidence of inadequate nutritional intake was found. All had been active before the onset of symptoms, and were in good health, except for one asthmatic who was found to have asymptomatic vertebral compression on chest roentgenography. 10 patients limped due to pain in the ankles and heels. 7 eventually required a wheel chair. 4 complained of backache. Minor injury at the onset of symptoms reported by 5 patients appeared unrelated to the generalized osteoporosis. The time of onset was usually definite but progression of symptoms was variable. The only physical signs were bone pain on passive movement and muscle weakness and atrophy. Roentgenographic examination revealed generalized osteoporosis of varying severity in all patients, compression of vertebral bodies in 9, and metaphyseal fractures, mostly in the distal ends of femur or tibia, in 8. 10 patients resumed usual childhood activities within three years and one is improving but walks with difficulty 2½ years after the onset of disease. Roentgenographic healing always followed clinical improvement but lagged by many months. 8 received no medication; 3 patients were given calcium supplements but with no clear-cut influence on the course of the disease. All received physiotherapy and it is our impression that swimming pool exercises speeded recovery. No patient has relapsed and none has any prominent deformities. However, as a group, they are short. 2 are less than the third percentile for height. Osteoporosis is important in the differential diagnosis of unexplained limp. Amongst the initially erroneous diagnoses applied to our patients were leukemia, primary neuromuscular disorder and malingering.

FASTING HYPOGLYCEMIA DUE TO INCREASED GLUCOSE UTILIZATION AND INAPPROPRIATELY HIGH INSULIN. Douglas S. Kerr, Oliver G. Brooke and Hazel M. Robinson. University of the West Indies, Tropical Metabolism Research Unit, Kingston, Jamaica. (Intr. by Paul Lietman).

The mechanism of hypoglycemia following malnutrition was studied in an identical twin with low birth weight and subsequent malnutrition (B) who had recurrent fasting "ketotic" hypoglycemia while well nourished at age 2 which did not occur in the larger birthweight twin (A). Between 8 and 16 hr fasting, glycogen oxidation (estimated from O_2 uptake and RQ) was 2.1 mg/kg/min in B vs 1.7 in A. After glycogen depletion, possible sources of glucose were gluconeogenic amino acids (estimated from urea and NH_3 excretion) potentially yielding 0.59 mg glucose/kg/min in B vs 0.44 in A, and glycerol (estimated from total fat oxidation), potentially yielding 0.39 mg glucose/kg/min in B vs 0.35 in A. The activity of the gluconeogenic enzymes pyruvate carboxylase, fructose diphosphatase and glucose-6-phosphatase in liver needle biopsy were not decreased in B. PEP carboxykinase activity was 3.5 U/g liver in B vs 5.6 in A. This did not result in accumulation in plasma of either alanine, 0.89 meq/l in B vs 1.18 in A, or lactate, 0.58 meq/l in B vs 0.69 in A. During infusion of 0.5g alanine/kg over 2 hours, plasma glucose rose from 19 to 41 mg% in B and from 39 to 60 mg% in A while alanine was 0.65 meq/l in B vs 1.60 in A and urea excretion increased more in B indicating increased alanine uptake in B. It is concluded that hypoglycemia in B is due to increased glucose utilization. A normal correlation was found between plasma immunoreactive insulin and glucose in A ($r=0.64$, $p<0.01$) which was reversed in B ($r=-0.49$, $p=0.01$) Inappropriately high insulin for glucose was also observed in each of 6 other children with fasting hypoglycemia, 5 of whom also had low birth weight or post-natal malnutrition.

INSULIN AND SODIUM BICARBONATE TREATMENT OF DIABETIC KETOACIDOSIS. Jerry J. Krumlik and Robert M. Ehrlich. (Intr. by John D. Bailey).

Forty-four episodes of diabetic ketoacidosis (DKA) were reviewed. A mean initial dose of 13.8 units of insulin (range 5-30) and 115.5 mEq of sodium bicarbonate (NaKO3) (range 40-300) were required to bring the initial blood pH and bicarbonate to 7.2 and 12 mEq/L (see table). For total correction of acidosis (pH > 7.3 and/or bicarbonate > 20 mEq/L) a mean of 18.2 units of insulin (range 5-80) and 144 mEq/L NaHCO3 (range 45-450) was required. The mortality rate was zero. Hypoglycemia (blood sugar < 60 mg.%) occurred in 3 and hypokalemia (k < 3.0 mEq/L) occurred in 12 cases.

The average of 0.4 units/kg. body weight of insulin was a safe and effective dose to correct DKA. It is much less than traditionally recommended. It indicates insulin sensitivity and a need to re-evaluate insulin doses in DKA in children. Three mEq/kg. body weight of NaHCO3 effectively raised the blood bicarbonate but may have contributed to the hypokalemia.

Time Hrs.	Blood Sugar mg.%	pH	Blood Bicarbonate	Anion Gap	Insulin Units	NaHCO3 mEq
0	415±138*	7.05±.09	7.6±2.7	20.7±4.1		
5.9	232±100	7.23±.03	12 ±2.7	15.3±5.3	13.8± 8	115.5±66.3
10.5	213±124	7.32±.03	15.8±4.2	14.8±4.8	18.2± 13	144 ±85.1

*Standard deviation.

HYPERGLYCINEMIA: IN VIVO COMPARISON OF NON-KETOTIC AND KETOTIC (PROPIONIC ACIDEMIC) FORMS. I. CSF GLYCINE CONCENTRATIONS AND BLOOD/CSF GLYCINE. Harvey L. Levy, Robert N. Nishimura, Arline M. Erickson, and Stanislawa E. Janowska, Harvard Med. Sch., Dept. of Neuro., Mass. Gen. Hosp., Boston; E.K.S. Center for Men. Ret., Waltham, Mass.

In general the permanent neurologic impairment associated with non-ketotic hyperglycinemia has been more severe than that seen in ketotic hyperglycinemia (propionic acidemia). Since the etiology of the neurologic manifestations in either disorder is unknown, the reasons for these neurologic differences are obscure.

We have studied an 18-month-old male with non-ketotic hyperglycinemia, severe hyperactivity, moderate developmental retardation and markedly hyperactive DTR. In comparison we studied a 13-month-old female with propionic acidemia who also has moderate developmental retardation but is hypotonic and has normal DTR. Glycine concentrations in CSF (obtained via lumbar tap) and blood were studied by the amino acid analyzer with the following results:

NONKETOTIC HYPERGLY=NK KETOTIC HYPERGLY=K

		Gly load (200 mg/kg PO)							
	Nl.	Ave. Random		2 Hours		6 Hours		24 Hours	
Gly(uM/100ml)	NK	NK	K	NK	K	NK	K	NK	K
(Blood)	26.6±6.3	142.8	63.6	255.5	425.4	256.2	402.6	185.3	196.9
(CSF)	.66±.18	9.8	1.1	16.1	13.7	22.2	11.9	14.4	6.1
Blood/CSF	35	14.5	58.9	115.8	31.1	11.5	33.7	12.9	32.2

The transport of glycine from blood to CSF and vice-versa would seem to be approximately equal in the two infants. Thus the high concentration of CSF glycine (and consequent low blood/CSF ratio) in non-ketotic hyperglycinemia indicate that in this condition glycine may accumulate in the CNS out of proportion to the hyperglycinemia. This may be a reflection of altered CNS glycine metabolism. Since glycine is an important neuroinhibitor in the spinal cord of mammals, increased CNS glycine may have important neurologic consequences.

GENERALIZED LIPOATROPHIC DIABETES. IN VIVO STUDIES OF ADIPOSE ORGAN LIPOLYSIS. Barbara M. Lippe, Mayer B. Davidson, and Solomon A. Kaplan, Dents. Ped. and Med., U.C.L.A., Sch. of Med., Los Angeles.

The pathogenesis of Generalized Lipoatrophic Diabetes is not known. Studies of in vivo lipolytic mechanisms in a 5 year old female during the early rapidly progressing pre-diabetic phase of this disorder have enabled us to postulate a defect in the lipolytic enzyme system in the adipose organ. Initial Free Fatty Acid (FFA) levels were extremely high(2.9mEq/L). Oral glucose tolerance test resulted in normal glucose levels but a prolongation of the insulin response, the insulin levels peaking at 3X baseline at 120 min. Plasma Growth Hormone responses were normal. Three months after the initial studies, plasma FFA responses to intravenous (IV) aminophylline, Nicotinic acid (NA) and insulin were studied in the patient and a normal younger sibling. At this time initial FFA levels of the patient were normal (0.38 and 0.84 mEq/L). However, she exhibited a prolonged lipolytic response to aminophylline. The patient's FFA levels peaked at 170% of baseline 40 min. after the infusion while her sibling's FFA peaked at 150% of baseline 10 min. after the infusion and were returning to baseline (120%) in 40 min. The patient had no initial antilipolytic response to NA IV while her sibling exhibited the anticipated FFA decline (50% of baseline at 30 min.). However, both showed characteristic rebound lipolysis with FFA at 90 min. of 160 and 180% of baseline respectively. At this time (90min. after NA) IV insulin produced a brief unsustained antilipolytic response in the patient. Her FFA levels fell to baseline 15 min. after insulin and rose subsequently while her sibling had falling FFA levels for the 60 min. time interval after insulin. Both had normal blood glucose levels which fell following insulin. The patient's failure to respond to NA, poor FFA response to insulin and abnormal response to aminophylline suggest enhanced adipose tissue cyclic AMP activity as the basis for increased lipolysis. Since genetically transmitted errors of metabolism are likely due to an enzyme deficiency a hypothesis based on adipose tissue phosphodiesterase failure is suggested.

p-HYDROXYPHENYLACETIC ACIDURIA: A NEW DEFECT IN PHENYLALANINE METABOLISM J. Alexander Lowden, E. Roberts Wong, Bernard Laski. The Hosp. for Sick Children, The Res. Inst. and Dept. of Paed., Toronto, Canada.

A 3½ month infant presented with cardiomegaly, hepatomegaly, hypotonia and anaemia. She weighed only 3.5 kg. Despite dietary manipulation she had 3 to 8 loose, watery stools each day. Cardiac catheterization indicated mitral regurgitation and a cardiomyopathy which had resulted in congestive failure. Digitalization alleviated the cardiac disorder but the child continued to deteriorate. She became flaccid, semiconscious and unable to tolerate feedings. Although her liver remained slightly enlarged and her serum albumin was only 2.5 gm/100 cc, her other liver function tests were normal. She was not acidotic. Serum and urinary aminoacid chromatograms showed low normal levels of phenylalanine and tyrosine. After acidification of urine the organic acids were extracted into ether and the trimethysilyl derivatives prepared. These were separated by GLC on a 3% SE 30 column and the peaks quantitated using eicosane as an internal standard. Only one significant GLC peak was found and this co-chromatographed with p-hydroxyphenylacetic acid (pHOPAA). Further characterization was made by thin layer chromatography and mass spectrometry. On a regular diet (Nutramigen) the excretion of pHOPAA was 65 mg/24 hrs. A phenylalanine load increased urinary pHOPAA to 120 mg/24 hrs. but after a tyrosine load the output was only 55 mg/24 hrs. Phenylalanine restriction decreased the excretion of pHOPAA to less than 5 mg/24 hrs. Although the chromatograms revealed little or no hippuric acid excretion on all these diets, when the child was loaded with sodium benzoate she excreted it quantitatively as hippurate. Our findings suggest a block in the conversion of phenylacetic acid to benzoic acid. (Supported by the Medical Research Council of Canada, Grant MT 1602).

DIPHENYLHYDANTOIN ASSOCIATED RICKETS. N. Matsuo, C.Y. Herrera, A. Tashjian, F. X. Fellers, Harvard Medical School, Harvard Dental School, and The Children's Hospital Medical Center, Boston, Mass.

Prolonged drug ingestion causing iatrogenic disease is becoming more frequent. Three children presented with symptomatic rickets following two or more years of diphenylhydantoin therapy for convulsive disorders. Each child had also another principal diagnosis which could have limited or interfered with usual daily activities; these were mental retardation and hydrocephalus. Decreased physical activity was the only presenting symptom. The double malleolar sign, large joints, and costo-chondral rosary were found on examination. X-rays showed typical osteomalacia and rachitic changes. Blood study showed lowered calcium and phosphorus, and markedly elevated alkaline phosphatase. Nutritional vitamin D deficiency was eliminated by the finding of normal levels of vitamin D-like biological activity in the serum. Calciuria persisted but was not excessive. Bone salt accretion study confirmed the avidity of bone for calcium. Direct serum assessment of parathormone and calcitonin were done. Clinical and biochemical response to oral vitamin D in a dosage of 1,000 units per Kg body weight daily was almost complete in 3 to 4 months. These observations would be consistent with an alteration of vitamin D metabolism which increases the vitamin requirement.

GLUCOSE AND UREA SECRETION INTO GINGIVAL CREVICE FLUID (GCF) IN DIABETIC CHILDREN -- RELATIONSHIP TO PERIODONTAL DISEASE. Luis L. Mosovich, Sebastian Ciancio, Charlotte Catz, Sumner J. Yaffe and Larry Golub. Departments of Pediatrics, School of Medicine, and Periodontics, School of Dentistry, State University of New York at Buffalo and School of Dentistry, University of Manitoba, Winnepeg, Canada.

Patients with diabetes mellitus are prone to develop periodontal disease. The volume of GCF, which is formed in the space between the inner aspect of the gingival margin and the tooth, is increased by chewing, mechanical stimulation and inflammatory processes. In order to clarify the role which the composition of the GCF may play in the evolution of periodontal disease, fluid was collected on filter paper strips from diabetic patients, aged 11 to 15 years. Ten non-diabetic children of comparable age served as controls. The samples were collected between 8 a.m. and 10 a.m. following a 12-hour fast and analyzed for urea and glucose. Fasting blood sugar were 86.6 mg% ± 1.5 (S.E.M.) in normal controls and 215.9 mg% ± 31.0 (S.E.M.) in diabetics. Crevicular glucose in the diabetic group was 300% higher than in the control group. The crevicular urea concentration was inversely related to gingival inflammation, but for a given degree of inflammation, it was 60% higher in the diabetic group. Higher urea and glucose concentrations in crevice fluid from diabetics may not only reflect higher rates of excretion of these compounds but may also determine the rate of periodontal destruction, since these substrates are rapidly metabolized by the dental plaque microflora.

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REQUIREMENT OF NA IN THERAPY OF PROTEIN-CALORIE MALNUTRITION. Buford L. Nichols, Jorge Alvarado, Carlton F. Hazlewood and Fernando Viteri. Section of Nutrition and Gastroenterology, Dept. of Ped., Baylor Col. of Med., Houston, Texas and Biomedical Div., Instituto de Nutrition de Centro America y Panama, Guatemala City, Guatemala, C.A.

Although edema is a constant feature of PCM, little is known of its relationship to sodium balance. The effects of 3 levels of sodium intake on its balance were studied at admission, during and following recovery. Balances were corrected by an indirect procedure for insensible Na loss. Obligatory requirements were increased to 5 mEq/kg/day at admission and during early therapy by increased fecal losses. After 15 days of therapy requirements were reduced to 3 mEq/kg/day. During later therapy insensible Na loss increased to 1/3 of total requirement and raised the minimal requirement to 5 mEq/kg/day. An excessive sodium diuresis occurred before therapy of the underlying protein deficiency state. This indicates that salt restriction may be hazzardous and that minimal requirements for Na must be carefully observed even in the presence of edema.

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RELATION OF ATP CONTENT TO SUBSTRATE UTILIZATION IN SUBCUTANEOUS ADIPOSE TISSUE FROM HUMAN NEONATES. Milan Novak, Ellen Monkus, Helmut Wolf, and William McGarey, Univ. of Miami Sch. of Med., Dept. of Ped., Miami, Fla. and Univ. of Goettingen Sch. of Med., Dept. of Ped., Goettingen, W. Germany.

The increased lipolysis which occurs shortly after birth, as well as later fatty acid activation for reesterification (acylCoA formation) in adipose tissue are energy requiring processes. Since this energy is derived from high energy phosphate bonds, the ATP content of subcutaneous adipose tissue from healthy fullterm newborn infants was examined using an enzymatic method. ATP content was 0.185 ± 0.011 (mean + S.E.) mg/g wet weight between 3.5 and 6.5 (n=18), 0.0785 ± 0.0094 between 10 and 33 (n=16) and 0.171 ± 0.017 between 42 and 192 hours of age (n=21). The ATP content of adipose tissue in the groups 3.5 to 6.5 and 42 to 192 hours old was significantly increased over that in the 10 to 33 hour group ($p<0.001$).

In our previous studies of subcutaneous adipose tissue, increased glycogen content, increased glycogenolysis (glycogen phosphorylase activity), and increased glycolysis and oxidation of carbohydrate (increased incorporation of universally labeled glucose into $^{14}CO_2$) were found shortly after birth. In the present study, ATP content was decreased at 10 to 33 hours in comparison with 3.5 to 6.5 hours of age. It appears that less ATP is formed when glycogen depots are depleted and when glycolysis in the adipose tissue has declined. A gradual increase in ATP content followed. This occurred at an age when increasing amounts of substrates for use in intermediary metabolism were being assimilated from the milk. Oxidation of fatty acids to form acetylCoA may become increasingly important in ATP formation after 24 hours of age. Our findings are in agreement with those of others with fasting and re-feeding in the adult rat. Thus, the availability of substrates for anaerobic glycolysis and terminal aerobic respiration via the Krebs cycle appears to correlate well with the ATP content of the adipose tissue in the first week of life. Secondary effects of these changes in ATP content, perhaps by a shift in cyclic AMP formation, may also be important in the adaptation of the human newborn to extrauterine existence.

EFFECT OF α-KETO DERIVATIVES OF BRANCHED CHAIN AMINO ACIDS, PHENYLALANINE, TYROSINE AND HISTIDINE ON PYRUVATE METABOLISM IN RAT BRAIN MITOCHONDRIA. MULCHAND S. PATEL and VICTOR H. AUERBACH. Dept. of Ped. and Biochem., Temple Univ. Sch. of Med., and St. Christ. Hosp. for Children, Philadelphia, Pa.

We previously reported from this laboratory that phenylpyruvate inhibited the metabolism of pyruvate via pyruvate carboxylase in isolated rat brain mitochondria and in human brain homogenates. Given the well known association of mental retardation with several inborn errors of amino acids including phenylketonuria, we investigated a toxic effect of α-keto derivatives of various amino acids on the metabolism of pyruvate by rat brain mitochondria. Using the fixation of $H^{14}CO_3^-$ in the presence of pyruvate by the intact rat brain mitochondria, we observed that the α-keto derivatives of three branched chain amino acids (valine, isoleucine and leucine) at a concentration of up to 10 mM had no effect. In contrast, phenylpyruvate, p-hydroxyphenylpyruvate and imidazolepyruvate inhibited the fixation of $H^{14}CO_3^-$ by brain mitochondria, and the inhibition was shown to be concentration dependent. However, when the effect of these keto acids on pyruvate carboxylase activity in the lyophilized brain mitochondria was studied, only phenylpyruvate and p-hydroxyphenylpyruvate inhibited this enzyme. Kinetic studies revealed that the addition of phenylpyruvate and p-hydroxyphenylpyruvate resulted in a 'mixed type' inhibition. The specificity of these two keto acids may be related to their structural configuration. The data presented suggest that the toxic effect of α-keto acids on pyruvate metabolism via cerebral pyruvate carboxylase in inborn errors of amino acid metabolism is not common to all amino acids, rather it is a specific phenomenon. It is suggested that an elevation of phenylpyruvate and p-hydroxylphenylpyruvate in brain would inhibit the flow of pyruvate via pyruvate carboxylase, an anaplerotic enzyme which plays an important role in the biosynthesis of lipids, acetyl choline and dicarboxylic amino acids. (Supported by Grants NS-10125, HD-2870 and RR-5624).

NON-KETOTIC HYPERGLYCINEMIA - TREATMENT FROM BIRTH

Elihu P. Rees, Matthew W. Spence, Margaret S. DeWolfe, (Intr. by Richard B. Goldbloom), Department of Paediatrics, Dalhousie University and The Izaak Walton Killam Hospital for Children, Halifax, Nova Scotia.

In the last two years we have treated three neonates with non-ketotic hyperglycinemia. All infants were products of separate consanguineous matings but all six parents shared a common ancestor.

J.A., moribund when admitted at two days and diagnosed at three days of age died three weeks later. Treatment included peritoneal dialysis, multiple exchange transfusions and low-glycine diet.

B.C., a twin, was diagnosed within twenty-four hours, but died at three days of age, after trial of synthetic diet. (Her fraternal twin died in the neonatal period with maple syrup urine disease (MSUD)). The two disorders were proven to be biochemically distinct in these infants.

J.P. was admitted at three hours of age, and a cord plasma glycine was 2.62 mg% (normal children 1.02 - 3.97 mg%). Lethargy and respiratory depression were profound by twenty hours with a plasma glycine of 8.17 mg%. Decarboxylation of branched-chain amino acids by leukocytes was normal, thus excluding MSUD. He was treated by a single exchange transfusion (post-exchange plasma glycine was 5.64 mg%) and started on a low protein diet with supplements of sodium benzoate, acetylsalicylic acid (ASA), B_6, B_{12}, and folic acid. Twelve hours later the plasma glycine was 2.18 mg% and his clinical condition was greatly improved. At no time was metabolic acidosis or ketonuria detected.

Subsequently, dietary protein was increased, ASA stopped and other supplements continued. Despite maintenance of normal plasma glycine levels, seizures and progressive mental and motor retardation developed. Early in his course reduction of sodium benzoate caused a prompt increase in plasma glycine. When all treatment was stopped after sixteen weeks, there was no change in his clinical state but a three-fold rise in plasma glycine.

Control of plasma glycine levels in J.P. was relatively simple, even on a normal infant diet. However, maintenance of normal plasma glycine from birth apparently is not sufficient to prevent severe central nervous system damage.

TREATMENT OF EXPERIMENTAL SALICYLATE POISONING. Ekkehard W. Reimold* and Howard G. Worthen. Univ. of Texas Southwestern Med. Sch., Dept. Ped., Dallas, Texas 75235

An experimental study of salicylate poisoning (Na-salicylate) in dogs three to six months of age was used to investigate the relative efficacy of water diuresis, bicarbonate alone, and acetazolamide plus bicarbonate as therapy for salicylate poisoning.

In Group 1 (water diuresis) only two out of nine animals survived, in Group 2 (bicarbonate) six out of nine, in Group 3 (acetazolamide) eight out of nine.

The rate of decline in salicylate blood level was similar in all three treatment groups; the salicylate half-life was 6.2 hours in Group 1, 5.2 hours in Group 2 and 4.8 hours in Group 3 ($P < 0.05$ for Group 1 vs. 3). The urinary salicylate excretion rose to a peak level (2 hour level: 2.5 mg/min, 3 hour level: 5.64 mg/min) within one hour following acetazolamide injection, paralleling a rapid rise in urine pH to 7.5-7.8. The same alkaline pH level and nearly the same rate of salicylate excretion was reached in Group 2, but only after three hours. Subsequently the urine pH remained at the same level in both groups. In contrast, animals treated with water diuresis had a continuous fall in urine pH and urinary salicylate excretion; they became progressively acidotic until death.

The potassium balance was negative only in animals receiving acetazolamide. Severe, fatal hypoglycemia (blood level 7-10 mg%) developed in all animals treated with glucose-free IV solutions.

While the rapid increase in salicylate excretion and the better survival rate would favor acetazolamide administration, pediatric age patients often cannot obtain the full benefit of this treatment under clinical conditions since they are usually in profound acidosis when first diagnosed, precluding the immediate administration of acetazolamide.

SCREENING TESTS FOR DETECTION OF MUCOPOLYSACCHARIDE (MPS)DISORDERS-EVALUATION OF A NEW TEST. Iraj Rezvani, Platon J. Collipp, Angelo M. DiGeorge, and Hope H. Punnett, Dept. of Ped., Temple Univ. Sch. of Med., St. Christopher's Hosp. for Children, Phila., Pa. and Nassau County Med. Ctr., East Meadow, N.Y.

To evaluate the efficacy of screening tests for detection of MPS disorders, random or 24 hr urine specimens from 6 pts. with Hurler, Hunter and Sanfilippo syndromes and from 63 normal or non-affected children, were screened by acid albumin gross turbidity test, 5% cetyltrimethylammonium bromide (CETAB) in 1M citrate and a newly developed spot test, "MPS" paper (Ames Co.). Results were correlated with amounts of urinary MPS measured by the carbazole reaction. Random urines from normal children contained as high as 30 µg uronic acid (60 µg MPS) per ml.

	Amount of MPS as Uronic Acid			Per Cent Positive		
	µg/ml	mg/24 hr	mg/gm Creat.	Acid Alb.	CETAB	"MPS" Paper
Normals	13.6±7	7.4±4	13.8±6	2	38	31
MPS I,II,III	85.8±20	47.5±6	123.9±39	100	100	100

To evaluate the sensitivity of the tests, increasing amounts of chondroitin sulfate were added to a urine sample with low MPS content and screened with the tests. The lowest detectable level was 20 µg MPS/ml for CETAB test, 30 µg MPS/ml for "MPS" paper and 50 µg MPS/ml for acid albumin. Proteinuria, glycosuria, ketonuria and the pH of the urine had no effect on the outcome of the tests. Sensitivity of the tests decreased as ionic strength of the urine increased. These data indicate (1) acid albumin gross turbidity is the most suitable test for detection of MPS disorders, (2) random urine samples from normal children may contain high levels of MPS, as compared to adults (3) If weakly positive results are ignored, "MPS" paper gives only 2% false positive tests.

ACTIONS OF CALCITONIN-MIMICKING AGENTS AND CALCITONIN ANTAGONISTS IN LEAD INTOXICATED RATS. John F. Rosen, Albert Einstein Col. of Med., Montefiore Hosp. and Med. Ctr., Dept. of Ped., New York. (Intr. by Laurence Finberg)

Previous studies in this laboratory demonstrated a dose-related, porcine calcitonin (CT)-produced decrease in blood lead (Pb) levels in Pb intoxicated rats. To further define this effect of CT, a potent inhibitor of bone resorption, CT-mimicking agents and CT-antagonists, all having known actions on the adenyl cyclase system, were studied in Pb intoxicated rats. Holtzman rats were intoxicated with Pb by adding Pb acetate to the drinking water at a Pb concentration of 300µg/ml for 2 weeks followed by 500µg/ml for 5 days. Groups of rats were then assayed with CT, 52 MRC u/mg (Armour), and with other agents commercially obtained, by standard CT-bioassay methods. Blood was drawn by cardiac puncture or by tail vein 1 to 4 hours after injection and was analyzed for Pb and calcium by atomic absorption. The results in Pb µg%±1 S.E. were: controls 100±3; CT 62±3 ($p<.001$); glucagon 84±2 ($p<.001$); imidazole 70±5 ($p<.001$); imidazole+D-CAMP 71±4 ($p<.001$); theophylline+CT 61±5 ($p<.001$). In CT-treated groups, the magnitude of the fall in blood Pb was proportionately greater as pre-treatment blood Pb levels increased; and CT produced a typical dose-response curve reflected simultaneously by decreases in serum levels of calcium, independent from the magnitude of effect on blood Pb. On the other hand, no significant changes in blood Pb levels were produced by parathyroid hormone (PTH), D-CAMP, theophylline, and isoproterenol. In thyroparathyroidectomized (TPTX) rats, however, PTH significantly ($p<.001$) raised blood Pb levels: TPTX controls 98±3; TPTX+PTH 139±6. Apparently, in intact animals, endogenous CT can block PTH's Pb-mobilizing action.

These results suggest that the concentration of blood lead is determined, to an extent, by hormones and agents known to regulate bone resorption through participation of the adenyl cyclase system. (Supported in part by The John A. Hartford Foundation).

EFFECT OF PYRIDOXINE ON ABNORMAL TRYPTOPHAN METABOLISM IN SOME CHILDREN WITH SEVERE BRONCHIAL ASTHMA. Raj K. Sharma, Platon J. Collipp, Joseph Thomas, Vaddanahally T. Maddaiah, and Shang Y. Chen. Nassau County Medical Center, East Meadow, New York.

Elevated urinary excretion of xanthurenic acid in human has been described in various conditions including bronchial asthma. Fifteen patients with severe bronchial asthma had abnormal increase in urinary kynurenine and xanthurenic acid excretion following oral tryptophan load. They were treated with large doses of pyridoxine. Urinary xanthurenic acid and kynurenine were measured in 4 patients while they were receiving 50 mg and 100 mg of pyridoxine. The levels of tryptophan metabolites decreased progressively as the dose was increased, but remained above basal levels, as listed below:

Patient	Baseline	Before Treatment	After 50 mg B6 for 3 months	After 100 mg B6 for 9 months
B. K.	K 0.4	K 4.0	K 2.9	K 1.9
	X 0.6	X 5.6	X 6.0	X 5.0
M. C.	K 1.6	K 7.6	K 5.9	K 3.6
	X 0.7	X 6.7	X 2.3	X 3.0
S. F.	K 6.5	K 11.0	K 4.7	K 3.0
	X 0.8	X 7.5	X 2.0	X 2.2
B. R.	K 0.6	K 7.4	K 1.9	K 0.7
	X 0.3	X 2.1	X 3.7	X 1.1

At the same time marked clinical improvement was noticed in these patients. The results suggest that these children with severe bronchial asthma had a metabolic block in the tryptophan metabolism, which was benefitted by long-term treatment with large doses of Vitamin B6.

EFFECT OF PYRIDOXINE IN SOME CHILDREN WITH ATOPIC DERMATITIS. Joseph Thomas, Raj K. Sharma, Platon J. Collipp, and Vaddanahally T. Maddaiah. Nassau County Medical Center, East Meadow, New York.

Five children with severe atopic dermatitis had abnormal increase in urinary xanthurenic acid (X) and kynurenine (K) following oral tryptophan load (2 gm or 100 mg/Kg) as listed below:

Patient	Baseline		After Tryptophan Load	
B. C.	X 0.3	K 0.4	X 3.2	K 15.0
V. S.	X 1.7	K 2.7	X 5.3	K 18.0
F. S.	X 2.2	K 4.6	X 3.8	K 12.0
T. P.	X 0.3	K 0.6	X 4.7	K 7.9
S. F.	X 1.1	K 0.9	X 4.7	K 14.0

They were treated with large doses (100-200 mg) of pyridoxine and marked improvement in clinical symptoms was observed in a period of two to four weeks. Therapy was discontinued and in a short period rash came back and became worse. When therapy was resumed, dermatitis improved again in a period of one to two weeks. These results indicate that these patients have relative unsaturated state of pyridoxine or pyridoxine dependency, which may be benefitted with pyridoxine therapy.

INSULINOPENIC LIPOATROPHIC DIABETES, MACROGLOSSIA, CONGENITAL HEART DISEASE AND ELEVATED GROWTH HORMONE (HGH) IN A NEONATE. Bernice Sigman, Salvatore Raiti, Fima Lifshitz, and Harold Magalnick. Univ. of Md. Sch. of Med., Dept. of Pediatrics, Baltimore, Maryland 21201.

This is the first report of a patient with lipoatrophic diabetes studied from birth with serial determinations of insulin and HGH levels. A white male infant of indeterminate gestation was born weighing 3 lb. 12 oz., with a large tongue and early feeding difficulties. At 48 hrs. of age, elevated blood sugar and glucosuria without ketonuria were discovered and treatment with insulin (0.5-1.5 U/day) was instituted and maintained for 6 wks. Other clinical manifestations noted were congenital heart disease (P.S., PDA and pulmonary peripheral vascular hypertension), generalized muscular hypertrophy with glycogen and normal lysosomal enzymes. He had prominent veins, a lack of subcutaneous fat, hirsutism, liver dysfunction (elevated LDH, high alk. p'tase, low phophorus, prolonged PTT and clotting time requiring 1/2 months of Vit. K for correction), seizures and poor weight gain, but height above the 90th percentile. Insulin levels have consistently been low. At 48 hrs., with a blood sugar of 278, the serum insulin level was 8 μU/ml. Insulinopenia persisted during stimulation with oral and IV glucose, tolbutamide, glucagon and arginine tolerance tests (range 4-8 μU/ml with occasional values of 0 and 16 μU/ml). IV glucose tolerance test resulted in a K_t of 0.78%/min. HGH was very high at 48 hrs. (128 ng/ml) and has remained elevated (20-40 ng/ml). At 12 weeks of age, HGH values were not suppressable during a 2-hr. IV glucose tolerance test (range 30-40 ng/ml) but were suppressed at 16 wks. with an oral glucose load (20 ng/ml to 4 ng/ml). Arginine and tolbutamide tolerance tests did not further increase the serum HGH. The lipotrophic effect of metopirone resulted in a 3-fold rise in triglycerides. Plasma TSH at birth was normal. Insulinopenia and elevated, but suppressable, values for HGH suggest a congenital endocrinological dysfunction that produced growth failure and malnutrition in utero.

POSSIBLE CAUSES OF HYPOGLYCEMIA IN MAPLE SYRUP URINE DISEASE. Jean Holowach Thurston*, Richard Fertel*, Janina Kotler-Brajtburg*, and Franz M. Matschinsky* (intro. by Philip Dodge, Wash. Univ. School of Medicine, St. Louis, Mo.)

It is currently believed that the hypoglycemia seen in Maple Syrup Urine Disease is caused by the elevated levels of leucine. However, we have results which strongly suggest that the three branched chain αketo acids that accumulate in this disorder are themselves powerful insulin releasing agents and may be involved in the pathogenesis of hypoglycemia. This was shown in vivo after the s.c. injection of 2 g/kg of αketoisocaproate into nursing mice of 3-16 days. Thirty min after injection the plasma glucose had dropped from 6.94 ± 0.47 (13) to 4.26 ± 0.28 mM ($p < 0.001$) and plasma insulin had increased from 40 ± 10 (13) to 207 ± 67 (14) μUnits/ml ($p=0.040$). Under comparable conditions the concentration of leucine in liver of control animals ranged from 0.09 to 0.27 (3) and increased to levels ranging from 1.38 to 1.79 (3) m-moles/kg wet weight in treated animals ($p=0.001$). This is in line with previously reported results of in vivo studies with αketoisocaproate. To determine the relative contribution of the amino acid leucine and its keto derivative to this insulin release, in vitro studies using the isolated perfused rat pancreas were performed. It was found that 5 mM αketoisocaproate was equipotent to 20 mM glucose in releasing insulin. Similar results were obtained with αketoisovalerate and αketo-β-methyl valerate. Maximal release occurred within 60 sec after addition of these metabolites and the temporal secretion profile was biphasic as is typical for glucose provoked secretion. In view of these findings, one must consider that the branched chain keto acids play a significant role in the etiology of hypoglycemia of Maple Syrup Urine Disease.

SERUM HISTIDINE LEVELS IN JUVENILE RHEUMATOID ARTHRITIS. Elizabeth M. Smithwick and Donald A. Gerber. State University of New York, Downstate Medical Center, Departments of Pediatrics and Medicine, Brooklyn.

The clinical diagnosis of juvenile rheumatoid arthritis (JRA) is often difficult and there are no consistently helpful laboratory aids. Adults with rheumatoid arthritis have a significantly lower mean serum histidine level (1.32 mg/100 ml) than adults with other diseases (1.80 mg/100 ml). Thus, a study of histidine levels in JRA seemed warranted as a possible diagnostic tool and as an aid to understanding the disease.

Serum histidine was analyzed by a specific fluorescence method using o-phthaldialdehyde. All measurements were done in duplicate on coded samples obtained from children. The results in mg/100 ml are tabulated below.

	No. pts.	No. sera	Mean	S.D.	P
Controls	113	125	1.84	0.46	---
JRA	20	78	1.57	0.55	<0.001
Severe	15	30	1.18	0.29	<0.001
Mild	19	48	1.83	0.52	>0.9
Systemic lupus	8	40	1.74	0.37	>0.1
Rheumatic fever	18	19	1.77	0.48	>0.5
Misc. arthritis	49	68	1.90	0.65	>0.8

This study suggests that hypohistidinemia characterizes JRA as well as the adult disease. In JRA the histidine level appeared to vary directly with clinical activity; as the disease became quiescent, the value returned toward normal.

THE EFFECT OF STARVATION ON THE PLASMA LEVELS OF ALANINE IN THE NEONATAL PIG. *J. Tyson Tildon and Marvin Cornblath. Univ. of Maryland Sch. of Med., Dept. of Ped., Baltimore, Maryland 21201.*

Since it has been reported that alanine is one of the principal amino acid substrates for gluconeogenesis, studies were initiated to determine if starvation hypoglycemia in newborn piglets was due to an alteration in alanine metabolism. The plasma alanine level in two week old animals that had been fasted for 72-96 hours was found to be significantly less than the values found in the fed controls (305 ± 20 versus 620 ± 34). However, the average blood glucose in these two groups was not significantly different (136 ± 14 versus 114 ± 8). In newborn animals (0-6 hours of age), fasted for 72-hour periods, there was a similar decrease in plasma alanine (293 ± 29 versus 540 ± 47) but these animals were unable to maintain a normal blood glucose (91 ± 15 versus 21 ± 7). In 2 out of 3 newborn piglets, the intravenous injection of glucose caused a significant decrease in alanine levels, but the intravenous injection of alanine in newborn pigs caused little or no effect on the glucose levels of these animals. It is, therefore, concluded that starvation in newborn pigs produces a decrease in plasma alanine which is similar to the changes observed in older animals. However, this decrease does not appear to be correlated with the maintenance of normal glucose levels. Thus, it would appear that diminished gluconeogenesis in the newborn pig is not the result of an altered alanine metabolism.

Supported in part by a grant from the National Institutes of Health (HD-03959-03).

REVERSAL OF METABOLIC ABNORMALITIES OF TYPE I GLYCOGEN STORAGE DISEASE (GSD) BY INTRAVENOUS ALIMENTATION. Wah-Jun Tze, John F. Crigler, Jr. and M. Judah Folkman. The Children's Hosp. Med. Ctr., Dept. of Med.and Surgery, Boston.

The effect of 30 days of continuous intravenous(iv) alimentation*[Periods I(3 days)-glucose(G), 0.5g/kg/hr; II(6 days)-G,1g/kg/hr; III(12 days)-G,1g/kg/hr, + aminoacids (AA), 0.16g/kg/hr; IV(9 days)-G + AA as in III + lipomul (oral), 5g/kg/day] on the clinical and metabolic [serum (or blood) and urinary electrolytes, creatinine, urea, uric acid, sugar, ketoacids and serum pH, CO_2, lactate, lipids (total, triglycerides, phosphoLipids, cholesterol) and insulin] state of 4 year old boy with GSD was studied. With iv feeding, blood sugar levels ranged from 69-132 mg% (N=38) and were significantly greater ($p<0.001$) in Periods I and II than in Periods III and IV although mean serum insulin levels (N=26) did not differ (10 vs 12.6 μU/ml). The metabolic acidosis began improving immediately but was not totally corrected until the 4th day of Period II. Serum lactate and ketoacids and urinary ketoacids returned to normal values more rapidly. Serum uric acid levels decreased from8-9 mg% before iv feeding to 5-7 mg% in Periods I and II and 3-4 mg% in Periods III and IV with an associated decrease in uric acid excretion. Total serum lipids decreased from 6-7 g% before iv feeding to 1g% at the end of Period II and 0.4 g% in Period IV. Other serum lipids showed similar decreases. Creatinine clearance increased 60% (11 to 18 ml/min) from Period I to IV with no significant change in urea clearance. Irritability, fever and sweating disappeared soon after iv feeding was begun. A weight gain of 1.5 kg occurred and xanthoma and liver size decreased significantly during Periods III and IV. Metabolic abnormalities of a comparable magnitude returned when iv feeding was discontinued. The data indicate a primary role for adequate iv feeding of these patients in treatment of intercurrent illnesses and in preparation for elective surgery and provide a possible explanation for the clinical improvement reported after creation of a portacaval shunt.

*all iv solutions contained the same amounts of minerals and vitamins.

QUANTITATIVE IMPACT OF GROWTH ON ACID-BASE METABOLISM. Gail S. Williams, James C. Chan, and Robert W. Winters. Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, N.Y.

The technique of net acid balance (NAB) developed by Kildeberg et al. (Acta Pediat. 58, 321, 1969) permits a study of the effects of growth on each component of the input and output of net acid, defined as non-carbonic, non-metabolized acid. Net input (NAI) consists of H^+ due to H_2SO_4 production ($H^+_{SO_4^=}$), to excretion of organic anions ($H^+_{OA^-}$) and to bone growth ($H^+_{Ca^{++}}$). Net acid output (NAO) equals net base absorbed (UA_{abs}) plus net acid excretion (NAE). NAB = NAI - NAO.

Each component of NAB was measured in normal adults and in rapidly growing infants fed either cows milk formula (CM) or Similac® for 5 day balance periods. The adults were supplemented with calcium for 2 weeks prior to the study in order to insure zero calcium balance while receiving the high calcium intakes provided by the formulas. The results are expressed in mEq/1000 Cal fed.

	$H^+_{SO_4^=}$	$H^+_{OA^-}$	$H^+_{Ca^{++}}$	UA_{abs}	NAE	NAB
CM (infant)	5.4	18.0	7.9	11.0	21.5	+1.2
CM (adult)	18.6	18.8	1.5	18.4	20.1	+0.4
Sim (infant)	1.8	13.9	5.3	5.0	17.0	-1.0
Sim (adult)	12.2	14.9	2.9	12.1	17.8	+0.1

With both formulas, NAI was less in infants than in adults, an effect due largely to a reduction in $H^+_{SO_4^=}$ incident to anabolism in the infant (+ nitrogen balance) compared to non-growing adults (0 nitrogen balance). The marked reduction in $H^+_{SO_4^=}$ in the infants was somewhat countered by the higher $H^+_{Ca^{++}}$ due to bone growth. $H^+_{OA^-}$ was not obviously affected by growth. NAO closely matched NAI in all groups giving essentially zero values for NAB.

This study provides an additional quantitative acid-base dimension to the general concept of homeostasis by growth. In addition, it points out the implications of formula composition upon the quantitative load of acid generated by metabolism.

NEONATOLOGY

First Session

TOTAL INTRAVENOUS NUTRITION IN LOW BIRTH WEIGHT INFANTS. John M. Driscoll, Jr., William C. Heird, John N. Schullinger, Robert D. Gongaware, and Robert W. Winters. Departments of Pediatrics and Surgery, Columbia University College of Physicians and Surgeons, New York, N.Y.

Nine infants with birth weights less than 1200 gm (mean = 891 gm) received only intravenous nutrients (total intravenous alimentation, TIA) for 5 - 24 days (mean = 18.4 days). In six infants, TIA was started within 48 hours of birth; in the other three, the procedure was started at 12-14 days of age. In general, initial weight was regained faster in the group receiving TIA (mean = 11.4 days) than in a comparable group of conventionally-fed infants (mean = 18.2 days). Once a caloric intake of more than 100 Cal/kg/d was achieved, weight gain averaged 15.5 gm/d, and nitrogen balance averaged +0.23 gm/d. Theoretical considerations suggest that the weight gain was principally lean tissue and fat and not ECF. Positive N balance persisted despite hypercapnia (P_{CO_2} up to 85 mm Hg) and/or acidemia (blood pH down to 7.15). No significant deviations were observed in plasma [Na^+], [K^+], [Ca^{++}], and [P] when close chemical monitoring was carried out and appropriate daily adjustments made in the electrolyte composition of the infusate.

The only severe metabolic complication observed was hyperglycemia (blood sugar more than 250 mg%); this was accompanied by osmotic diuresis and dehydration on 2 occasions. One fatal catheter-related complication (Candida sepsis) occurred. There were three other deaths; all were due to pulmonary insufficiency of prematurity and unrelated to the technique of TIA.

Although these preliminary results are encouraging, they neither prove, nor even suggest, that TIA has an accepted place in the routine management of low birth weight infants. These results do demonstrate that the inherent risks of the technique, when it is properly monitored, are not unacceptably high, and they suggest that careful future clinical investigation of the technique is warranted.

INTRAVENOUS SUPPLEMENTATION OF PURE L-AMINO ACIDS AND DEXTROSE IN LOW BIRTH WEIGHT INFANTS. Rajam Subramanyam, Gladys V. Cordero, Paul W. K. Wong, and Rosita S. Fildes, Abraham Lincoln Sch. of Med. of Univ. of Illinois Col. of Med., Chicago Med. Sch., Cook County and Mount Sinai Hospitals, Chicago.

The effect of intravenous supplementation of L-amino acids and dextrose on mortality, weight gain and biochemical parameters were examined in 55 low birth weight newborn infants.At 24-48 hours of age, the infants were divided according to birth weight into Group I(701-1000g), Group II(1001-1250g) and Group III(1251-1500g).Each group was subdivided randomly into(A) amino acid-treated and(C)controls.All infants were fed the same formula orally as tolerated.(A) groups also received 10% dextrose and 3.5% pure L-amino acids (Freamine), 55Cal/100ml via a peripheral vein.(C) groups received the usual maintainance intravenous fluid of 5% dextrose in 0.2%NaCl.No significant difference in mortality at 21 days was observed in groups(A)and(C); 6 out of 8 in I(A) and 6 out of 7 in I(C) died.A significantly greater increase in weight was found in II(A)(178±26g) than in II(C)(54±51g) at 21 days,($p<.05$). Weight increase at 21 days was significant in III(A)(207±27g) when compared to that of III(C)(58±24g)($p<.001$).No edema or other abnormalities were observed in both(A) groups.Serial determinations of serum electrolytes and blood glucose showed no significant difference in groups(A)and(C).Serial BUN was significantly higher in groups(A)than in groups(C),but returned towards normal by day 21.Serum albumin was significantly higher inII(A) than inII(C) but there was no significant difference in serum albumin in III(A)and(C) groups.Infants in II(A)andII(C) were discharged on 45.22±11.16 and 55 ± 9.08 days respectively($p>.05$).Infants in III(A) were discharged significantly earlier than those in III(C)(41±1.1 and 49±2.0 days respectively,$p<.005$).While intravenous supplementation of pure amino acids and dextrose does not improve the survival of low birth weight infants, it is not accompanied by the usual complications of hyperalimentation and it enables infants to be discharged from the hospital earlier.

MECHANISM OF LATE FETAL BRADYCARDIA. L. Stanley James, H.O. Morishima, Edward Bowe, Wendell Niemann, and Salha S. Daniel. Division of Perinatology, College of Physicians and Surgeons, Columbia University, New York, New York.

Late fetal bradycardia, which commences during a uterine contraction and persists for 30 to 60 seconds after, is associated with depression and hypoxia at birth. However there are no data on the fetal cardio-vascular and acid base state associated with this type of bradycardia. We have developed an experimental model in the sub-human primate in which the cardio-vascular and acid-base state of the near term fetus can be directly monitored during labor. In a series of 30 experiments, labor progressed with no abnormal heart rate pattern in a control group of 10 fetuses, while late bradycardia was observed in 20. The fetuses which exhibited late bradycardia became acidotic, hypoxic, and hypotensive as labor advanced, and there was an increase in base line heart rate; bradycardia followed each uterine contraction at a fetal PaO_2 of 15 mmHg and was accompanied by a further decrease in oxygen levels. In those fetuses which remained well oxygenated there was no change in heart rate nor in the level of oxygenation during uterine contraction of similar intensity. Late deceleration was abolished or suppressed when the level of fetal oxygenation was raised above 15 mmHg by administering a high concentration of oxygen to the mother. Since the fetal acidosis and hypotension remained, it is concluded that fetal hypoxia is the essential component producing late deceleration of the heart rate.

Presented in part in Newark, November, 1971 and submitted to the American Journal of Obstetrics and Gynecology, January, 1972.

CONTROLLED TRIAL COMPARING AGAR, INTERMITTENT LIGHT, AND CONTINUOUS LIGHT FOR MANAGEMENT OF NEONATAL HYPERBILIRUBINEMIA. H.M. Maurer, C.N. Shumway, D. Draper, and A. Hossaini, Medical College of Virginia, Richmond, Virginia. (Intr. by W.E. Laupus)

Low birth weight infants, less than 24 hrs of age, were randomly assigned to one of four therapy groups: 1) Agar (U.S.P.,Difco,Lot #554882) 125 mg, P.O., q3hrs for 4 days beginning at 18 hrs; 2)exposure to blue light, 200-300 footcandles, 12 hrs daily for 4 days (intermittent light); 3)exposure to blue light continuously for 4 days (continuous light); and 4) no therapy. Infants with a positive Coomb's test or sepsis were excluded.

Total Serum Bilirubin Concentration, mg% (mean±S.E.)

	No.	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Control	15	2.3±0.6	5.1±0.8	7.3±0.8	8.7±0.9	8.6±1.3	7.3±1.2
Agar	17	3.1±0.4[a]	5.7±0.6[a]	6.9±0.6[a]	6.7±0.7[b]	6.8±0.7[a]	6.1±0.7[a]
Intermittent Light	18	2.5±0.2[a]	4.6±0.3[a]	5.9±0.5[a]	6.3±0.5[b]	6.0±0.7[a]	5.6±0.9[a]
Continuous Light	19	1.6±0.4[a]	3.1±0.5[b]	3.4±0.5[c]	3.0±0.5[c]	3.6±0.6[c]	2.8±0.7[c]

p between treated groups and controls a=N.S., b= <.05,c= <.01

From the second day on, infants who received light continuously had significantly lower mean bilirubin concentrations than any of the other 3 groups. Infants who received light intermittently or agar had daily mean values which were not significantly different from those of the controls except on day 4. Side effects were minimal in both light-treated groups and consisted of occasional mild diarrhea. Agar was well tolerated and no significant ($p>.05$) weight loss occurred during therapy. The findings indicate that agar and intermittent phototherapy reduce neonatal hyperbilirubinemia little, if at all. Continuous phototherapy results in the lowest bilirubin concentrations and should be the treatment of choice.

THE DISPLACEMENT OF ALBUMIN-BOUND BILIRUBIN BY BENZOATE: A HAZARD OF THE USE OF DIAZEPAM IN NEWBORN INFANTS.

Sanford N. Cohen, and Lucy M. Fern, New York Univ. School of Medicine, Departments of Pediatrics and Pharmacology and The Guttman Laboratory for Human Pharmacology, New York, N.Y.

Diazepam (Valium(R)) is a potent drug for the management of alcohol and narcotic withdrawal symptoms and status epilepticus in adolescents and adults. It has also been used to treat neonatal seizures and to manage withdrawal in newborn infants born to heroin-addicted women. However, our studies on the effect of parenteral diazepam upon the protein-binding of bilirubin and other compounds indicate that this preparation is a potential hazard to the newborn infant.

Injectable diazepam contains benzoate (B) (3.73×10^{-5}M) as a buffer. We have found that B significantly disrupts the binding of bilirubin by human serum albumin at pH 7.4 at concentrations as low as 0.0077×10^{-5}M in studies utilizing cholestyramine resin as a trap for free bilirubin. This effect was apparent with either pure B or with appropriately diluted injectable diazepam. Bilirubin was displaced by this concentration of B when the original M bilirubin/M albumin was 0.6, 1.1, and 1.25. The lowest ratiorepresents a bilirubin concentration of 9.0 mg/100 ml.

B was also studied for its effect on the albumin binding of sulfadiazine at pH 7.4. In equilibrium dialysis experiments, we found that 0.0037×10^{-5}M B had a greater inhibitory effect upon the binding of sulfadiazine than did 1.2×10^{-5}M salicylate. Thus, B appears to be a far more potent inhibitor of binding than salicylate, a known inhibitor of bilirubin binding.

Our data indicate that any injectable preparation that contains a B buffer should be excluded from use in newborn infants.

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PROGNOSIS OF CHILDREN SURVIVING WITH THE AID OF MECHANICAL VENTILATION IN THE NEONATAL PERIOD. John D. Johnson, William J.R. Daily, Natalie C. Malachowski, Rose Grobstein and Philip Sunshine, Stanford Univ. Med. Ctr., Dept. of Ped., Stanford, California.

Follow-up evaluation has been performed on 26 children surviving with the aid of long-term intermittent positive pressure ventilation (IPPV) in the newborn period. These children were evaluated between the ages of 2 5/12 and 9 3/12 years (mean age 5 11/12 years) and 19 of the 26 infants were 5 years of age or older. The indications for the use of IPPV were severe RDS (22), meconium aspiration (2), post-operative atelectasis (1), and neonatal apnea (1). Birth weights of the infants requiring IPPV ranged from 1020 to 3200 grams. Chest radiographs were normal in 18 (69%); 8 children (31%) had radiographic evidence of mild-moderate chronic lung disease and 2 of these children had asthma. One child with known congenital heart disease had a definitely abnormal electrocardiogram; 6 others had questionable EKG abnormalities. Neurological examination was entirely normal in 22 (85%) and definitely abnormal in 4 children (15%); 2 children had hemiparesis, and 2 had spastic diplegia. Electroencephalograms were normal in 18 (69%) and abnormal in varying degrees in 8 (31%). Three children had severe hearing loss (two of these had a family history of deafness). Not one child had retrolental fibroplasia or severe loss of vision. The mean I.Q. (Stanford-Binet) of the study group was 109 with a range of 77-138. Only one child had an I.Q. below 85. In 18 instances in which the I.Q.'s of siblings were determined for comparison, the mean difference between the I.Q.'s of study patients and their siblings was - 5.9. From these data, it appears that those neonates with respiratory failure who survive with the aid of IPPV generally have a very good prognosis. Residual intellectual or neurological impairment were infrequently encountered and could be correlated with the severity of their disease at the time IPPV was initiated.

THE HEMODYNAMIC ASSESSMENT OF EXPERIMENTAL RESPIRATORY DISTRESS SYNDROME. Welton M. Gersony, Hisayo O. Morishima, Steve Kohl, Salha S.Daniel, and L. Stanley James. Divisions of Pediatric Cardiology and Perinatology, Department of Pediatrics, College of Physicians and Surgeons, Columbia University, New York, N.Y.

Hemodynamic studies were carried out on 41 lambs with experimental respiratory distress syndrome (RDS), gestation age 129-144 days. The syndrome was produced by one hour of maternal hypotension with trimethephan (Arfonad(R))induced twenty-four hours prior to delivery by Caesarian section. Catheters were placed in a pulmonary vein or pulmonary artery, ascending and descending aorta, jugular vein and right atrium. Serial determinations of O_2 saturation, Hgb, pH, PO_2 & PCO_2 were made from the various sites, while the animals breathed room air, or 80 to 100% oxygen, during artificial ventilation.

These experiments demonstrated that: 1) R→L shunting occurs primarily at the foramen ovale (F.O.); mean total F.O. R→L shunt as a proportion of cardiac output (QS/QT)=35%. Pulmonary R→L shunting was trivial; mean QS/QT= < 5%(31 observations in nine animals). There was significant R→L shunting across the ductus arteriosus (DA)only among severely affected acidotic animals. 2)Elevation of systemic and pulmonary artery (PA) pressure occurred with increasing hypoxia, PA pressure approximating systemic in the terminal state. 3)Oxygen administration, as compared to ambient air breathing, resulted in decreased overall R→L shunting, increased A-V difference, decreased PA pressure, and L→R shunting across the DA. 4)The single finding of a large R→L shunt was neither a definite indicator of severity nor useful as a predictive index of response to therapy. 5) Oxygenation and circulatory stability was frequently irreversibly compromised following only five minutes of air breathing.

These experiments suggest that shunting in early experimental RDS occurs at the F.O. and D.A., and not within the lungs. Volume and direction depend upon the relative resistance of the pulmonary and systemic vascular beds, which in turn are profoundly influenced by the degree of oxygenation and acid base state.

SYSTEMIC HYPERTENSION FOLLOWING OCULAR ADMINISTRATION OF PHENYLEPHRINE TO THE NEONATE. Virginia Borromeo-McGrail, Joseph M. Bordiuk, Hans Keitel (Intr. by Welton Gersony) St. Vincent's Hosp. & Med. Ctr., Dept. of Ped., New York.

10% Phenylephrine is the routine mydriatic used in many newborn nurseries in preparation for fundoscopic examination. Skin blanching following local application of Phenylephrine has been noted and a possibility of an associated systemic response has been suggested. It is the purpose of this communication to report the occurrence of significant hypertension during this procedure.

Studies were carried out on healthy, low birth weight infants ranging in age from 1 to 30 days and weight from 907 grams to 2438 grams. All infants were in a thermoneutral state. Blood pressure was determined using a Doppler method with the cuff placed over the brachial artery. Pulse and respiration were recorded from standard monitors. A single blind study was carried out, using 10% and 2.5% Phenylephrine. A separate group of patients was studied with 10% Phenylephrine instillation, at random, in an open study.

Infants receiving 10% Phenylephrine eye drops showed an increase in blood pressure, ranging from 12 mm. Hg. (18%) to 16 mm. Hg. systolic (25%), and from 10 mm. Hg. (22%) to 14 mm. Hg. (46%)diastolic. There was no alteration in pulse or respiration. The infants who received 2½% Phenylephrine eye drops or physiologic saline had no significant alteration of blood pressure. Application of 2 drops of either 10% or 2½% Phenylephrine onto the abdominal skin caused local blanching although no alteration in blood pressure, pulse rate and respiratory rate was observed.

All patients receiving Phenylephrine had full pupillary dilatation in 25 to 30 minutes. This study demonstrates that 2.5% Phenylephrine eye drops are effective and safe for mydriasis in the low birth weight infant, whereas systemic hypertension results from instillation of 10% Phenylephrine.

SERUM TRYPSIN INHIBITOR LEVELS AND THE RESPIRATORY DISTRESS SYNDROME Hugh E. Evans, Steven Keller and Ines Mandl, Columbia University College of Physicians and Surgeons, Department of Pediatrics and Obstetrics and Gynecology, New York, New York

A relationship between RDS and deficient umbilical cord serum enzyme inhibitor capacity has been suggested by us in a previous communication (Am. Rev. Resp. Dis. 101:350, 1970). A prospective, controlled study was completed to further evaluate this relationship and to extend the earlier observations. Levels of total serum trypsin inhibitory capacity (T.I.) were measured by biochemical assay using benzoyl arginine p-nitroanilide as a substrate and alpha-1-antitrypsin and alpha-2-macroglobulin by radial immunodiffusion in cord sera of 37 newborns with RDS (mean birth weight = 1254) 35 premature controls (mean birth weight = 1230 grams) and 23 healthy full-term newborns. The values of each of the 3 components were significantly reduced among those with RDS compared with either the premature controls or full-term newborns. For example, mean alpha-1-antitrypsin levels were 111 in those with RDS, 253 among control prematures and 228 mg/100 ml among full-term newborns. ($p<0.01$). Levels of TI, alpha-1-antitrypsin and alpha-2-macroglobulin were normal in 16 mothers of newborns with RDS. In 17 cases of RDS serial determinations were carried out. Among survivors with low initial T.I. levels values returned to normal in 6 of 7 cases over the first 4 days of life. In 2 other surviving cases levels were normal throughout. Among fatal cases the levels remained low or declined further over a 10 hour interval (7 of 8). Inhibitor levels were not affected by sex, gestational age or intrauterine growth. Studies of cord serum enzyme inhibitor levels may be of diagnostic significance in RDS. Studies of serial measurements suggest prognostic and pathogenetic implications.

EFFECTS OF PHOTOTHERAPY ON TOTAL BLOOD FLOW AND BLOOD FLOW IN THE SKIN AND MUSCLE. Paul Y.K. Wu, Woon H. Wong, Joan E. Hodgman and Norman E. Levan. (Intr. by Paul F. Wehrle). Depts. of Pediatrics and Dermatology, Los Angeles County-USC Medical Center, Los Angeles, Calif.

Little is known of the photobiology of the skin of neonates when subjected to phototherapy containing wavelengths 300-600 nm. In adults, the radiation quanta from 300 nm on entering the skin exerts its direct action on the epidermis, causing vasodilation in the dermis. Since homeostatic mechanisms are more precarious in infants the effect of radiation delivered in current methods of phototherapy was measured on skin temperature and blood flow. The electrocapacitance plethysmograph with local counter pressure (Hymen, et al, Am. Heart J. 68:508, '64) was adapted for measurement of calf blood flow in pre-term infants. Twenty healthy pre-term infants, mean B.W. 1691 ± 264.7 G, mean age 5 ± 1.5 days, for whom phototherapy was indicated, were studied. Each infant was studied twice, once before and once during phototherapy. Study I (10 infants) was designed to measure changes in blood flow, skin, rectal and incubator temp., heart rate (HR), respiration rate (RR) during phototherapy (450 candlewatts, 300-600 nm). Significantly increased ($p<0.01$) skin, muscle and total blood flow were observed with mean values ± 1 S.D. of 224.2 ± 83.7%, 35.1 ± 20.5% and 116 ± 30.1% respectively. Concommitant increases in HR 18 ± 8.5/min, RR 15 ± 3.8/min, skin 0.7 ± 0.3°C and incubator 1.5 ± 0.9°C temps. were found. No changes were observed in rectal temp. (0.3 ± 0.3°C). In study II (10 infants) the skin temp. was kept constant at 36.5°C, before and during phototherapy by adjustment of incubator temp. Significant increases were observed in skin and total blood flow, with mean values ± 1 S.D. of 52.3 ± 27% and 37.4 ± 14.4% respectively. Muscle blood flow remained unchanged. Rectal temp. fell significantly, 0.6 ± 0.2°C, while RR and HR remained unchanged. Increase in surface temp. and direct effect of light resulted in augmentation of total blood flow in the calf. Temp. change appears to affect both skin and muscle blood flows while light appears to affect skin blood flow only.

NEONATOLOGY

Second Session

PERINATAL BILIRUBIN METABOLISM: EFFECTS OF HEMOLYSIS. John A. Kerner, David L. Gemes, Nancy H. Dawber and M. Michael Thaler, Dept. of Ped., Univ. of California, San Francisco.

Unconjugated hyperbilirubinemia develops rapidly in newborns with hemolytic disease. Heme catabolism and bilirubin conjugation in hemolysis have not been investigated. Heme oxygenase (HO), the enzyme catalyzing heme breakdown to bilirubin, and bilirubin UDP-glucuronyl transferase (GT), the conjugating enzyme, were assayed in liver of fetuses and newborn rats. Severe hemolysis was induced with i.p. injections of phenylhydrazine (1 mg/5 g B.W.). Controls received saline.

Hematocrits fell to 40-60% of control values, 18-24 hours after treatment. Serum bilirubin averaged 0.8 mg% in newborns treated in utero, and 2.5-3.0 mg% in those treated after birth. Control animals had no detectable bilirubin.

At birth, HO activity (mg bilirubin produced/g liver) equaled adult activity, while GT activity (mg bilirubin conjugated/g liver) was 20% adult activity. During the first 2 days after birth, HO reached twice adult activity while GT activity was still below adult values. Hemolysis stimulated HO by 30-100%, and reduced GT by 50%. Inhibition of GT by hemolysis varied inversely with postnatal age. Heme i.p. (0.4 umoles/5 g B.W.) yielded similar results.

These findings indicate that newborn liver develops greater metabolic capacity for bilirubin production than for bilirubin conjugation. This imbalance is accentuated by the effects of hemolysis on bilirubin metabolism. The resulting inability to eliminate bilirubin leads to hyperbilirubinemia in experimental animals, and may explain the rapid accumulation of pigment in newborns with hemolytic disease. Supported by USPHS Grant HD-03148.

BILIRUBIN BINDING CAPACITY IN HUMAN NEWBORN PLASMA. Joseph Krasner, Lewis J. Stern and Sumner J. Yaffe. Department of Pediatrics, State University of New York at Buffalo, School of Medicine, Children's Hospital of Buffalo, New York.

The present management of neonatal hyperbilirubinemia is not optimal because of the lack of a reliable clinical laboratory method for estimating bilirubin binding to plasma proteins. Bilirubin binding capacity of plasma protein would serve as a useful index of the relative risk for bilirubin encephalopathy. A fluorometric method which measured the direct interaction of bilirubin with albumin in 20 microliters of plasma was utilized to determine binding capacity. Plasma samples from 50 individual newborn infants showed that the primary bilirubin binding capacity varied from a ratio of 0.9 to 2.2 moles of bilirubin bound per mole of albumin. A ratio of one means that 9 mg of bilirubin is bound to one gram of albumin. Purified albumin obtained from pooled cord blood had a binding capacity of 0.85 to 1.0 moles of bilirubin per mole of albumin. Differences in the shape of the experimental curves of relative fluorescence as a function of bilirubin concentration were found between purified albumin and individual neonatal plasma. Several alternative explanations can account for these differences in binding capacity: (1) Binding of bilirubin to secondary sites on albumin without fluorescence; (2) binding to proteins other than albumin; (3) dimerization of bilirubin or binding of a molecule of bilirubin to one already bound to albumin without a further increase in fluorescence.

These data suggest that knowledge of the concentration of bilirubin at which binding to secondary sites is first evident may be a far greater predictor of bilirubin risk than total bilirubin binding capacity.

Supported by USPHS Grant HD 04287.

FACTORS AFFECTING PARATHORMONE RESPONSIVENESS AND THE ROLE OF HYPOMAGNESEMIA, URINARY CA LOSS AND HYPERPHOSPHATEMIA IN NEONATAL HYPOCALCEMIA (NHC) OF PREMATURITY. Reginald C. Tsang*, Leonard I. Kleinman*, Irwin J. Light* and James M. Sutherland, Univ. of Cincinnati, Dept. of Pediatrics, Cincinnati.

Parathormone (PTH) unresponsiveness, hypomagnesemia, increased urinary Ca losses and hyperphosphatemia can cause hypocalcemia. To evaluate these factors, 58 premature neonates of 30-37 weeks gestation were studied. Parathyroid extract (PTE) was given at 24 and 48 hours of age to 24 prematures. Transient rises of serum Ca and Mg occurred 12 hrs after the first PTE compared with 24 untreated prematures matched for sex, gestation and perinatal complications (paired t $p<0.05$). Although NHC correlated with gestational age, Apgar score and acidosis (corr. coeff. $r=0.495$, 0.559 and 0.546, $p<0.01$), PTE calcemic responsiveness was not related to these factors. Greater response to PTE occurred with lower serum Ca ($r=0.711$, $p<0.01$). Thus, NHC is more likely due to PTH deficiency rather than PTH unresponsiveness, since in the latter case, PTH responsiveness at lower serum Ca would be low, and in the former case high. Serum Mg did not correlate with serum Ca from 0 to 72 hrs nor with responsiveness to PTH. Urinary Ca or Mg on day 1, 2 or 3 did not correlate with serum Ca, and urinary Ca loss was insufficient to cause NHC. Hyperphosphatemia at birth correlated with hypocalcemia 48 hrs later ($r=0.30$, $p<0.05$). Low serum Ca at 24 to 72 hrs correlated with low Apgar scores ($r>0.409$ $p<0.05$). These findings indicate that PTH unresponsiveness, hypomagnesemia and urinary Ca losses do not cause NHC but that NHC is more likely due to functionally immature parathyroids unable to maintain normocalcemia in the presence of asphyxia and hyperphosphatemia.

PLASMA PRESSOR ACTIVITY(PPA) DURING NEONATAL STRESS. Reuben B. Young, Dept.of Ped., Med.Col. of Virginia, Richmond, Virginia(Intro. by W.E. Laupus).

Studies of plasma catecholamine levels in newborn infants have been carried out using a highly sensitive in vitro bioassay(rabbit ear artery) which allows measurement of plasma pressor activity(PPA) in 0.2 ml of plasma. Specificity studies have shown that this PPA in human plasma is caused primarily by norepinephrine and epinephrine.

Prior studies reported from our laboratory have shown umbilical artery mean PPA values of: 1.6±0.4 ng/ml in 14 full term infants; 8.6±3.7 ng/ml in 8 infants whose mother had mild pre-eclampsia; 42.7±19.9 ng/ml in infants with asphyxia neonatorum and marked acidosis(pHa 7.06±0.05). Five infants born following emergency C-sections demonstrated a mean PPA level of 16.0±3.1 ng/ml and acidosis(pHa 7.17±0.06) while 4 infants born following elective C-section showed a mean PPA level of 1.5±0.34 ng/ml and no acidosis(pHa 7.35±0.08).

Current studies in LBW infants(1750-2500 Gm) have shown PPA values ranging from 2.5 ng/ml to non-detectable levels in 15 normal infants and 5.5±3.4 ng/ml in 8 acidotic(pHa 7.13±0.05) infants. PPA values during the course of RDS in 13 infants showed a mean PPA value on Day 1 of 6.4±3.4 ng/ml with good individual correlation to the degree of acidosis. PPA values on subsequent days also correlated well with the degree of acidosis. Three infants were studied 3 to 15 minutes prior to death and showed marked acidosis($pHa < 7.09$) with striking elevations of PPA-30.5±2.8 ng/ml. The intracardiac PPA value in 12 infants(1750 to 3000 Gm) with cardiac arrest ranged from 12 to 36 ng/ml and all showed a $pHa < 7.15$. It was of interest that three other infants gave suggestive evidence of catecholamine depletion with intracardiac values of 2.3 to 3.6 ng/ml in spite of marked acidosis $pH < 7.09$.

These studies have shown that acidosis is a prime stimulus of catecholamine secretion during the neonatal period and that most LBW(1750 to 2500 Gm) infants are capable of a considerable catecholamine response to acidosis. Preliminary evidence suggests that a small number of infants may show catecholamine depletion at death.

IMPAIRED OPSONIC ACTIVITY OF NEWBORN SERUM AS ASSESSED BY A QUANTITATIVE IODINATION PROCEDURE. Michael S. Kaplan and E. Richard Stiehm, Department of Pediatrics, University of California, School of Medicine, Los Angeles.

Utilizing a new technique to measure serum opsonic activity, we compared the relative phagocytosis-enhancing ability of serum from normal newborn infants (NNB), low birth weight infants (LBW) and normal adult controls. Subjects studied included 29 NNB infants and 8 LBW infants, 4 of whom were < 1,500 gms, and normal adults. Opsonic activity of the test sera was assessed by enhancement of iodination of normal adult polymorphonuclear leukocytes (PMN) in the presence of test particles and I^{131} (Pincus, S. and Klebanoff, S., NEJM 284:744, 1971). Particles utilized included zymosan (primarily for complement function), live Staphylococcus aureus 502A, and live E. coli. Results of the assays are expressed in nanamoles $I^{131}/10^7$ PMN/hour. The assay is adaptable to any bacteria or particle, uses any serum dilution, and permits multiple simultaneous assays by scintillation counting.

Optimal iodination was obtained utilizing zymosan; the opsonic activity of adult sera was 6.64 ± 3.20 compared to 4.20 ± 1.94 for NNB sera and 2.39 ± 1.91 for LBW sera. These are significantly different ($p < .05$) and indicate a progressive impairment of opsonic activity with increasing immaturity. The lowest value was .14 in a 1,400 gm LBW infant. Opsonic activity of adult sera for S. aureus was .89 ± .52, for NNB sera was .69 ± .43, and for LBW sera was .47 ± .39. There was no significant decrease in opsonic activity of newborns except among LBW infants. Mean opsonic activity of adult sera toward E. coli was .87 ± .65, NNB sera was .50 ± .52 and LBW sera was .38 ± .36. 4 NNB and 2 LBW sera had no detectable opsonic activity for E. coli. This significant reduction of opsonic activity ($p = .05$) among newborns is not correlated with their degree of maturity. These results indicate a deficiency of serum opsonins in both term and low birth weight infants to organisms for which the mother lacks IgG antibodies. This deficiency is accentuated in very low birth weight infants. Quantitative iodination provides a new and sensitive method to assess opsonic deficiency.

CARDIOVASCULAR EFFECTS OF APNEA IN PREMATURE INFANTS. Bijan Siassi, John S. McDonald, E. Hon and Joan E. Hodgman. (Intr. by Paul F. Wehrle) Depts. of Obstetrics and Gynecology and Pediatrics, Los Angeles County-USC Medical Center, Los Angeles.

Thirteen premature infants weighing 780 to 1560 G, with recurrent apneic spells of at least 20 seconds duration or persistent apnea requiring respirator treatment were studied during the first week of life. After measurement of arterial blood gases, impedance changes across chest, calculated respiratory rate, instantaneous (beat-to-beat) heart rate, electrocardiogram (EKG) and blood pressure were recorded. In 8 infants with arterial oxygen tension (PaO_2) of 35 to 96 mmHg, apnea-induced bradycardia commenced 2-4 seconds after the onset of apnea. The mean decrease in heart rate was 20% by 10', 34% by 20' and 42% by 30'. In all instances the EKG revealed sinus bradycardia. Hyperoxia (PaO_2 >125 mmHg) always markedly reduced or completely abolished apnea-induced bradycardia. Similarly, administration of atropine modified or abolished apnea-induced bradycardia. Blood pressure was measured in six apneic infants showing widening pulse pressure with no significant change in mean pressure; however, blood pressure was only affected when associated bradycardia was present. Three infants with signs of marked CNS depression did not have bradycardia during 30' apnea. From this study it is concluded that apnea induced bradycardia is vagally mediated and triggered by a sudden change in arterial oxygen tension within the physiologic range. Hyperoxygenation, depression of CNS or atropine will modify or abolish this response.

LOWER DISCHARGE WEIGHT AND SHORTENED NURSERY STAY FOR LBW INFANTS

Robert G. Dillard, M.D. and Sheldon B. Korones, M.D. (Intr. by J. N. Etteldorf)
Department of Pediatrics, University of Tennessee, Memphis

Three hundred and ninety-four infants whose birth weights were 2268 grams or less were randomly assigned at birth to Group A (mean discharge weight 2077 grams) or Group B (mean discharge weight 2291 grams). The mean duration of nursery stay was 18.1 days for Group A and 24.7 days for Group B. Management in the hospital was identical for both groups. There were no significant differences between the two groups with respect to mean maternal age, gravidity, or birth weight, or between incidence of gestational age below 32 weeks, intrauterine growth retardation, or birth weight below 1500 grams. Social data were available for approximately two-thirds of the families. All babies were from families of low socioeconomic status. There were no significant differences in years of maternal education, housing density, or marital status.

Eight of 195 Group A infants and 11 of 199 Group B infants were readmitted to the hospital within 4 weeks after discharge. Chart reviews did not indicate any apparent relationship between time of discharge and reasons for readmissions.

Analysis of weight gain at 1 and 4 weeks after discharge was possible for 195 patients. At one week, the mean weight gain from time of discharge was 191 grams for Group A and 223 for Group B. At 4 weeks, Group A and Group B gained 918 and 959 grams respectively. These differences were not statistically significant.

It was thus concluded that for this indigent population, the nursery stay can be shortened substantially (22 percent) by lowering the weight required for discharge, and that the resultant earlier discharge is a safe practice not associated with an increased rate of hospital readmission or with impaired weight gain.

THERAPEUTIC CONSEQUENCES OF PARTIAL EXCHANGE TRANSFUSION IN SYMPTOMATIC POLYCYTHEMIC NEONATES

D. Gary Benfield, Ronald J. Lubbe, and James M. Sutherland, Univ. of Cincinnati College of Medicine, Department of Pediatrics, Cincinnati, Ohio.

Polycythemia has been implicated as a cause of seizures and cardiorespiratory distress in neonates. Thirteen symptomatic newborns with capillary hematocrits between 71-87% were treated by partial exchange transfusion using 5% human plasma replacement according to the formula: blood volume removed = body weight (kg) X estimated blood volume (cc/kg) X $\frac{Hct_1 - Hct_2}{Hct_1}$

where Hct_1 = initial Hct and Hct_2 = desired Hct. Measurements were made of pre and post-exchange Hct, blood viscosity, plasma protein, and fibrinogen. Blood viscosity measurements were performed at eight shear rates between 768 and 3.8 sec^{-1}. Mean post-exchange umbilical vein Hct, protein, fibrinogen, and blood viscosity for all shear rates studied were significantly less than mean pre-exchange measurements ($p<0.001$). An 11% decrease in mean pre to post-exchange Hct was associated with a mean blood viscosity decrease of 31% at 3.8 sec^{-1} (as in the microcirculation), demonstrating that a relatively small decrease in Hct resulted in a large decrease in blood viscosity. Moreover, signs and symptoms seemed to improve rapidly following treatment, clinically reflecting the fall in blood viscosity.

SURFACTANT APPEARANCE AND SECRETION IN FETAL LAMB LUNG IN RESPONSE TO DEXAMETHASONE.

Arnold C.G. Platzker, Joseph A. Kitterman, John A. Clements[1] and William H. Tooley, Cardiovascular Research Inst., NHLI Specialized Center of Research in Pulmonary Disease, and Dept. of Ped., University of California, San Francisco, California.

We have used a quantitative assay for surface active material (SAM) to study the effects of dexamethasone treatment of fetal lambs on SAM in tracheal fluid and lung tissue. We performed tracheotomies on twin lamb fetuses and diverted tracheal fluid into large, thin walled latex bags placed in the uterine cavity. We collected tracheal fluid every 12 hours for 1-3 weeks and measured volume and SAM concentration in 400 samples. After a control collection period we infused dexamethasone 400 µg/day into one twin until we detected SAM or until SAM increased in the tracheal fluid of the treated fetus. Tracheal fluid collection rate was 2.3-3.8 ml/kg/hr and did not change with dexamethasone or gestational age. SAM became detectable in tracheal fluid of 6 untreated fetuses at 120-122 days gestation. After 2-4 days of dexamethasone SAM became detectable in tracheal fluid as early as 108 days gestation. At 126 days tracheal fluid SAM concentration was 5.2 µg/ml in 4 lamb fetuses and 2 days after dexamethasone it was 22.3 µg/ml in treated and 4.5 µg/ml in control fetuses, a 370% increase in tracheal flux of SAM. At 132 days tracheal fluid SAM was 15.8 µg/ml in 3 lamb fetuses and after 2 days of dexamethasone it rose to 162 µg/ml in treated and 37 µg/ml in control fetuses, a 455% enhancement in flux. Thus, after 132 days the rise in tracheal flux of SAM induced by dexamethasone corresponded when pregnancy was interrupted to a decrease from 85 to 17 hours in time required to replace an alveolar surface layer of SAM.

[1]Career Investigator, American Heart Association.

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ASSISTED VENTILATION IN THE TREATMENT OF HYALINE MEMBRANE DISEASE: THE USE OF CPAP WITH OR WITHOUT ASSISTED VENTILATION UTILIZING A SINGLE VENTILATOR SYSTEM.

R.A. deLemos, G.W. McLaughlin, H.W. Diserens and R.R. Kirby (intr. by M.J. Sweeney). Depts. of Pediatrics and Anesthesiology, Wilford Hall USAF Medical Center, San Antonio, Texas and the Dept. of Pediatrics, Univ. of Texas Medical School at San Antonio, Texas.

A ventilator was designed which provides a continual flow of gas to the patient throughout all phases of the respiratory cycle (abs. Amer. Thor. Soc., Apr. 1971). This system can be used to maintain CPAP and, if assisted ventilation is required, it can be added without changing the ventilator.

105 newborns with respiratory failure (ph 7.1, pO_2 50 torr in 100% O_2 pCO_2 70 and rising) from hyaline membrane disease were evaluated. Initial therapy consisted of intubation and CPAP. If, after a reasonable period on CPAP alone, the blood gases or clinical condition had not improved, assisted ventilation was added. Ventilator rate and volume were decreased depending on the pCO_2 and assisted ventilation was discontinued when tolerated. Gradual reduction of CPAP was then accomplished, extubation being performed when the infant maintained a pO_2 50 torr in 40% O_2 at 2 mm Hg or less CPAP.

Therapy with CPAP alone was successful in only 29 of 105 infants, the remainder requiring at least 12 hours of assisted ventilation. 81 infants survived. The frequency of complications appeared related to the duration of intubation and not to the presence or absence of assisted ventilation. A single infant developed chronic pulmonary disease.

NEONATOLOGY

Read by Title

PLACENTAL RESPIRATION IN THE FIRST THIRTY SECONDS AFTER DELIVERY.

Bruce D. Ackerman and Lisa Marquis (Intr. by Thos. L. Nelson). University of Calif. Irvine, Department of Pediatrics, Irvine, California.

For 30 vigorous term infants, the umbilical cord was double-clamped from one second before to 37 seconds after birth. From zero to 6 breaths occurred before clamping. Blood was obtained from the umbilical artery (UA) and umbilical vein (UV) for $_pH$, $_pCO_2$, and $_pO_2$. The object was to determine the effect of interval from birth and number of breaths prior to clamping on the difference between the UV and UA values. For 9 infants, clamping occurred within 4 seconds of birth, and no breaths preceded clamping. For 5 infants, clamping occurred 30-37 seconds after birth, and 3-6 breaths preceded clamping. There were no significant differences in $_pH$, $_pCO_2$, or $_pO_2$ between these 2 groups of infants, for either UA or UV blood. Therefore, data for all 30 infants were analyzed in terms of difference between UV and UA. The mean UV minus UA differences were: for $_pH$: 0.10±.04; for $_pCO_2$: -17±11 mm Hg; for $_pO_2$: 14±6 mm Hg. For all 3 parameters, the size of the difference was no smaller at 30-37 seconds than it was in the first 4 seconds. Therefore, it is concluded that placental gas exchange is just as efficient for at least the first 30 seconds after delivery as it is at the moment of birth. The mean UV hemoglobin concentration was 16.7±1.8 gm/100 ml. Using each infant's values for hemoglobin concentration, UV $_pO_2$ and $_pH$, and UA $_pO_2$ and $_pH$, it was calculated that the mean difference in oxyhemoglobin concentration (Δ[Hgb-O]) between UV and UA was 5.6±2.7 gm/100 ml. According to Stembera et al, umbilical blood flow persists at a rate of 75 ml/kg body wt/min for the first 100 seconds after birth. Using this value for flow rate, each infant's oxygen consumption (V_{O_2}) can be estimated from the Δ[Hgb-O]. The mean V_{O_2}, so calculated, was 5.6±2.7 ml/kg body wt/min. This value is similar to accepted values for neonatal V_{O_2}. Therefore, it is concluded that, so long as the umbilical circulation is not interrupted, the infant's oxygen requirements, at least during the first 30 seconds, can be met by placental respiration.

PREDICTABILITY OF pH, P_{O_2} and Hgb SATURATION WITH O_2 OF FETAL BLOOD FROM COMPONENT ANALYSIS OF LATE DECELERATION.

Karlis Adamsons, Ronald E. Myers and Eberhard Mueller-Heubach; NIH, NINDS, Lab. Perinatal Physiol., Mt. Sinai Sch. Med., Dept. Ob-Gyn, NYC, N.Y., and Columbia Univ. Dept. Ob-Gyn, NYC, N.Y.

Clinical and laboratory studies have established that only in the presence of a reduced O_2 content of fetal blood normal uterine contractions create changes in fetal heart rate of the type designated as late deceleration. The purpose of this investigation was to elucidate whether pH, P_{O_2} and Hgb saturation with O_2 of fetal arterial blood could be predicted with reasonable accuracy by a quantitative analysis of the various components of this phenomenon.

Fifteen rhesus monkeys near term were used. Under pentobarbital anesthesia the fetus was prepared for continuous monitoring of heart rate, blood pressure, ECG., pressure within the amniotic cavity, and for intermittent sampling of arterial blood. Blood flow through the intervillous space was progressively reduced by a constricting device placed around the maternal aorta until the appearance of late deceleration. The sampling of fetal blood preceded by a short time interval the uterine contraction eliciting late deceleration. pH and P_{O_2} were determined with appropriate electrodes for micro samples, and Hgb saturation with O_2 was derived from the nomogram of Behrman et al.

It was found that the length of the time interval between onset of uterine contractions and onset of late deceleration was a relatively good indicator of P_{O_2} and Hgb saturation with O_2. The same also pertained to the rate of deceleration (beats/Sec^2). Neither of these variables, however, were suitable for an accurate estimation of pH. The magnitude of fall in fetal heart rate during late deceleration correlated well with the degree of fetal oxygenation, particularly when the duration of uterine contraction was taken into consideration. In agreement with previous findings, late deceleration was a late symptom of impaired fetal oxygenation.

FETAL AND NEONATAL RESPONSE TO STRESS; A SLIDE TAPE FOR MEDICAL STUDENTS COMPARING THE SEAL TO THE HUMAN NEWBORN, Robert A. Beargie, (Intr. by Warren E. Wheeler), University of Kentucky Medical Center, Department of Pediatrics, Lexington, Kentucky.

This synchronized audio-slide unit presents the diving reflex of the seal as background to understanding the human fetal and neonatal response to stress. The objective is to enable the junior medical student to relate his newborn observations to the concept of selective vasoconstriction. The elements of the seal's diving reflex emphasized are: intense selective vasoconstriction to effect a shunting of blood to the brain and heart, maintainence of central arterial pressure in spite of profound bradycardia, realization of minimal oxygen debt during the dive and the lactic acid washout phenomenon occuring with relief of vasoconstriction following the dive. The newborn with hyaline membrane disease is then presented as the prototype for neonatal stress. The student is asked to examine this stressed infant in terms of his vasoconstrictive problem, specifically as decreased perfusion relates to function in lung, gut, and kidney. For interest, the student is referred to Scholander's work with the seal and for general information, to Nelson's article "On Etiology of Hyaline Membrane Disease." He is asked to answer three questions. Depending on his performance, he is instructed to either review the unit or proceed to the tape "Treatment of Neonatal Stress."

FACTORS AFFECTING THE NORMAL BLOOD PRESSURE IN NORMAL NEONATES. Virginia Borromeo-McGrail, Hans Keitel, Joseph M. Bordiuk (Intr. by Welton Gersony) St. Vincent's Hosp. & Med. Ctr., Dept. of Ped., New York.

Neonatal systemic blood pressure (BP) has been studied in a variety of disease states, but there is little data available on the normal blood pressure in the healthy neonate beyond the 1st day of life. The recent availability of a unit* for accurate blood pressure measurement in the low birth weight infant has made it possible to study the blood pressure of normal neonates in a usual clinical setting.

Systemic blood pressure was recorded in over 100 neonates age 0 to 30 days, weighing from 800 gms. to 6 kgms. Blood pressure was found to correlate with body surface area and weight. There was little correlation with age.

Several factors were demonstrated to alter the normal blood pressure. Feeding causes an increase in blood pressure lasting 30 to 60 minutes. Mild thermal stress caused an increase in blood pressure proportional to the degree of stress. The maximal increase in blood pressure was achieved with a core-skin gradient of 0.5°C.

Tilt testing, in reverse Trendelenberg position, caused a consistent and sustained decrease in blood pressure. This hypotension may be of great practical value in the infant with respiratory distress syndrome.

These studies demonstrate the need for the control of environmental factors in establishing norms for blood pressure in neonates.

* Arteriosonde® 1010 Prototype
Roche Medical Electronics, Inc., Cranbury, N.J., 08512

THE POSSIBLE ROLE OF LOW ENVIRONMENTAL HUMIDITY IN EXACERBATING APNEIC SPELLS IN PREMATURES. Teertharaj K. Belgaumkar and Kenneth E. Scott. (Intr. by R. B. Goldbloom). Dalhousie University Department of Pediatrics and Grace Maternity Hospital, Halifax, Nova Scotia.

Apneic spells are common in premature infants, are potentially damaging, and are frequently of obscure etiology. The heating phase of incubators has been implicated in their causation but the effect of changes in humidity has not been explored. Low humidity is often advocated to prevent skin maceration and bacterial overgrowth.

Of 17 prematures subjected to alternating high humidity (75% or more) and low humidity (35% or less) to assess the effect on temperature stabilisation, eight developed apneic spells. These 8 weighed 775 to 1300 gm., were 26 to 32 weeks gestation, and were reared in incubators servo-controlled to 36.1±0.3°C.

In 27 high humidity phases lasting a total of 190 hours, 98 apneic spells were recorded,and in 21 low humidity phases lasting 125 hours, 108 apneic spells were recorded. Three of 27 high humidity and 19 of 21 low humidity phases showed lowering of rectal temperature below abdominal skin temperature. 48% of apnea during high humidity and 70% during low humidity were associated with bradycardia ($p<0.01$). 75% of apneic spells in both groups occurred during heating and cooling phases with no preponderance in either phase. The range of incubator temperature was 33.3 to 35.8°C in high humidity and 35.0 to 38.0°C in low humidity.

In these infants, environmental humidity of 35% or less was associated with an increased incidence and severity of apneic spells.

AIR BLOCK SYNDROME WITH GAS EMBOLISM IN HYALINE MEMBRANE DISEASE. Frank W. Bowen, Jr., Roma Chandra, Gordon B. Avery, Children's Hosp. of D.C., Dept. of Ped., George Washington Univ., Washington, D.C.

Gas embolism after positive airway pressure has been produced experimentally as an extension of air block syndrome. Gregory and Tooley (1970) reported gas embolism in an infant with HMD who received positive pressure ventilation. We are reporting the second case of gas embolism in HMD and are suggesting air block syndrome as the etiology. Our patient was a premature female with severe HMD which progressed to stage II bronchopulmonary dysplasia (BPD). She required ventilation with the Bourns respirator at peak inspiratory pressures of 50 cm. H_2O and 9 cm. H_2O of positive end expiratory pressure (PEEP) for 133 hours.

Air block syndrome commences with alveolar rupture secondary to high airway pressures and results in interstitial emphysema, pneumothorax and pneumomediastinum. Pneumopericardium and gas embolism occur as gas dissects through the subadventitial plane of the pulmonary veins. Death occurs as a result of either hilar compression of pulmonary veins by subadventitial gas or massive systemic gas embolization.

Air block syndrome in our case may be related to decreased compliance and uneven ventilation seen in HMD and BPD. Also, any obstruction of either the endotracheal tube or the expiratory tubing of the respirator would cause prolonged high airway pressures. A respirator malfunction was not evident in this case.

Although the contribution of PEEP in the production of gas embolism has not been assessed, the widespread use of PEEP may make this previously rare complication a significant threat.

TWO NEW TECHNIQUES FOR RECORDING APNEIC SPELLS IN THE NEWBORN. Teertharaj K. Belgaumkar and Kenneth E. Scott. (Intr. by R. B. Goldbloom). Dept. of Ped., Dalhousie University and Grace Maternity Hospital, Halifax, Nova Scotia.

Investigation of the etiology of apneic spells has been slowed by the difficulties of recording. Apnea monitors alarm only after a set interval and do not record shorter episodes, preceeding events, nor secondary effects. Previous work from this unit has reported frequent short apneic spells in term infants recorded by expiratory CO_2 analysis and by strain gauge.

Two techniques for recording apneic spells in prematures are described. The first is based on the observation in adults that cardiac output and blood pressure increase during inspiration and decrease during expiration. These changes are reversed in the newborn due to shunting through the ductus secondary to changes in pulmonary vascular resistance. A catheter is passed through an umbilical artery into the aorta, and connected through a transducer to a single channel paper recorder. The rhythmic pressure variations during respiration impart a slow wave pattern, superimposed on peak systolic pressure, which disappears during apnea, as cardiac output ceases to fluctuate with respiration. As the apneic spell progresses bradycardia and changes in blood pressure and pulse pressure are documented. Activity, crying, deep breathing, gasping, hicoughs, twitching, spasms, and convulsions are recorded and can be identified by the patterns produced.

The second technique uses a non-collapsing balloon attached air tight to a pressure transducer, mounted on the precordium with its long axis crossing the subcostal region. Respiratory kinetics are produced in the balloon and recorded as respiratory waves. Cardiac kinetics are superimposed on the respiratory wave and during apnea indicate the onset of bradycardia.

Combining these techniques with clinical observations, 200 apneic spells have been monitored in 12 infants. From analysis of these records 4 types of apneic spells were differentiated; Type I- spontaneous apnea; Type II- apnea preceeded by hyperactivity, crying, or deep breathing; Type III- apnea preceeded by swallowing movements; Type IIII- apnea associated with convulsion. Recognition of the type of apnea may indicate etiology.

RADIATION HAZARDS ON THE FIRST DAY OF LIFE. Robert L. Brent. Jefferson Med. Col., Dept. Ped., Phila.

The effects of x-irradiation on the mammalian embryo vary with the dose, dose rate and embryonic age. The response of the embryo during the preimplantation period is unique to any other stage of gestation in that irradiation at this stage can result in embryonic death but does not result in a high incidence of congenital malformations. Furthermore, none of the survivors manifest intrauterine growth retardation or extrauterine growth retardation even at doses just below the LD 100. We have investigated the rat and mouse embryo on the first day of gestation in order to determine the minimal x-irradiation exposure that results in embryonic mortality. Previous investigations indicate that 150 R will result in a 65-70% mortality of the exposed embryos, so that exposures of 10, 20 and 30 R were selected. The first day of pregnancy was considered to begin at 9 a.m. on the morning the sperm were present in the vagina. Irradiation was performed at 4 p.m. of the first day. At least 40 pregnant rats were in each experimental group and in the control group. The resorption rates observed at term in the 0 R, 10 R, 20 R and 30 R groups were 5.3%, 10.6%, 14.1% and 18.2%. There was no decrease in the number of implantations so that all embryonic deaths occurred after implantation. The incidence of congenital malformations was similar in all four groups and there was no manifestation of growth retardation. Chromosome damage occurring spontaneously or induced by irradiation on the first day of gestation results in "selective genetic filtration" during the organogenetic period which protects the species. This same phenomenon was reported decades ago in embryos carrying unbalanced translocation. This information can and should be utilized in evaluating and establishing guidelines for radiation protection standards for the embryo.

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EFFECT OF NEONATAL INTENSIVE CARE ON MORTALITY RATES IN THE PROVINCE OF QUEBEC. Charles Carrier, Bernard Doray, Leo Stern and Robert Usher, Perinatal Mortality Committee, Ministry of Health, Province of Quebec.

The effectiveness of neonatal intensive care (NIC) was evaluated by comparing neonatal mortality rates in maternity hospitals utilising A) intramural, B) referral, or C) neither form of NIC. There were in the Province of Quebec in 1967-69, 2971 neonatal deaths among 297,259 over 1000 gm livebirths in 156 maternity hospitals. Three large hospitals providing intramural NIC to 20,176 births were compared to 28 others of similar size and metropolitan situation. Seven of these delivering 33,233 infants utilised referral NIC, transferring their sick infants to one of two children's hospital referral centers, such that 2-5% of their livebirths were transferred and 2/3 of their neonatal deaths occurred in the referral center. The remaining 21 large hospitals utilised neither form of NIC for their 107,523 births. Incidence of low birth weight was similar in A, B, and C. Neonatal mortality/1000 varied from 6.2 (A) to 7.4(B) to 9.2(C), and perinatal mortality from 14.7(A) to 16.9(B) to 19.0(C) (P0.001). In 14 smaller Montreal area hospitals, neonatal mortality was 35% lower in the 9 which utilised referral NIC services than in the 5 which did not.

Throughout the province, neonatal mortality in the 62 hospitals delivering more than 500 infants/year ranged from 4.6 to 20.2/1000. Ten of 13 hospitals with rates below 7.5 utilised NIC; 27 of 28 with rates of 10.0 or higher did not. (P 0.001). There were 2506 neonatal deaths among 230,236 liveborn infants delivered throughout the province in hospitals not utilising NIC; 10.9/1000. Had referral NIC been utilized, 32% of these deaths might have been prevented, while delivery in hospitals providing intramural NIC might have prevented 43%. The data clearly indicate the effectiveness of NIC in reducing neonatal mortality.

TRANSPORTING INFANTS WHO ARE TOO SICK TO BE TRANSPORTED. M. Douglas Cunningham*, Jeffrey B. Gould*, Franklin R. Smith*, Linda A. Randolph*, Werner N. Keidel* and Louis Gluck, Univ. of Calif., San Diego Sch. of Med., Dept. of Ped., Div. of Perinatal Med., La Jolla, Calif.

Many newborns are too ill or stressed with a wide range of problems, most often respiratory, for transport to regional centers by usual modes. To cope with this, intensive care teams identical to those which would care for infants on admission were dispatched to outlying hospitals to transport infants to test whether intensive care were advantageous if begun from the moment of call. From Feb. through Dec., 1971, teams composed of 1 perinatal fellow, 1 house officer, 1 nurse and 1 inhalation therapist from the Infant Special Care Center transported 115 severely ill infants requiring ICU care from 21 hospitals in San Diego and Imperial Counties usually by ambulance but also by helicopter. Stabilization and definitive care were begun at the parent hospital and continued en route. Equipment included a transport incubator, extensive medical and surgical supplies and ventilatory equipment adapted for continuous positive pulmonary pressure for infants with respiratory distress syndrome (RDS). Patients included 49 RDS, 17 aspiration syndrome, 12 congenital heart disease, 2 pneumothorax and 34 with: sepsis, congenital lobar emphysema, meningitis, multiple congenital defects, asphyxia, narcotics withdrawal, hemolytic disease, immaturity. Anticipated mortality of this severely ill group would have been 85%. Actual mortality was 43%. The experience suggests that intensive care of sick newborns should begin with transport and be a community medical resource from perinatal centers.

FETAL AND PLACENTAL LESIONS IN 100 CASES OF OLIGOHYDRAMNIOS. Pierre Deglon and William A. Blanc. Columbia Univ. Col. Physicians and Surgeons, Dpt. of Path., New York.

This supposedly rare condition occurs at least once in 600 deliveries. Oligohydramnios permits the deposition of vernix on the amnion, followed by necrosis of underlying epithelium and possibly organization resulting in pathognomonic "vernix granulomas" (amniotic nodules). The etiological factors are a) resorbtion of amniotic fluid (AF) in macerated fetuses (25) or in marked postmaturity (1), b) fetal oliguria, transfuser fetus in twin transfusion syndrome (6), renal agenesis (7), polycystic diseases (19), low urinary obstruction (9) and c) chronic leakage of AF (31, comprising 4 extramembranous pregnancies.) The anatomo-clinical syndrome: Potter's facies, anomalies of external ear, "hammy" hands, positional deformities of feet and legs, small stomach, respiratory distress due to pulmonary hypoplasia and its complications (pneumothorax, interstitial emphysema), dilated ductus arteriosus, is exceptional in group a) and almost constant in group b). In group c) external malformations occurred in 12 and RDS in 24. Of 59 liveborn infants, 53 presented RDS. Of 10 survivors, (1 postmature, 9 of group c)) 7 had moderate RDS. This study stresses the unsuspected frequency of chronic leakage and the diagnostic value of placental examination (of 100 cases, only 5 were diagnosed clinically at birth). The inhibition of pulmonary growth is apparently associated with external compression.

THE EFFECT OF EXCHANGE TRANSFUSION ON ALTERING MORTALITY IN INFANTS WEIGHING LESS THAN 1300 GRAMS AT BIRTH AND ITS ROLE IN THE MANAGEMENT OF SEVERE RESPIRATORY DISTRESS SYNDROME (RDS). Maria Delivoria-Papadopoulos, Leonard D. Miller, Walter W. Tunnessen Jr. and Frank A. Oski. Univ. of Pennsylvania, School of Medicine.

Exchange transfusion of infants with fresh adult blood results in a prompt increase in the recipient's P_{50}(P_{O_2} for 50%HbO_2 saturation at pH 7.40). Studies were conducted to determine if this decrease in the affinity of hemoglobin for oxygen would produce therapeutic benefits. Two treatment groups were evaluated. The first consisted of 21 infants weighing less than 1300g at birth; 11 were exchanged (mean weight 1100g) with Citrate Phosphate Dextrose anticoagulated blood within the first 8 hours of life while 10 served as controls, (mean weight 1035g). Nine of the eleven exchanged infants survived, while only 3 of the 10 in the control group lived. The second group consisted of 26 infants with severe RDS; 12 received an exchange transfusion (mean weight 1680g) in addition to the usual supportive care. Of these, 10 survived while only 5 of 14 of the non exchanged babies (mean weight 2000g) lived ($p<0.05$). Measurements of pH, P_vO_2, P_{50}, P_aCO_2, and P_aO_2 were serially determined in all. In the infants with the severe RDS, exchange transfusion produced, in average, within 3 hrs. a rise in P_vO_2 from 33 to 42 mm Hg, a rise in P_{50} from 17.5 to 25.5 mm Hg, and a decrease in P_aCO_2 of 15 mmHg. The P_aO_2 rose by 30mm Hg. In the control infants these values were either unchanged or deteriorated. The increase in P_aO_2 following exchange transfusion indicates an improvement in pulmonary function. These results suggest that exchange transfusion, by facilitating tissue oxygenation is of value in the management of infants with severe respiratory distress syndrome and possibly in those of low birth weight.

NUTRITIONAL SUPPORT TO THE UNDER-1500GM PREMATURE INFANT WITH INTRAVENOUS FAT, PROTEIN HYDROLYSATE AND GLUCOSE. Duncan, J. & Usher, R. Royal Victoria Hospital and McGill University, Montreal. Department of Pediatrics.

An attempt was made to nourish adequately from birth 7 infants weighing 1010-1425 gm. Milk feeds were supplemented with Intralipid, Amigen and Dextrose, administered via scalp veins for 6-25 days. Six infants survived. The limits of ability of the small premature to metabolize these nutrients were assessed. Rates of postnatal growth were achieved that approximated estimated intrauterine growth in all dimensions.

The following metabolic limits of parenteral nutrition were found: fluid intake greater than 150-200 ml/kg/day produced edema; more than 10-14 gm/kg/day of carbohydrate caused hyperglycemia; more than 4 gm/kg/day of protein resulted in azotemia. Persistent lipemia did not occur with 4 gm/kg/day of Intralipid, but cholesterol levels were elevated. Acidosis developed, but was readily controlled with $NaHCO_3$. Jaundice was not a problem. Electrolytes, liver function and coagulation studies were normal.

These infants received up to 100 cal/kg/day of parenteral feeds in addition to whatever milk could be tolerated, until milk feeds exceeded 120 cal/kg/day. By 21 days they had gained 34% in weight, 2.9 cm in length and 2.1 cm in head circumference, compared with estimated intrauterine growth rates of 38%, 3.7 cm and 3.0 cm respectively. These infants were discharged home at an average age of 59 days, with normal weight and measurements for their gestational age (3063gm at 39-4/7 weeks). Followup studies 6-12 months later show healthy babies with normal growth patterns.

DEVELOPMENTAL ASSESSMENT OF THE TINY PREMATURE INFANT. Harry S. Dweck, Samuel A. Saxon, John W. Benton, and George Cassady. Univ. of Alabama Sch. of Med., Univ. Hosp. and Clinics, Dept. of Ped., Birmingham, Alabama.

Fourteen of fifteen surviving low birth weight (LBW) infants with birth weights 1100 grams or less born 7/68 through 6/70 and 14 control infants matched for age, race and sex were subjected to standard medical and neurological examination, psychological and I.Q. testing, and EEG at ages 11 - 38 months (mean 25 months).

In contrast to the control subjects' benign perinatal courses, the tiny LBW infants were products of complicated pregnancies and deliveries (13) with neonatal problems including asphyxia (12), umbilical catheterization (12), supplemental O_2 (13), respiratory distress (9), hypoglycemia (6), hyperglycemia (3), jaundice (5), apnea (8), seizures (4), and infection (6).

Normal neurological examinations were obtained in 11/14 infants in each group. Borderline normal results were obtained in 3 control subjects and 1 LBW infant. Neurological deficits observed in 2 LBW infants, one of which was the only intrauterine growth retarded infant in the series, included hyperactive deep tendon reflexes, irritability, poor coordination, and delayed developmental milestones. Visual and auditory deficits were notably absent in all infants and EEG was normal in all low birth weight and 13 of the control infants. Residual pulmonary complications were absent in all infants. Although mean I.Q. of 88.8 in the LBW group was significantly lower than the mean of 100.6 of the control group ($p < .01$), the LBW group was born a mean of 11 weeks earlier. Correction of postnatal to conceptual age revealed almost identical mean I.Q.'s in the 2 groups (100.2 LBW; 100.6 control). Developmental milestones and social quotients were similarly identical in both groups.

Past predictions have condemned 1/3 to 3/4 of surviving premature infants to a handicapped existence with severity inversely related to birth weight. Contrary to the grim predictions of the past, our data suggest an encouraging prognosis for even the smallest surviving premature infant.

GLUCOSE INTOLERANCE IN INFANTS OF VERY LOW BIRTH WEIGHT. Harry S. Dweck, Alan M. Siegal, and George Cassady. Univ. of Alabama Sch. of Med., Perinatal Research Lab., Depts. of Ped. and Med., Birmingham.

Twenty one newborns, 500-1100 grams in birth weight, were given 0.5gm/kg of glucose by umbilical vein 1-15 h. after birth. Serum glucose and insulin were obtained at 3-120 min. by umbilical vein (UV; n = 117) and/or artery (UA; n = 71). Paired UA and UV measurements of glucose (20, glucose oxidase) and insulin (12, radioimmunoassay) were nearly identical (r = 0.99 and 0.92, respectively), therefore data were not analyzed separately by sample site. Mean rate of glucose disappearance (K_t) was calculated by semi-log plot of 10 and 30 min. total glucoses.

Baseline glucose, insulin and K_t values were all profoundly affected by prior glucose exposure. In the absence of parenteral glucose (n = 10; Group I) mean glucose was 39 mg% with range 10-78; in 7 of 10, glucose was 40 mg% or less. Mean insulin was 7μu/ml with range 0-14; in 8 of 11, insulin was < 8. In 11 babies receiving prior parenteral glucose (Group II), mean zero-time glucose was 193 (range 70-382); in 8 of 11, glucose was > 145. Mean insulin in 9 of 11 was 41μu/ml with range 8-114; in 5 of 9, insulin was > 33.

Mean K_t for all 21 babies was 1.16% per min. (range 0.53-2.17). In 7 of 10 Group I babies, K_t was greater than this while in 8 of 11 Group II babies, K_t was less than this ($\chi^2 = 3.834$; $p = 0.05$). Mean K_t was not significantly affected ($p > 0.05$) by hypothermia (cold, 1.20; warm, 1.03), RDS (1.09; no RDS, 1.23), death within 1½-24 h. of study (1.03 vs. lived, 1.23), birth weight (500-750g., 1.06; 751-1000g., 1.23; > 1000g., 1.02), or catheter position (above diaphragm, 1.13; below, 1.09).

The tendency to either fasting hypoglycemia or hyperglycemia with prior glucose exposure attests to the fragile nature of carbohydrate metabolism in these tiny babies. Further, the low mean zero-time insulins regardless of carbohydrate experience as well as the unexpectedly diminished K_t after prior glucose exposure suggests a limited, probably diminished, insulin secretory ability and provides an explanation for our previous observations of frequent hyperglycemia found in these infants.

THE EFFECTS OF MATERNAL DISEASE ON MATURATION OF HUMAN FETAL LUNG. Louis Gluck, Marie V. Kulovich* and Jeffrey B. Gould*, Univ. of Cal., San Diego Sch. of Med., Dept. of Ped., Div. of Perinatal Med., La Jolla.

Mature fetal lung postnatally synthesizes enough surface active (SA) phospholipids (esp. lecithins) to line and stabilize the fine air spaces, preventing expiratory alveolar collapse seen in RDS. Synthesis of SA lecithin is developmentally determined (two pathways with different timetables). Biochemical maturation is at about 35 weeks gestation. Fetal lung secretes SA phospholipids into amniotic fluid. Densitometric lecithin/sphingomyelin (L/S) ratios > 2.0, predict pulmonary maturity. L/S ratios correlate with gestational age (GA) and birth weight (BW) in normal pregnancies but not in many high risk pregnancies with maternal disease. Among these latter L/S ratios may vary from, e.g. 2.4 in a 29 week, 890 gm. infant, no RDS; to 1.2 in a 35 week 3700 gm. infant with severe RDS. 350 pregnancies were studied with conditions associated with intrauterine stress, dysmaturity and small placentas and accelerated lung maturity of 2-6 weeks as compared to normal gestations and include: ruptured membranes (>72 hrs), hypertension (both renal and cardiovascular), placental insufficiency, (chronic) toxemia, sickle-C disease, chronic retroplacental bleeding, circumvallate placenta, narcotics addiction and class D and E diabetes. Thirty-four cases of class A and B diabetes had a 1-2 wk delay in fetal lung maturation. Seen with accelerated lung maturation was accelerated liver function (no jaundice) and better neurological performance than normal GA and BW peers (see abstract by Gould et al). These experiments of nature which influence normal fetal developmental timetables of crucial systems for extrauterine adaptation also are key models with future therapeutic implications. Supported by USPHS grant HD-04380.

THE REGIONAL NEWBORN CENTER-EFFECT ON NEONATAL MORTALITY OF REFERRING HOSPITALS: W.C. Ellis, J. Bharara, R. Snyder: Hahnemann Med. Col. & Monmouth Med. Ctr., Dept. of Pediatrics, Long Branch, NJ (Intr. by Giulio Barbero).

Effectiveness of Regionalization of Newborn Care is still considered "An Undescended Testimonial". 7 Hospitals in 2 suburban counties with annual live births of 10,000 are retrospectively classified as Users or Non-Users of a Regional Newborn Center. 3 periods are identified: 1-"Control" (1962-67) (<40% AO_2; 2-"Study A" (1968) (<40% AO_2, H_2O, bicarb, calories; 3-"Study B" (1969-71) H_2O, bicarb, calories, >40% AO_2 & Regional Center.

4% or more of Users' newborns have been treated in the Center vs. <1% of Non-Users'. Survival and mortality are assigned to the hospital of birth. By Chi square analysis, comparison of mortality for Users, Non-Users, and the 3 periods are listed. Table indicates: mortality : births.

	501-1500 GRAMS			LOW BIRTH WEIGHT			ALL WEIGHTS		
	CONTROL:	STUDY A	(p)	CONTROL:	STUDY A	(p)	CONTROL:	STUDY A	(p)
Users	154:221	31:53	*	239:1621	48:334	*	309:23501	59:4403	*
Non-Users	89:123	32:48	*	196:1096	61:289	*	240:15835	80:5036	*
(p)	*	*		<.05	<.05		*	*	
	CONTROL:	STUDY B	(p)	CONTROL:	STUDY B	(p)	CONTROL:	STUDY B	(p)
Users	154:221	45:98	<.0005	239:1625	70:626	<.05	307:23501	97:9673	<.05
Non-Users	89:123	98:129	*	196:1096	189:642	**	240:15835	172:10886	*
(p)	*	<.0005		<.05	<.0005		>.05	<.0005	
	STUDY A:	STUDY B	(p)	STUDY A:	STUDY B	(p)	STUDY A:	STUDY B	(p)
Users	31:53	45:98	*	48:334	70:626	*	59:4403	97:9673	*
Non-Users	32:48	98:129	*	61:289	189:642	**	80:5036	172:10886	*
(p)	*	<.0005		<.05	<.0005		*	<.0005	

Users %Referred 501-1500 gm = 58% L.B.W. = 50% ALL = 4.5%

Non-Users %Referred 501-1500 gm = 12% L.B.W. = 4.3% ALL = 0.3%

Results indicate that regionalization of newborn care appropriately organized, can reduce mortality significantly in the weight categories at highest risk.
*Not Significant **Significantly worse for Non-Users.

INCREASE IN LUNG VOLUME AND ABSENCE OF RIGHT TO LEFT DUCTAL SHUNT WITH CONTINUOUS POSITIVE AIRWAY PRESSURE IN IDIOPATHIC RESPIRATORY DISTRESS SYNDROME. George A. Gregory, Joseph A. Kitterman, Roderic H. Phibbs, Mureen A. Schlueter and William H. Tooley. Depts. of Anes. & Ped. and Nat. Heart and Lung Inst. Specialized Ctr. of Research-Pulmonary Diseases, Univ. of Cal., San Francisco.

Application of continuous positive airway pressure (CPAP) to infants with the idiopathic respiratory distress syndrome (IRDS) raises arterial oxygen tension (PaO_2) in the descending aorta. Two possible mechanisms for this are an increase in lung volume with an improved relation of ventilation to perfusion or a drop in pulmonary vascular resistance with a decrease in right to left shunt through the ductus arteriosus.

To evaluate these possibilities, we measured lung volumes by helium dilution and the difference in PaO_2 above and below the ductus arteriosus at different levels of CPAP in infants weighing 1.1 to 3.0 kg being treated for IRDS.

On 13 occasions in 9 infants we measured lung volumes and abdominal aortic PaO_2 at 2 or 3 levels of airway pressure between zero and 12 mm Hg. When we increased CPAP, lung volume always increased (mean change + 81%, S.D. = 73%) and aortic PaO_2 rose from an average of 62 mm Hg (S.D.=17) to an average of 106 mm Hg (S.D.= 41).

On 10 occasions in 6 infants we measured PaO_2 on simultaneously sampled temporal arterial (TA) and descending aortic (UA) blood at each of 2 or 3 levels of airway pressure between zero and 12 mm Hg. At zero pressure there was no appreciable difference in PaO_2 or in calculated right to left shunt between TA & UA. When we raised airway pressure, PaO_2 in the TA was 10 to 24 mm Hg higher than UA in 3/10 (in one of these three the difference in calculated right to left shunt [representing the shunt thru the ductus arteriosus] was 6%; in the other 2 the difference was less than 1.5%). In 7/10 there was no meaningful difference in either PaO_2 or calculated shunt between TA and UA when we raised CPAP.

We conclude that CPAP probably raises PaO_2 in infants with IRDS by increasing lung volume and that CPAP does not alter right to left shunt through the ductus arteriosus.

DECREASE IN NEONATAL MORTALITY FOLLOWING LEGALIZATION OF VOLUNTARY ABORTIONS. Leonard Glass, Hugh E. Evans, Donald P. Swartz, B. K. Rajegowda. Departments of Pediatrics and Obstetrics, Columbia University, College of Physicians and Surgeons, Harlem Hospital Center, New York, N.Y.

A comparison of neonatal mortality rates at Harlem Hospital Center for a 4 year period (1966-1969) prior to the legalization of voluntary abortions with that of the first complete calendar year following the institution of this program (1971) showed a significant decrease during the latter period. This was due primarily to the marked decline in incidence of live born infants weighing 750 grams or less, of whom only 3% survived.

Year	Live births per year	Neonatal mortality (per 1000 live births)	Liveborn infants birth weight≤ 750 gms (per 1000 live births)
1966-1969 (yearly average)	2504	33.9	18.9
1971	2319	18.9*	8.3**

*$p < 0.005$ **$p < 0.01$

While definitive analysis of demographic effects of the legalized abortion program is not yet possible, there is highly suggestive evidence that "illegal" second trimester abortions were responsible for a high proportion of the immature live births occurring prior to 1970.

RESPIRATORY AND CIRCULATORY RESPONSES OF THE TERM LAMB TO COLD STIMULATION

Herbert S. Harned, Jr.
Jose I. Ferreiro
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The effects of environmental temperature change on the initiation of respiration and the concurrent circulatory alterations were studied in the term lamb. Each lamb was delivered by hysterectomy into a watertight Plexiglass environmental box with careful attention paid to maintaining umbilical blood flow. The fetus was submerged initially in water at 40°C thus maintaining a more basal state than that of the exteriorized non-submerged animal which has been studied so extensively. With gradual decrease in water temperature to 26°C, slow rhythmic breathing was induced in 12 consecutive experiments. Rewarming the water stopped the breathing. Breathing was not initiated by altering the environment from warm water to room air or from warm air to cool air, indicating that altering the water temperature provided a stronger stimulus.

Circulatory changes were measured by electromagnetic flow meters during cold exposure and revealed expected shifts from extremities while umbilical venous flow was constant. Epinephrine and norepinephrine secretion rates, as measured in the left renal venous blood, rose only slightly during cold exposure. Significant changes in brachiocephalic blood gas tensions were not observed during these challenges.

The stimulus of cold in the ambient environment appears to be adequate to induce rhythmic breathing under the conditions of these experiments presumably through neural stimulation of the respiratory centers.

THE IMPORTANCE OF DIMINISHED BOWEL GAS IN NEONATES. Rita G. Harper, E. George Kassner and Erlinda L. Koo. Depts. of Ped. and Radiology. Downstate Med. Center, Brooklyn, New York. (Intr. by Margaret G. Robinson)

Diminished or absent bowel gas in neonates has been observed in newborns receiving assisted ventilation. We have studied the clinical and biochemical factors associated with diminished bowel gas in newborns receiving assisted ventilation. The clinical course and x-rays of all newborns requiring assisted ventilation between Jan. 1971 to Dec. 1971 in our institution were reviewed. In those infants where diminished bowel gas was noted, prenatal and neonatal factors possibly associated with diminished bowel gas were evaluated; i.e., weight, spontaneous activity, respiratory pattern, acidosis, electrolyte imbalance, bowel abnormalities, central nervous system injury, etc. Cessation of spontaneous respiration and/or diminution of spontaneous bodily movements were associated with diminution or absent bowel gas in a matter of hours. There was no correlation with weight, degree of acidosis, abnormality of PaO_2, electrolyte imbalance or localized bowel abnormalities. Absence of bowel gas preceded death in every observed case. The combination of decreased respiration, decreased muscular activity and loss of bowel gas appears to be an ominous prognostic sign.

THE USE OF A BETA ADRENERGIC DRUG (RITODRINE HCl) FOR THE INHIBITION OF LABOR. Calvin J. Hobel and Robert N. Fiorentino, Harbor Gen. Hosp., UCLA Sch. of Med., Torrance, Calif. (Intr. by William Oh)

Ritodrine HCl was given by intravenous infusion to 23 pregnancies to determine its effect on uterine motility, and on the maternal and fetal cardiovascular system.

In 12 term pregnancies an infusion of Ritodrine HCl (100 mcg/min) was begun during established labor (3-4 cm cervical dilation) and increased until uterine contractions were considerably reduced. The infusion was then maintained at that effective dose for 1 hour. Uterine motility and fetal heart rate were monitored by internal methods. There was a significant reduction in frequency of contractions for 90 min. amplitude for 150 min. and units of activity for 150 min. The fetal heart rate increased, however, this increase was significant only for the first 30 min. post infusion. There was a significant increase in maternal heart rate during and 1 hour post infusion; a significant decrease in mean diastolic pressure during the infusion but no significant increase in systolic pressure. There were no significant changes in fetal scalp or maternal venous pH, PO_2, pCO_2, or base deficits during or post infusion.

In 11 cases of premature labor Ritodrine HCl was infused either until labor stopped or until there was evidence for treatment failure. Uterine motility and fetal heart rate was monitored by external methods. Labor was successfully inhibited in 7 cases. Similar significant findings were observed for fetal and maternal heart rate and maternal diastolic pressure during the infusion. The infusion was maintained for approximately 12 hours after which an oral preparation of Ritodrine was given. In six cases labor was successfully prolonged on the oral preparation. In 4 infusion cases (2 marginal abruptions, 1 incompetent cervix, 1 normal) Ritodrine failed to control uterine motility.

These preliminary studies suggest that Ritodrine hydrochloride effectively inhibits uterine motility with relatively few maternal or fetal side effects. It may be useful in certain cases of premature labor.

CONTINUOUS POSITIVE AIRWAY PRESSURE APPLIED BY FACE MASK. Thomas R. Harris, Dept. of Ped., Univ. of Arizona College of Medicine, Tucson, Ariz. (Intr. by Vincent Fulginiti).

Continuous positive airway pressure (CPAP) has recently found wide use in the treatment of idiopathic respiratory distress syndrome (IRDS) in neonates. CPAP has generally been applied by way of an endotracheal tube or chamber enclosing the head. We demonstrate that CPAP may be employed simply and effectively by way of a face mask system (mask-CPAP).

Six of our last six newborns with IRDS who went into respiratory failure (PaO_2 less than 40 mm Hg while breathing 100% O_2) have been treated with mask-CPAP. Average birth weight of the group was less than 2500 grams and estimated gestational age less than 36 weeks. Four of the six required no additional respiratory support, remained on the mask-CPAP system for an average of 50 hours (range 46 to 56), demonstrated an average initial fall in their alveolar to arterial oxygen gradient of 160 (range 117 to 180) or improvement in oxygen transport of 28% (range 25 to 30) and were discharged with no obvious sequelae. The fifth infant weighing 2020 grams at birth died at 48 hours and was found to have massive cerebral ventricular hemorrhage at autopsy. The sixth infant had to be transferred to a volume respirator with added positive end-expiratory pressure (PEEP) after eight hours of mask-CPAP because of increasing $PaCO_2$ (maximum 67 mm Hg), but could be returned to mask-CPAP 12 hours later and weaned successfully on the fifth day.

PREDICTING THE NEONATE AND INFANT AT RISK BY A PROSPECTIVE ANALYSIS OF PRENATAL AND INTRAPARTUM HIGH RISK FACTORS. Calvin J. Hobel, Marcia Hyvarinen, Allen M. Kaplan and William Oh. Harbor Gen. Hosp., UCLA Sch. of Med., Torrance, Calif.

A prospective study was designed to screen patients during prenatal visits for the presence of 50 prenatal and during labor for 42 intrapartum high risk factors. Numerical scores of 1, 5, and 10 were arbitrarily assigned to each factor depending upon its clinical significance. A high risk mother and neonate was defined as a patient with a score of 10 or greater. All high risk neonates were matched with a non risk neonate delivered of a non risk mother (control group) and entered into an infant follow-up program.

The following table shows the relationship between the prenatal and intrapartum events with the neonatal morbidity and perinatal mortality of 725 mothers studied:

	Score 10 or >				Neonatal Morbidity*		Perinatal Mortality	
Group	Prenatal	Intrapartum	Number	%	Number	%	Number	Per 1000
I	-	-	208	29	30	14.4	1	5
II	+	-	254	35	26	10.5	3	12
III	-	+	144	20	26	18.1	4	28
IV	+	+	119	16	31	26.2**	14	118**
Total			725	100	113	15.9	22	30

Fifty high risk infants and their matched controls have had complete exams at 6 months of age. The Group IV high risk infants have significantly lower developmental quotients than do control infants (91.3±17.9 vs 104±11.1) (±1 S.D.) ($P = < 0.001$).

This data indicates that a screening system can be utilized to identify high risk mothers and neonates. If a patient is at risk during both the prenatal and intrapartum periods, she is more likely to have a fetus, neonate and infant at risk, with respect to neonatal morbidity, perinatal mortality and subsequent developmental performance.

*Neonatal Morbidity=Neonatal Score > 10 **Significantly higher than Group I, II, & III.

PATTERN OF DRUG INGESTION IN GRAVID FEMALES. Reba M. Hill, Marjorie Horning, and E. C. Horning (Intr. by L. Leighton Hill). Baylor Col. of Med., Dept. of Ped., Inst. for Lipid Research, St. Luke's Episcopal Hosp., Houston, Texas.

The pattern of drug ingestion was studied in 116 gravid females from a group of middle socio-economic patients delivering between 1969-1971. The peak period for drugs consumed was between 16 - 36 weeks gestation. The range in number of intra-uterine drug exposures per infant was 6-31, with a mean of 13 drugs per patient.

Analgesic agents were the most frequent drugs ingested throughout pregnancy, and 20% of the drugs were prescription drugs. Acetyl salicylic acid was identified in neonatal urine and blood in significant levels 6 days post delivery.

Ingestion of diuretic agents occurred from 24 weeks until birth. Antibiotics were prescribed between 16-36 weeks predominantly for respiratory infections. Four mothers received tetracycline after the fourth month of gestation and dentition in two infants shows pigmentation of the primary teeth.

Roentgen examinations were performed on 58% of the mothers. Dental and chest x-rays represented 59% of the studies performed. During the last 4 weeks of pregnancy 17% of the patients received drugs reported to have enzyme priming effect.

ASA, caffeine, Nembutal, Seconal, Demerol, Valium, Dilantin, Mysoline, Mebral, or metabolites of these drugs were identified in neonatal urine by the method of gas chromatography-mass spectrometry.

EFFECTS OF COMBINED INSPIRATORY AND EXPIRATORY POSITIVE PRESSURE IN ASSISTED VENTILATION FOR CRITICAL RDS. Carl E. Hunt (Intr. by Russell V. Lucas, Jr.) University of Minn. Hospitals, Department of Pediatrics, Minneapolis, Minn.

A series of 33 newborns with critical RDS is presented. All had major symptoms within the first hour of life. Despite high ambient O_2 and/or CPAP, all 33 rapidly progressed to hypoxia and apnea and were begun on assisted positive-pressure ventilation (PR-2 Special). In no patient, however, could a minimally acceptable paO_2 be maintained. Previous mortality with this severity of RDS has been 100%. When a paO_2 of at least 40 mm. Hg. could not be maintained, a PR-2 respirator adapted for positive end-expiratory pressure (PEEP) was introduced, with an initial PEEP of 10 cm. H_2O. As the paO_2 then improved, ambient O_2 was decreased to 30%, PEEP then weaned to 0 and the patient returned to a conventional PR-2, or CPAP.

Group	No.	Birth Weight (kg)	Age PR-2 begun (Hours)	Age PEEP added (Hours)	paO_2 before PEEP (mm.Hg)	Best paO_2 after PEEP (mm.Hg)	Incidence of IIE and/or Pneumothorax
A	22	1.82	10.5	19.9	32	122	68%
B	11	1.86	8.7	20.3	39	190	36%

The 33 patients are divided into 2 groups: Group A if they died before age 1 month, Group B if they survived the neonatal period (see Table). Compared to Group B, those in Group A tended to be admitted later, had less severe radiologic evidence of RDS but less paO_2 response to PEEP, twice the frequency of intrapulmonary interstitial emphysema (IIE) and/or pneumothorax, acidosis out of proportion to hypoxia or CO_2 retention, and a 100% incidence of intracranial hemorrhage (IH). Of the 11 patients in Group B, 4 died of bronchopulmonary dysplasia in early infancy, 4 remain hospitalized, and 3 have been discharged and continue to demonstrate progressive improvement in pulmonary status. The addition of PEEP has improved our ability to ventilate critical RDS. No deaths occured in the neonatal period unless IH was also present. Neonatal mortality in critical RDS has been reduced from 100% to 79% and long-term survival has thus far been achieved in 9%.

EVALUATION OF INFANT TRANSPORTERS. Leonard Indyk (intr. by L. Joseph Butterfield) The Newborn Center, The Children's Hosp., Denver, Col. and York Col., C.U.N.Y., Dept. of Physics, Jamaica, N.Y.

Two commercial infant transporters and one incubator widely used as a transporter were tested in a controlled environment chamber to determine their performance under field conditions. We simulated the least favorable weather conditions likely to be encountered on a heliocopter flight in Colorado. We continuously monitored the temperature at several points within the transporter, the environmental temperature within the chamber and the power consumption of each of the units. The units were powered by fresh manufacturer-supplied batteries, by an external DC supply when the batteries were exhausted and by 115v AC.

Various performance characteristics which were measured included:

(A) the lowest external temperature against which the units were able to maintain 90°F air temperature;
(B) the drop in air temperature when the units were opened for one minute for simulated routine baby care;
(C) the change in air temperature when the power was turned off for a short period and the recovery time;
(D) the performance of the units at pressures equivalent to an altitude of 14,000 feet (Continental Divide);
(E) the temperature profile within the transporter.

We have thus determined those environmental conditions under which it is possible to maintain adequate internal temperature in each of these units. We will compare these findings with the manufacturers' performance specifications.

INCIDENCE OF DEPIGMENTED NEVI IN 1000 HEALTHY TERM NEWBORNS. Joseph L. Kennedy, Jr., and Geoffrey H. Kalish, Tufts University School of Medicine, St. Margaret's Hospital, Department of Pediatrics, Boston (Intr. by Sydney S. Gellis).

Depigmented nevi are believed to be present from birth in 85% of infants who subsequently develop tuberous sclerosis. It has been suggested (Fitzpatrick 1968) that all newborn infants be screened with a long wave ultraviolet lamp to determine the presence or absence of such lesions. One thousand healthy full term infants were examined with a long wave ultraviolet lamp (100 watt) during the first four days of life. Traces of antibiotic and diaper ointments fluoresced brightly and required cleaning and re-examination. Four infants showed depigmented macular lesions, one solitary, three multiple. The former was an 0.6 cm oval lesion. Of the latter, one infant had a patch of multiple small (1 mm) depigmented macules together with congenital neurofibromatosis; one infant had two 3 mm lesions and a small sebaceous nevus of the scalp; and one baby had three fused ovoid/ash-leaf lesions. None of the lesions became erythematous with irritation. The lesions did not give a wheal and flare reaction in contrast to the surrounding normal skin. No infant had seizures; all have remained neurologically normal. All lesions were first noted prior to Wood's light examination by the nursing or medical staff. Five additional infants had depigmented lesions with a central pattern of tiny blood vessels. Several of these have become strawberry hemangiomas.

It is concluded that: 1. screening with long wave ultraviolet light finds no more lesions than careful medical or nursing observation, 2. depigmented nevi are easily seen against the background erythema of the normal newborn, 3. depigmented nevi may not be uncommon in infants and their incidence (4/1000) does not approach the incidence of diagnosed tuberous sclerosis (1/150,000). Thus the finding of depigmented nevi in normal newborns may well be associated with a normal prognosis.

SURVIVORS OF RESPIRATORY DISTRESS SYNDROME (RDS): - A 4 YEAR FOLLOW UP. Lois H. Johnson, John J. Downes, P. Jayalakshmi, Thomas F. McNair Scott, Thomas R. Boggs. The Children's Hospital of Philadelphia, Pennsylvania Hospital, Department of Pediatrics University of Pennsylvania.

46 children surviving RDS and 87 controls matched for birthweight, race and sex, born at Pennsylvania Hospital and managed on a standard protocol as part of the Collaborative Perinatal Study were compared. The following results were obtained.

	Study	Control	
***5" Apgar <7	16 (46)	7 (83)	
Lower Resp. Dis. 1st year	9 (46)	20 (82)	
Neurological Normal 1 yr.	24 (36)	55 (72)	
8 mos. Psych. Norm. overall	22 (38)	44 (72)	
8 mos. Psych. Norm. Fine Motor	16 (29)	34 (58)	( )=# Observed
8 mos. Psych. Norm. Gross Motor	21 (30)	39 (60)	
8 mos. Psych. Norm. Mental	20 (30)	42 (60)	* P=<0.05
**4 year Psych. Norm. Fine Motor	10 (35)	42 (79)	** P=<0.02
*4 year Psych. Norm. Gross Motor	24 (32)	72 (80)	*** P=<0.01
**4 year Psych. Norm. Concept	23 (35)	67 (78)	
4 year Psych. Norm. Behavior	24 (35)	64 (81)	
4 year mean I.Q.	85 (35)	90 (79)	

From this table it can be seen that the survivors of RDS are more likely to show impairment of fine and gross motor function and concept formation than matched controls at 4 years of age. On the other hand no difference was found in overall I.Q. or behavior at this age, in the Bayley Scale Scores at 8 months, in incidence of neurological abnormalities or serious respiratory infection in 1st year after birth. No apparent correlation has been found between the extensive biochemical data obtained on 23 RDS group and outcome. Survivors of RDS seem to have a good overall prognosis but the data suggest that they should have pre school screening to detect possible learning difficulties.

ACID-BASE BALANCE IN THE CEREBROSPINAL FLUID OF NEONATES. A.N. Krauss, D.W. Thibeault, P.A.M. Auld. Dept. Pediatrics, Cornell University Medical College, New York City.

The acid-base balance of the cerebrospinal fluid (CSF) has been shown to be of importance in the control of respiration in adults. No published data exists on the CSF acid-base balance in human neonates. The present study was undertaken to determine if an appropriate relation between arterial and CSF pH could be established in neonates. Forty-two lumbar punctures were performed on 34 neonates ranging in age from 2 hours to 33 days, and weight from 700 to 3940 grams. CSF pH, Pco_2, and HCO_3 were correlated with that in an arterial sample drawn within 15 minutes.

	pH	Pco_2 mmHg	HCO_3 mEq/L
Artery Normal	7.38±.05	40±6	23±3
CSF N=17	7.33±.08	46±7	23±5
Artery Respiratory Alkalosis	7.51±.02	25±7	20±6
CSF N=4	7.38±.06	38±8	22±7
Artery Metabolic Alkalosis	7.49±.07	43±3	35±4
CSF N=3	7.36±.16	50±7	27±6
Artery Mixed Acidosis	7.23±.07	61±19	26±9
CSF N=9	7.31±.11	64±17	30±9
Artery Compensated Acidosis	7.41±.04	25±3	17±2
CSF N=4	7.38±.03	38±12	20±6

These values are similar to those found in adults and older children with similar arterial acid-base balance. This data suggests that neonates are capable of forming CSF of an appropriate pH and Pco_2, and that inability to do so cannot be implicated as a cause of respiratory abnormalities.

NEONATAL SERUM SODIUM CONCENTRATION AND ITS RELATION TO PRENATAL, PERINATAL AND POSTNATAL FACTORS. Geoffrey H. Kalish, Anthony J. Sbarra, and Joseph L. Kennedy, Jr., Tufts University School of Medicine, St. Margaret's Hospital, Department of Pediatrics, Boston, (Intr. by Sydney S. Gellis).

An attempt was made to correlate cord blood serum sodiums of term babies with prenatal, perinatal and postnatal factors. Cord bloods were collected on 1000 consecutive newborn infants with serum sodium and potassium determinations performed by flame photometry. Only results on full term (38-42 weeks gestation), singleton births, without evidence of sample hemolysis (serum K <7) were considered (206 patients). Statistical analysis was performed to correlate cord blood sodium with the following factors: maternal medications, diet, illness, and weight change during pregnancy; clinic vs private prenatal care; parity; apgar scores; sex; birth and discharge weights of newborn; abnormalities of the newborn; and postnatal morbidity and mortality.

	Diuretics		Na restricted diet		Vaginal Delivery		IV fluids	
	Yes	No	Yes	No	Yes	No	Yes	No
Na mean (mEq/L)	132.6	134.3	132.8	134.1	133.8	133.4	133.7	133.7
p	<.005		<.005		> .5		> .5	

The above data reveal that the cord sodiums of term infants varied only if the mother was on diuretics and/or a salt restricted diet. Factors such as Caesarean section delivery and routine IV fluids during labor had no bearing, which is at variance with recently published data. Term cord sodiums (which represent maternal sodium at time of delivery) are significantly lower than values usually reported for normal adult females (even when values for infants born to mothers on diuretics or salt restricted diets during pregnancy are excluded) with the range 125.0 mEq/L to 144.0 mEq/L and the mean 133.7 mEq/L. Term cord blood serum sodiums thus are lower than those usually reported and are lowered even further only by the practice of prenatal sodium depletion.

PHOSPHOLIPIDS AND FATTY ACIDS AND THE ONSET OF LABOR. Jonathan T. Lanman, Rosemarie Thau, and Llewellyn Herod. Dept. of Pediatrics, Downstate Medical Center, Brooklyn, New York.

In 1963 Luukkainen and Csapo reported that intravenous administration of a soya bean phospholipid (SBP) mixture prematurely sensitized the pregnant rabbit uterus to oxytocin, permitting premature delivery which otherwise could not be induced. We have sought to characterize the biochemical nature of the material in SBP which is capable of influencing the onset of labor. SBP is a mixture of phospholipids with lecithins predominating. Dilinoleyl lecithin (DLL) a major component of SBP, duplicated its biological activity, whereas dipalmitoyl lecithin did not. Hydrogenation of SBP, saturating its fatty acids, destroyed its biological activity (Ogawa et al., Gynec. Invest., 1:240, 1970). These observations suggested a requirement for an unsaturated fatty acid. Attempts to evaluate by the intravenous route the activity of individual fatty acids were not successful because of toxicity and the short half-life of fatty acids in the circulation, but testing by the intrauterine route proved feasible. Methyl esters of stearic (C18:0), oleic (C18:1), linoleic (C18:2), linolenic (C18:3) and arachidonic (C20:4) acids were tested; of these, C18:2 and C20:4 were biologically active; the others were not. These two active fatty acids are potential precursors of prostaglandin $F_{2\alpha}$, an agent with known luteolytic and myometrial stimulatory capability. C18:3 is also a prostaglandin precursor, but of a different series (PGE_3) for which as yet few pharmacologic data are available. We postulate that certain phospholipids given intravenously serve as a transport molecule to carry appropriate fatty acids to the target organ, presumably uterus or ovary. The intrauterine route, which supplies the fatty acids directly to the uterus, appears to avoid the necessity of a transport molecule. Fatty acids thus far found to be active are precursors of $PGF_{2\alpha}$; their influence on the onset of labor may be via conversion to this compound. Whether linoleic or arachidonic acids play a role in the physiologic onset of labor is unknown and is under study.

FEEDING IN THE FIRST THREE HOURS AFTER BIRTH
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Data on the acceptance and utilization of early feeds by newborn infants, i.e., at 1 and 3 hours after delivery, is of interest in deciding when ad lib feedings might begin in the routine care of term infants and other birth weight-gestational age groupings. Investigation of the effect of feedings within the first 3 hours of life was undertaken in 40 healthy, term appropriate-for-gestational-age infants as determined by maternal dates and physical examination. They were divided randomly into 4 groups of 10, immediately after birth. Serum glucose values were determined on cord blood and from capillary heelstick blood obtained one-half hour after birth, a.c., one-half hour p.c. and at hourly intervals. Clinical behavior and axillary temperatures were recorded. Groupings and response to feedings were as follows:

	Feeding	Time	Infants c Incr. Glucose a.c. to p.c.	Mean Increase
Group G1	5% glucose water	1 hr	6/10	+6.6 mg %
F1	Cow's milk formula	1 hr	7/10	+6.6 mg %
G3	5% glucose water	3 hrs	10/10	+26.6 mg %
F3	Cow's milk formula	3 hrs	10/10	+16.7 mg %

The type of feeding did not produce a statistically significant difference in response. The 3-hour feeding does demonstrate a more reliable serum glucose elevation and correlates theoretically with Desmond's second period of reactivity in extrauterine recovery.

HUMAN CHORIONIC SOMATOMAMMOTROPIN (HCS) AND THYROID STIMULATING HORMONE (TSH) IN THE SMOKING MOTHER AND HER BABY.
Russell J. Moser, Dorothy R. Hollingsworth, and C. Charlton Mabry. University of Kentucky Medical Center, Lexington.

Smoking mothers have small babies, yet the mechanism and significance are unknown. To assess this phenomenon we measured the placental hormone HCS and the pituitary hormone TSH in mothers and their babies. These protein hormones are known to be essential for early growth and development.

Thirty-five primiparous girls (ages 12-18 years) who were tobacco smokers and fifty non-smoking primiparous controls were studied. One-third in both groups have delivered. Serum HCS and TSH were measured by radioimmunoassay: double-antibody techniques with NIH standards were used. Maternal specimens were obtained at nine through forty weeks gestation and at delivery. Infant specimens were obtained at birth through one day. Placentas and babies were weighed.

In all the mothers, HCS increased throughout pregnancy; TSH did not. However, HCS was present at significant lower levels in the smoking mother throughout pregnancy; TSH was present at lower levels in the smoking mother during first two trimesters. At birth, the placentas and babies were smaller in the smokers than in the non-smokers. Only trace amounts of HCS were present in the babies of both groups, diminishing to nil during the first day. However, these trace amounts were in greater concentration in the babies of smoking mothers. In contrast, TSH was in greater concentration in the newly born infants of both groups than in the mothers, with TSH being even higher in the smoker's baby.

Lower levels of HCS in the smoking mother throughout pregnancy, as compared with the non-smoking mother, are parallel with the findings of smaller placentas and babies in the smoking mother. The data suggest that smoking tobacco impairs the growth of the placenta and, in turn, the growth of the baby. Further, the finding of greater amounts of HCS and TSH in the newborn baby of the smoking mother suggests that smoking tobacco impairs the placental barrier.

THE OUTCOME OF LARGE, PRE-TERM INFANTS: AN UNEXPECTED HIGH-RISK POPULATION, Lubchenco, L.O., Little, G.A., Division of Perinatal Med., Univ. Colo. Med. Ctr., Denver.

Children of 36-37 completed weeks of gestation, with birth weights of 2500-3000 grams, were found to have a 30% incidence of central nervous system (CNS) abnormality at 4 years of age. 23/106 infants in this birth weight-gestational age block were selected randomly. 3/23 had congenital anomalies, of which only 1 was related to CNS problems. 7 had CNS handicaps; IQ's in the 80's (2), spastic diplegia &/or minimal cerebral dysfunction (5). 5 of the normal children had some evidence of minimal cerebral dysfunction. A high incidence of obstetric complications surrounded their births (13/23) but their neonatal courses were essentially benign. The records of 106 infants were examined, plus a control group of 70 consecutively-born, term, appropriate-for-gestational-age (AGA) infants from the same years.

	B Wts 2501 - 3000 Gms GA 36 - 37 Wks			B Wts 3001 - 3500 Gms GA 40 - 41 Wks
	# Followed	# Not Followed		Term AGA Controls
# Newborns	23	83		70
Tot Obstet Comp	13 (57%)	34 (41%)	44.0%	26 (37%)
Toxemia	4	6	9.4%	2 (2.8%)
Breech	5	2	6.6%	2 (2.8%)
Cesarean section	2	2	3.7%	2 (2.8%)
No prenatal care	3	9	11.3%	3 (4.2%)
Mother's Age				
< 20 yrs	3	25		25
20-29	15	48		52
30+	5	10	14.1%	4 (5.1%)

Well-developed, pre-term AGA infants of relatively large size and a gestational age, shortened by only 2-3 weeks, are at a greater risk of long-term handicap than mortality data would suggest. Although a high incidence of obstetrical factors may be causally related to pre-term delivery, the etiologic factors producing CNS problems are unclear.

THE EFFECTS OF RESUSCITATION WITH OXYGEN OR AIR IN LAMBS ASPHYXIATED IN UTERO. A PROGRESS REPORT. Ronald J. Martens, Brett B. Gutsche, Giuseppe G. Pietra, Aron B. Fisher, Walter W. Tunnessen, Jr., Maria Delivoria-Papadopoulos and Lewis A. Barness. University of Pennsylvania, School of Medicine, Philadelphia, Pa.

The effect of short term exposure to 100% oxygen, administered by assisted ventilation, on the rate of oxygenation and lung tissue alterations, was studied in 15 lambs asphyxiated in utero. Fetal lambs (140-150 days gestation) were delivered by Cesarean section under epidural anesthesia. Indwelling catheters were placed in the carotid and femoral arteries for blood sampling, pulse rate and blood pressure monitoring. Stress was induced in all animals by occlusion of the umbilical circulation and documented by a mean PaO_2 7.6 mmHg and pH 6.9, mean blood pressure of 9 mmHg and pulse rate 60/min. Upon initiation of resuscitation serial blood samples were taken every 4 seconds for 2 minutes and thereafter every 15 min. for the determination of PaO_2, $PaCO_2$, pH and SO_2. Four lambs (group A) were ventilated with air (O_2 21%); of these 3 survived and 1 died. Six lambs (group B) were resuscitated with 100%, of these 3 survived and 3 died. Five additional lambs (group C) of whom 3 were resuscitated with 100% O_2 and 2 with air were sacrificed at the end of 5 minutes for metabolic and electron microscopy studies including rate of utilization of substrate by lung mitochondria. At 30, 60 and 120 seconds of ventilation, group A had a mean P_{O_2} of 58, 59 and 57 mmHg respectively with a S_{O_2} greater than 92%, group B had a mean P_{O_2} of 209, 355 and 357 mmHg respectively with a S_{O_2}, greater than 98%. In both groups, pH and $PaCO_2$ were comparable during resuscitation. The results to date suggest that lambs were sufficiently oxygenated in 30 seconds when ventilated with air and that an elevated $F_{I}O_2$ is not necessary to establish adequate oxygenation.

A NEW RETINOPATHY IN LOW BIRTH WEIGHT INFANTS. Andrew Q. McCormick, Sydney Segal and Gordon E. Pirie. University of British Columbia. Depts. of Ophthalmology and Paediatrics. Vancouver, Canada.

Abnormal retinal vessels were noted clinically in 12 of 300 unselected newborn infants weighing less than 2500 grams. The clinical profiles were:

				Preterm	Term	Post-term	Total
Retinal Vascular Pathology				5	4	3	12
Low Apgar Scores				2	2	1	5
Low Blood Sugar				2	1	1	4
Hematocrit = or > 65%				2	2	2	6
Growth:	Normal			2	0	0	2
	Abnormal	Wt.	ChL. OFC.				
		↓	↓ ↓	1	1	3	5
		↓	↓ n	0	3	0	3
		↓	n n	2	0	0	2

These babies were born with widely dilated and unusually tortuous retinal blood vessels. The vessels returned to normal caliber within the first 6 days of life. However, in 6 infants the retinal arteries showed marked segmental constrictions. Two of these developed intra-arterial thromboses and hemorrhagic retinal infarctions followed by neovascularization. This closely resembled early proliferative retinopathy of prematurity (RLF) although oxygen therapy was not implicated.

Of the 12 infants, 1 developed necrotizing enterocolitis and 1 now has a spastic hemiparesis at the age of 11 months, suggesting a common vascular pathogenesis for these conditions.

ChL. = Crown-heel length
OFC. = Occipital frontal circumference

DEVELOPMENTAL FOLLOW-UP OF ARTIFICIALLY VENTILATED INFANTS WITH NEONATAL RESPIRATORY FAILURE. Eugene W. Outerbridge and Leo Stern. McGill Univ.-Montreal Children's Hosp. Research Inst.

Follow-up evaluations have been carried out on 84 (88%) of 95 infants who had respiratory failure in the newborn period and required support with a negative pressure respirator. Their birth weights ranged from 1050 to 4360 gm and their gestational ages from 27 to 42 weeks. Seventy-four infants were ventilated for the Respiratory Distress Syndrome (RDS) as the cause of the respiratory failure. The infants are currently from 1 to 6 years of age. Thirteen (17.6%) of the 74 RDS survivors have had 28 readmissions to hospital for bronchiolitis, bronchopneumonia or both. Twenty-one (28%) have abnormal radiographs showing peribronchial thickening and/or hyperinflation. Neurological examination is normal in 68 (84%) of the 84 children. One infant is spastic and retarded and has been institutionalized. Two have hydrocephalus with some increased tone. Four are hyper-reflexic and 4 are hyperactive without other neurologic abnormalities. One infant has retrolental fibroplasia. Developmental milestones were assessed in 45 children > 24 months of age. After correction for prematurity, 20 (44%) were considered to be slow, 17 being so in speech development only. However, 4 of 5 children now in their fifth year who were previously similarly considered to be slow, now show normal speech development and normal IQ's, suggesting that one can anticipate adequate "catch-up" in these children. Of 12 children older than 5 years, 11 have IQ's within the normal range. This plus the small number of gross neurological defects is encouraging, and suggests that the majority of these children will ultimately have the potential to lead useful and rewarding lives in society.

TOTAL PARENTERAL NUTRITION(TPN) IN PREMATURE INFANTS

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Thirteen premature infants with RDS who were unable to tolerate conventional feeding methods were given TPN by central venous catheter. The infusate contained 3.3% beef fibrin hydrolysate, 20% glucose, electrolytes and vitamins. Birth weights ranged from 709 to 1715 Gm. Eight infants survived, 6 of whom had birth weights less than 1500 Gm. Three of five infants who died had birth weights less than 1000 Gm.(709,709,880 Gm.). The duration of TPN ranged from 32 hours to 58 days.

Nitrogen retention was equal to that reported for full-term neonates fed orally, During TPN and subsequently weight gain of appropriate-for-gestational-age infants was equal to that reported for healthy premature infants fed orally, but weight gain of small-for-gestational-age babies was not as good.

Balance studies indicated that provision of Na^+ and K^+ in amounts of 3 mEq./Kg./d. each preserved a positive balance of 1.5 to 2.5 mEq./Kg./d. for both. Glucose in the infusate was utilized almost totally. Most of the infants were unable to tolerate initial glucose infusion rates greater than 0.8-0.9 Gm./Kg./hr., but tolerance of 1.2 Gm./Kg./hr. could be achieved by gradually increasing the rate. Problems encountered were hyperglycemia with osmotic diuresis, migration of catheters, and venous thrombosis.

A CONTROLLED TRIAL OF PHOTOTHERAPY IN PREMATURES: MORTALITY RATES AND CAUSES OF DEATH. Kenneth E. Scott, Teertharaj K. Belgaumkar, Sharon H. Stone R.N., and S. Bustamante.(Intr. by R. B. Goldbloom). Department of Pediatrics, Dalhousie University and Grace Maternity Hospital, Halifax, Nova Scotia.

Recent studies have shown that phototherapy reduces peak bilirubin in jaundiced neonates. Logically, it would also reduce the need for exchange transfusion in prematures, as well as mortality from the procedure and from kernicterus of prematurity.

One hundred premature infants 501-2000gm and less than 35 weeks were randomly assigned to a treated or control group, matching for weight and sex. Treated infants were given phototherapy for 96 hours from birth, otherwise management was similar. Exchange transfusion was carried out if the bilirubin level reached 15 mg%.

Thirty of 50 controls but only 9 treated infants reached 10 mg% total bilirubin ($p<0.001$). Nine controls and 2 treated infants reached 15 mg% ($p=0.056$); 9 controls and 2 treated infants required exchange transfusion ($p=0.056$).

Thirteen control infants died, 3 after exchange transfusion. In one infant death was directly attributable to the procedure. Seventeen treated infants died, none after exchange or due to the procedure. Two infants of the control group who died demonstrated kernicterus at autopsy whereas none of the treated did so. Seven control and 12 treated infants died of R.D.S. These differences were not statistically significant.

Routine phototherapy of premature infants from birth significantly reduced the need for exchange transfusion to prevent kernicterus, but did not reduce mortality rates.

UREA CONCENTRATION IN AMNIOTIC FLUID AS AN INDICATOR OF INTRA-UTERINE GROWTH IN THE RAT. Pedro Rosso & Mary Rudolf. (Intr. by Myron Winick) Cornell Medical Center, Dept. Pediatrics, N.Y.,N.Y.

It has been reported that urea concentration is markedly reduced in urine of malnourished children. Since fetal malnutrition & early postnatal malnutrition have many biochemical similarities and fetal excretion of urea into the amniotic fluid has been reported, it seems possible that a decreased excretion of urea into urine and consequently into amniotic fluid might also occur during fetal malnutrition. Such a change might provide useful clinical information on the assessment of fetal growth. To test this possibility normal rats were sacrificed at different times during pregnancy to study the normal developmental changes in urea concentration in amniotic fluid. Another group was submitted to unilateral uterine artery ligation on the 17th day of pregnancy and animals sacrificed and amniotic fluid collected from the ligated and control uterine horns 24 and 48 hr later. Urea concentration increased in amniotic fluid from the 17th day of pregnancy and its values correlated linearly with increments in fetal weight. Uterine artery ligation did not produce significant differences in urea concentration in "ligated" fetuses whose body weights were reduced less than 25% of control. However highly significant reductions in urea concentration were found when the decrease in body weight was more than 30% of control values. The results demonstrate that in the rat urea concentration in amniotic fluid correlates with fetal body size and that it is reduced when intrauterine growth retardation of a certain magnitude occurs. These data encourage the exploration of the existence of a similar correlation in humans where no means of diagnosing intrauterine growth retardation is currently available.

ENTEROVIRUS EPIDEMIC IN A NEONATAL UNIT: CONTROL WITHOUT SEPARATE ISOLATION FACILITIES. Kenneth E. Scott and Sharon H. Stone. (Intr. by R. B. Goldbloom). Dept. Ped., Dalhousie Univ., and Grace Maternity Hosp., Halifax, Nova Scotia.

The threat of epidemic infection in premature nurseries has influenced the design of such units for many years. In spite of improved control of bacterial enteritis, many neonatal I.C.U.'s retain isolation rooms for management of infants considered to be infected.

Our intensive care-observation unit serves a hospital with 3500 deliveries per year. The unit includes an incubator room of 12-15 capacity served by one sink, for intensive, transitional, premature and observation care, one cot room for convalescent and growing infants, and 6 "normal" nurseries.

In August 1971 a 3 day old infant was transferred from a normal nursery to I.C.U. with pyrexia, maculo-papular rash, and diarrhea. C.S.F. and blood grew no bacteriae. The infant quickly recovered on antibiotics, and was discharged 11 days later. Subsequently 6 other infants developed similar symptoms, pyrexia (5), abnormal C.N.S. signs (4), abdominal distention (3), diarrhea (3), and skin rash (2). Echo virus 17 was cultured from the stools of all 7 affected infants and from the C.S.F. of one with seizures.

A total isolation technique was applied to the unit, iodine hand soap, disposable diapers sealed in plastic bags before removal from the incubator, all material removed from the incubator immersed in ethanol-iodine, washing portholes after each use, and disposable gloves for all patient care.

Admissions from the obstetrical unit continued and parents continued to visit and handle their infants in incubators. No new cases presented subsequent to the introduction of the technique, and weekly viral cultures from new patients and staff were negative.

If the index case became infected per vaginam the incubation period was 3 days. If subsequent cases developed from the index case, then incubation periods were 4 to 6 days.

The epidemic was aborted without recourse to classical separate room isolation techniques and without interfering with the function of the unit.

BILIRUBIN DETERMINATION BY DIRECT SPECTROPHOTOMETRY IN THE NEWBORN. Kenneth E. Scott. (Intr. by R. B. Goldbloom). Department of Pediatrics, Dalhousie University and Grace Maternity Hospital, Halifax, Nova Scotia.

The use of the direct-reading spectrophotometer* to determine bilirubin levels in neonates has recently been advocated. Tests to determine the accuracy of this instrument were carried out.

Comparative studies using Versatol** Pediatric Standard (20.5 mg%) showed the direct-reading spectrophotometer to register 0.5 mg% lower than our reference method (Van Den Berg). Further comparisons using sera from neonates showed results from the direct-reading method to be consistently 2 mg% below the reference method.

As patient sera had been obtained by heel puncture it was postulated that hemolysis might have been producing a false elevation of results obtained by the reference method. Experimental hemolysis produced a 1 mg% elevation by the reference method but no change in the 2 mg% lower values by the direct-reading method.

Weighed samples of bilirubin were dissolved in neonatal serum exposed for one week in sunlight with a bilirubin determination of 0 mg%. At 5 mg% bilirubin the direct-reading spectrophotometer gave accurate results, but at 20 mg% was 2.3 mg% low, in comparison to the reference method of 0.2 mg% high.

If such an instrument is to be used in clinical practice or research, the observed differences should be taken into account in making clinical decisions or in comparisons of data.

* A.O. Bilirubinometer

** Warner-Chilcott

ARTERIAL AND CENTRAL VENOUS PRESSURE, BLOOD GASES, OXYGEN CONTENT AND THEIR RELATION TO TISSUE HYPOXIA IN HYALINE MEMBRANE DISEASE. Bijan Siassi, Carlos E. Blanco, Raymond K.Y. Li and Paul Y.K. Wu. (Intr. by Paul F. Wehrle.) Dept. of Pediatrics, Los Angeles County-USC Medical Center, Los Angeles.

Multiple factors are involved in the delivery of oxygen to tissue during hypoxia. The relative significance of certain factors over others as a measure of severity of tissue hypoxia has not been clearly defined. Some of the factors important in tissue oxygenation in idiopathic respiratory distress syndrome (RDS) were evaluated in 12 premature infants with moderate to severe distress during their first 72 hours of life. Their weight ranged from 820 to 1720 grams. Six infants expired while 6 survived their illness. Umbilical arterial and central venous catheters were inserted and left at the level of the diaphragm. Serial simultaneous arterial and central venous blood pressures, blood gases, hemoglobin and lactic acid levels were obtained (total of 73 simultaneous measurements). Significant lactic acidemia (>3.0mM per liter) was associated with arterial oxygen tension <45 mmHg ($p<0.01$) central venous oxygen tension <30 mmHg ($p<0.02$), oxygen content of arterial blood <17 volume per cent ($p<0.01$), mean arterial blood pressure <40 mmHg ($p<0.05$) and the mean central venous pressure >3 mmHg ($p<0.01$).

The data suggests that of the factors studied, the best predictive parameters for the degree of tissue hypoxia were values of arterial oxygen tension and content. Lactic acidemia was associated with increasing central venous pressure and decreasing central venous oxygen tension. Arterial blood pressure had the least correlation with lactic acidemia because of wide individual variations.

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EFFECTS OF HYPERTONIC SODIUM BICARBONATE INFUSION TO INFANTS WITH RESPIRATORY DISTRESS. Sharon R. Siegel, Dale L. Phelps, Rosemary D. Leake, & William Oh. Harbor Gen. Hosp. UCLA Sch. of Med., Torrance, Calif. & St. Mary's Hosp., Long Beach, Calif.

The immediate physiologic effects of rapid infusion of hypertonic $NaHCO_3$ were evaluated in 6 full-term and 12 premature infants with predominant metabolic acidosis associated with respiratory distress. The infants were divided into: Grp. I, 8 infants, mean birth weight, 2425 gms, mean pH 7.22 and treated < 7 hours of age, and Grp. II, 10 infants mean B. W. 2810 gms, mean pH 7.30, treated between 24-120 hours. Baseline, 3-minute, and 30-minute postinfusion determinations of direct aortic blood pressure, arterial hematocrit, serum sodium, and osmolality were measured following intravascular infusion of 0.9M $NaHCO_3$ at a single dose of 4 to 6 mEq/Kg and given at a rate of 2 mEq/min. Grp. II demonstrated a significant increase in mean aortic pressure within 3 minutes after infusion, while Grp. I showed a significant fall below the Baseline at 15 minutes. Grp. I showed a significant increase in serum osmolality (277 ± 7.3 to 291 ± 7.4 mEq/L, $p < .01$) within 3 minutes after infusion but no significant increase in serum sodium. At 30 minutes serum osmolality remained elevated. Group II did not show significant alteration in serum sodium or osmolality. The hematocrit fell from 50% to 44% & 46% respectively at 3 minutes after infusion in Groups I & II ($p < .05$). These data suggest that rapid infusion of 0.9M $NaHCO_3$ may induce significant influx of body fluid from extravascular to intravascular compartments as a result of osmolar load. However, hypernatremia or hypertonicity did not occur as a result of infusion.

THE EFFECTS OF GESTATIONAL WEIGHT GAIN COMPONENTS ON BIRTHWEIGHT. Charles R. Stark, James J. Schlesselman, Alfred D. Godfrey, Daniel G. Seigel, and Patricia Quinn. NIH, Bethesda, Md. and Dept. Ped., Georgetown Univ. Hosp., Washington, D.C. (Intr. by Philip L. Calcagno).

Several studies have shown that maternal gestational weight gain (GWG) has a biologically significant correlation with birthweight (BW). We noted, however, that BW is a component of GWG and in none of the above-mentioned studies had BW been removed from the GWG value before determining the regression of BW on GWG. Thus, to a certain extent, BW was being regressed on itself. In our study we subtracted BW from GWG and performed a multiple *regression analysis of BW on placental weight (PW), maternal tissue gain* (MTG = GWG - (BW + PW)), and maternal prepregnancy weight (PPW). For all 274 births occurring at Columbia Hospital for Women, Washington, D.C. during August 1971, one of us (P.Q.) weighed placentae, abstracted charts, and interviewed mothers to obtain the necessary data. Our results showed that PW, MTG, and PPW accounted for 0.187 of the BW variance. Partial correlation coefficients were as follows: PW = 0.35 (t = 5.2), PPW = 0.14 (t = 1.9), and MTG = 0.08 (t = 1.1). From this we infer that placental weight is the component of gestational weight gain that affects birthweight most profoundly. Augmentation of maternal tissue mass without a concommitant increase in placental weight may have little effect on birthweight.

MATERNAL HYPEROXIA AND UMBILICAL CORD COMPRESSION by Molly E. Towell and Herminia S. Salvador, Department of Obstetrics & Gynaecology, University of British Columbia, Vancouver, B.C. (Intr. by S. Segal).

The oxygen tension of fetal blood can be raised by administration of high concentrations of oxygen to the mother but it is not known whether the same holds true when there is interference with placental exchange due to compression of the umbilical cord. Furthermore it is not known whether maternal hyperoxia is effective in relieving fetal acidosis under these circumstances. We have studied this problem in the fetal goat prepared with intravascular catheters at a hysterotomy carried out at a gestational age of 100 to 120 days. After recovery from the operative procedure, intrauterine asphyxia was induced by a compression device which had been secured around the umbilical cord. Maternal oxygen breathing was compared with air breathing during experiments in which the fetus was subjected to severe or mild compression of the umbilical cord. During severe compression, maternal oxygen breathing did not significantly raise fetal arterial PO_2 or O_2 saturation above values found during air breathing experiments; nor did it relieve fetal acidosis. During mild cord compression, however, fetal arterial PO_2 and O_2 saturation was significantly higher when the mother breathed oxygen although fetal acidosis remained unaffected. It is concluded that maternal oxygen breathing will only relieve fetal hypoxia due to umbilical cord compression when compression is mild and placental gaseous exchange is not severely impaired.

POSTNATAL GROWTH AND BODY WATER COMPARTMENTS OF THE SMALL PREMATURE INFANT, WILLIS, Diana M. and USHER, Robert H. Royal Victoria Hospital and McGill University, Montreal, Department of Pediatrics.

Small premature infants can attain intrauterine growth rates given sufficient caloric intake with concentrated feedings and parenteral alimentation to provide 150 to 180 calories per kilogram per day. The expected intrauterine weight gain is maintained in such infants; however, growth in length is retarded. At 4-6 weeks postnatal age they appear very pudgy with excess fat and fluid, associated with signs of chronic respiratory distress with chest retractions, rales, increased broncho-vascular markings, oxygen need and CO_2 retention. These can often be relieved with diuretic therapy (ethacrynic acid 1-2 mgm/kilo/dose).

Four such infants (1080-1350gm and 27 to 32 weeks gestation at birth) were followed serially, to assess body composition. Determinations of weight, length, total body water (antipyrine space), extracellular fluid (corrected bromide space) and lean muscle mass (creatinine excretion) were made at birth, 4-6 weeks and 4-6 months postnatal age.

Antipyrine space and corrected bromide space were normal at birth and at 4-6 months of age. At 4-6 weeks of age, body weight was as much as 800 gm greater than predicted for body length. This excess is explained partly by measured increases in proportions of the total body water and extracellular fluid. The possibility that the remaining excess body weight is due to excess fat is consistent with their pudgy clinical appearance.

These studies demonstrate that markedly premature infants fed sufficient calories to maintain intrauterine growth rates, accumulate excess body fluid and possibly fat. These factors may contribute to the pattern of chronic respiratory distress of the premature.

NEPHROLOGY

First Session

THE VALUE OF ANTIBIOTHERAPY WHEN USING INDWELLING UMBILICAL ARTERY CATHETERS IN THE MANAGEMENT OF RESPIRATORY DISTRESS SYNDROME. F. Teasdale, G. Albert, H. Bard, B. Doray, B. Martineau (Intr. by J.R. Ducharme) Univ. of Montreal, Hôpital Ste-Justine. Indwelling umbilical arterial catheters have become accepted for the monitoring of arterial PO_2, pH, PCO_2 and for the infusion of parenteral fluids. This practice is important whenever oxygen therapy must be strictly controlled as in the management of the low birth weight preterm infant with respiratory distress syndrome(R. D.S.). The purpose of this study was to evaluate the role of antibiotics in diminishing the incidence of sepsis and bacterial catheter contaminations in infants with R.D.S. Radiopaque catheters were inserted in the abdominal aorta up to the level of L_3-L_4 and the catheter tips localized by X-rays. Fluid therapy was continuously infused via the catheter by pump. The infants were randomly divided in two groups one receiving ampicillin(100mg/Kg/24hrs.) and kanamycin (15mg/Kg/24hrs.), the other no antibiotics Blood samples for cultures were drawn on the day of insertion and on each day thereafter. When the catheter was withdrawn the distal end was cultured and peripheral blood was drawn for culture. In the 51 infants studied to date the blood withdrawn through the catheter for cultures showed 6/24 bacterial contaminations with antibiotics as compared to 18/27 without antibiotics, $x^2=10.61$($P < .005$.) Catheter tips demonstrated 12/24 bacterial contaminations with antibiotics and 6/20 without antibiotics, $x^2=2.73$($P < 0.1$). All peripheral blood cultures were negative except in 1 case in the group without antibiotics. There was no difference in mortality between the two groups. Since there was only a significant difference between the two groups in regard to bacterial contaminations in blood withdrawn via the catheter and a single positive peripheral blood culture, the value of prophylactic antibiotics is questionable in the use of arterial catheters.

SERUM IgE LEVELS IN MINIMAL CHANGE NEPHROTIC SYNDROME. Louis M. Mendelson*, Ted D. Groshong*, Michael G. Bazaral*, Bruce M. Tune*, Stanley A. Mendoza* and Robert N. Hamburger. Univ. of Calif., San Diego, Sch. of Med., Dept. of Ped., La Jolla, Calif. 92037, Stanford Univ., Sch. of Med., Dept. of Ped., Palo Alto, Calif. 94305, and Ped. Dept., Naval Hosp., San Diego, Calif. 92134.

Serum IgE levels were measured by a radioimmunosorbent assay in twenty-eight patients with renal disease. Ten of these children had the biopsy proven diagnosis of minimal change nephrotic syndrome (MCNS) and their serum IgE levels were significantly higher than the twelve patients with other renal diseases ($p < .01$ by U test). Five of the six children with nephrotic syndrome (not biopsied) had serum IgE values greater than 600 Units/ml. In MCNS the lowest serum IgE levels were found in the patients who required cytoxan therapy.

Serum IgE levels are listed in Units relative to WHO IgE standard 68-341. Levels greater than 1000 U were taken to be 1000 U for the purpose of calculations.

Diagnosis	Number of Patients	Serum IgE U/ml Mean(Range)	Age Mean (Range)	Atopy Number(%)
1.MCNS by biopsy	10	324(82-790)	8.0(3-16)	6(60%)
a)Cytoxan treated	5	152(82-245)	8.5(3-16)	3(60%)
2.Nephrotic Syndrome (no biopsy)	6	788(55->1000)	7.0(4-12)	3(50%)
3.Other renal diseases	12	128(50-410)	10.5(4-20)	1(9%)

These patients were not selected for atopy, yet 60% of the patients with MCNS had a history of atopy compared to 9% of the patients with other renal diseases.

This data provides further evidence that IgE may play a significant role in the pathogenesis of MCNS.

SERUM PROPERDIN AND β1A LEVELS IN GLOMERULONEPHRITIS. R. H. McLean, N. G. Westberg and A. F. Michael, Univ. of Minnesota, Dept. of Peds., Minneapolis, Minnesota.

Activation of the "alternate complement pathway" in certain forms of renal disease is suggested by a decrease in the late reacting complement components in chronic membranoproliferative glomerulonephritis (CMPGN), and glomerular deposits of properdin, often without immunoglobulins, in CMPGN and poststreptococcal glomerulonephritis (AGN). Serum properdin was measured by a radial immunodiffusion assay using rabbit antisera to purified properdin in the sera of 33 normal controls and 75 patients: CMPGN (18 patients); AGN (25 patients); lupus erythematosus (LE) (12 patients); and other renal diseases (20 patients). Immunodiffusion assay for β1A and the classical zymosan assay for properdin were also carried out. Normal serum properdin by immunodiffusion is 106.7 ± 26.9 (1.S.D.) % of normal pool; normal β1A is 164.6 ± 41.1 mg%.

Compared to normal controls, a statistically significant decrease in serum properdin was seen in CMPGN when the serum β1A was ≤79 mg% (properdin 70.2 ± 18.5 (1.S.D.), p <.001). A significant decrease was present in AGN (properdin 63.3 ± 26) (p <.001) and a less significant decrease in LE (properdin 82.8 ± 23.9) (p <.05) when serum β1A was ≤79 mg%. There was no significant decrease in properdin in CMPGN (100.9 ± 26.3), AGN (104.9 ± 23.5), or LE (103.9 ± 21.4) when the serum level of β1A was normal (≥80 mg%). No significant decrease in properdin was found in other patients with other renal diseases (vasculitis, anaphylactoid purpura, focal nephritis, nephrotic syndrome and others). Properdin assay by the zymosan assay showed much scatter but tended to be low in CMPGN when the immunodiffusion properdin assay was low.

These findings suggest that reduction in the level of serum properdin in glomerulonephritis is associated with a decrease in β1A and provides indirect evidence but not proof of activation of C3 by the "alternate pathway".

INTEGRITY OF RENAL ACIDIFICATION MECHANISM IN POST-RENAL TRANSPLANT PATIENTS James C.M. Chan, Carl M. Grushkin, Mohammad Malekzadeh, Ori Better and Richard N. Fine (Introduced by George N. Donnell). Univ. So. Cal. Sch. Med.; Childrens Hospital of Los Angeles, and Rambam Hospital, Haifa, Israel.

Twenty-five children, aged 6 to 18 years, who received kidney allografts from ten live-related (LR) and fifteen cadaveric donors (CD) were studied 30-1440 days (mean 100 days) after transplantation to determine the integrity of the renal tubular acidification mechanism, with the single dose ammonium chloride (NH_4Cl) loading test (75 mEq/M^2). The allografts were functioning well (mean sodium iothalamate clearance of over 77 ml/min/1.73 M^2 and serum creatinine of less than 1.5 mg%). The same studies were performed in normal adults and in the donors (200 days post-unilateral nephrectomy). The mean GFR in these two groups was 114 and 74 ml/min/1.73 M^2 respectively. The results are presented in the table:

2-4 hours post - NH_4Cl	BLOOD			URINE		
	pH	tCO_2	BE	TA	NH_4^+	NAE
		mEq/L		μEq/min/1.73 M^2		
Normals	7.34	17.0	- 9.0	36.9	65.6	102.5
Donors	7.34	16.3	- 9.0	23.1	36.8	59.9
LR allografts	7.34	14.8	- 9.9	19.6	36.6	56.6
CD allografts	7.30	14.2	-11.6	11.2	33.6	49.2

These data indicate that: 1) a renal tubular defect to excrete H^+ ion is present in well-functioning allografts irrespective of the source of the allograft or proximity to transplantation; 2) despite 70-100% recovery of the GFR in the donors, the same acidification defect was found, suggesting that tubular compensation after unilateral nephrectomy may take a longer time than previously suspected or may not fully occur at all.

DEMONSTRATION OF SPONTANEOUS CHEMOTACTIC ACTIVITY IN HUMAN GLOMERULONEPHRITIS AND ITS RELATIONSHIP TO THE COMPLEMENT SYSTEM. Michael E. Norman* and Michael E. Miller. Univ. of Pa., Sch. of Med., Dept. of Ped., Phila., Pa.

Experimental data has indicated that complement mediated neutrophil (PMN) chemotaxis may play a role in producing glomerular basement membrane injury in some forms of human nephritis (GN). However, evidence demonstrating chemotactically active materials in human nephritic sera (NS) is lacking. These studies measured the cellular and humoral components of chemotaxis, in vitro, in 50 adults and children with GN. A modification of the Boyden chamber assay (Miller, 1970) was used. Chemotactic factor (CF) was generated from control sera (CS) and NS using immune complexes (human albumin and rabbit anti-human albumin antibody). There were 7 patients (pts) with acute, Post-Streptococcal GN, 8 with Lupus Erythematosus GN, 18 with proliferative, membranous or Membrano-Proliferative GN, 10 with the Nephrotic Syndrome, and 7 with unclassified glomerular disease. Controls included normal adults, 12 normal, age related children, 12 children with acute bacterial infections and 6 with non-renal collagen vascular disease. The data indicated that chemotactically active materials are, indeed, present in NS and may densensitize PMN receptors to further chemotactic stimuli: 1) "Spontaneous" generation (i.e. sera which was immediately heat inactivated upon collection) of CF was significantly higher in NS than in CS; 2) The addition of immune complexes to NS failed to increase amounts of CF over those spontaneously generated; 3) NS generated significantly less CF towards nephritic or normal PMN's than CS; 4) PMN's from nephritic pts showed deficient responses to CF generated from CS.

Preliminary observations demonstrated no correlation of these findings with renal function, serum B_1C globulin or total hemolytic complement levels, or the use of steroids or immunosuppressive therapy. To date, no evidence of a serum inhibitor of chemotaxis has been found.

GROWTH FOLLOWING RENAL TRANSPLANTATION: DAILY VS. ALTERNATE DAY STEROID THERAPY. Carol J. Wilson, Joel Kaye, Folkert O. Belzer, Samuel L. Kountz and Donald E. Potter (Intr. by Malcolm A. Holliday). Univ. of California, San Francisco and San Francisco General Hosp., Dept. of Ped., San Francisco.

Fifty-four children 1 to 17 years of age have received kidney transplants at the Univ. of California, San Francisco since April 1964--31 from living related donors and 23 from cadaver donors. The linear growth of 28 children who had not reached adult height prior to transplantation was evaluated for periods > 1 year post-transplant and was compared with the 50th percentile growth rate of normal children of similar height. Thirteen were treated with daily prednisone for 6 months or less (mean dose > 0.5 mg/Kg/day) and then changed to alternate day prednisone, usually 1-2 mg/Kg every 48 hours, for periods of 6-18 months. Four grew at a normal rate while on alternate day therapy (range 81-116%). Fifteen were treated with daily prednisone in doses of 0.1-0.5 mg/Kg/day for periods of 12-48 months and none grew at a normal rate. Eight of these children were subsequently changed to alternate day therapy for periods of 6-18 months and none grew at a normal rate. Three had a serum creatinine concentration > 2.0 mg%. Six of 10 kidney rejections occurred during the first 6 months post-transplant, while 2 occurred in children receiving daily prednisone and 2 in children receiving alternate day prednisone 7-45 months post-transplant. Although changing to alternate day therapy has resulted in increased growth rates (and a reduction in toxic steroid effects), true catch-up growth is rare and is unpredictable. The problem of growth failure is complex and remains a major problem in children following transplantation. The data suggest that prolonged daily steroid therapy (> 12 mo) may preclude the benefit of increased growth from subsequent alternate day therapy. Earlier introduction of alternate day therapy may be indicated.

THE ENHANCEMENT OF COMPENSATORY RENAL GROWTH BY ANTILYMPHOCYTE GLOBULIN. Baiba Ausinsch, George A. Richard. Dept. Ped., Univ. Fla. Col. Med., Gainesville. (Intr. by W. A. Altemeier)

It has been nearly 20 years since immunosuppressive agents were first used to treat renal disease in childhood; yet, there are no reports of their effect(s) on normal and compensatory renal growth. Previous work in our laboratory did not demonstrate an effect of Immuran, low dose Steroids, Actinomycin C, and Actinomycin D on compensatory renal growth. However, high dose steroids inhibited and Cytoxan promoted compensatory renal growth. This experiment was designed to investigate the effect of Rabbit Antirat Lymphocyte Globulin (RALG) on normal and compensatory renal growth.

Unilateral nephrectomized (UN) and intact adult male Sprague Dawley rats (12/group) were given 8 daily intraperitoneal injections of a potent, hemadsorbed RALG, normal rabbit serum (NRS) or phosphate buffered saline (PBS). The RALG treatment groups developed a marked reduction in peripheral white cell count and at sacrifice demonstrated a notable decrease in thymic mass, as well as, a statistically significant increase in spleen and renal mass (P<.01). The urine, serum urea nitrogen, and histology of the kidney demonstrated no evidence of renal disease in any of the groups.

Compensatory renal growth was determined by comparing the increase in the right to left kidney weight ratios. The ratios were 1.019 (intact animal), 1.291 (UN-SPB), 1.301 (UN-NRS), 1.312 (UN-RALG:1cc.) and 1.378 (UN-RALG:2cc.) Analysis of these data demonstrate that RALG (2cc./day) significantly enhances (P<.01) compensatory renal growth following unilateral nephrectomy.

This enhanced compensatory renal growth may be due to RALG inducing the production of an increased number of mitotically competent lymphoid cells. Several investigators have demonstrated that RALG is a potent in vivo mitogen. These activated lymphocytes according to the theory of Birch and Burwell could carry back Mitotic Control Protein to the kidney. This study supports the idea that a controlling cycle may exist to regulate compensatory renal growth and that it may be mediated by the lymphoid system.

ACCURATE MEASUREMENT OF GLOMERULAR FILTRATION RATE(GFR)USING A COMPUTERIZED CUMULATIVE INTEGRAL METHOD(CIM). R.Morrison Hurley,John D.Harries,and Keith N.Drummond. McGill Univ.-Montreal Children's Hosp.Research Inst.,Dept. of Nephrology,Montreal.

The standard formula for GFR: amount of tracer in urine(A_u)/plasma tracer concentration x time(t)may be conceptualized in the integral form: GFR=A_u from time $t_o \rightarrow t_1$/area under the C_p curve from $t_o \rightarrow t_1$,i.e.,$A_u \int_{t_o}^{t_1} / \int_{t_o}^{t_1} C_p dt$. Using this concept a method for precise GFR determination was developed in which,following a single bolus of 5-10 μc of I^{125} iothalamate,plasma was sampled at c. 3,7,20,60,120&240 mins. with urine collections at c. 30,120& 240 mins. ad lib. A computer program was developed to fit exponential curves by the method of least squares,to calculate GFR by the integral method for each urine collection period and for the total cumulative interval from $t_o \rightarrow t_1$(CIM),and for the projection of $\int C_p dt$ to infinity.At infinity A_u should equal A_o - the amount injected - and GFR=$A_o / \int_o^{\infty} C_p dt$.This latter plasma predictive method(PPM)requires no urine collection.In the CIM the cumulation of A_u over the period of the test minimizes errors due to transit time,A-V differences and bladder residual.This test was done in 40 children of which 10 were normal.The mean GFRs in the normal subjects for sequential periods expressed in ml/min/m^2 are:

	20 minutes	60 minutes	120 minutes	240 minutes
PPM	147	100	90	79
CIM	61	81	75	76

In general the PPM overestimates the GFR even when sampled to 3 hours.The CIM gives reproducible values(within 5%)by 1-2 hrs. Normal values with this technique are 76 ± 7 ml/min/m^2.This new approach utilizing the integral formulation is theoretically incontrovertible,eliminates the assumptions and practical difficulties of the constant infusion test and is the most precise means for GFR determination currently available.(Supported by MRC grant MT-1579.)

MEASUREMENT OF RENAL FUNCTION WITHOUT URINE COLLECTION: EVALUATION OF THE CONSTANT INFUSION TECHNIQUE FOR DETERMINATION OF INULIN AND PAH CLEARANCES. Barbara R. Cole, Joseph Giangiacomo, Julie R. Ingelfinger and Alan M. Robson. Wash. Univ. Sch. of Med., St. Louis, Mo.

The measurement of renal function in children is difficult, due in part to problems in obtaining complete urine collections. If a compound is infused into a patient at a constant rate and is excreted only through the kidneys, then at steady state the infusion rate of the compound must equal its rate of excretion in the urine. Clearances can thus be calculated by dividing infusion rate by the plasma level reached at equilibrium.

This technique has been investigated using inulin and PAH in 50 children with glomerulonephritis, pyelonephritis, cystic kidneys or with no renal disease; glomerular filtration rates (GFR) ranged from 2 to 133 ml/min. Simultaneous determinations of inulin and PAH clearances using the traditional technique involving urine collections and the infusion technique were undertaken in each child.

Values for the 2 methods of inulin clearance correlated closely ($r=0.993$, $p < .001$) the mean value for infusion clearances being 103.4% that of the traditional values-an insignificant difference. Correlation of the 2 methods was good at both high and low levels of GFR and in markedly edematous patients. Blood inulin levels stabilized within 2 hr of commencing the infusion, remaining stable for at least 8 hr. Increasing blood inulin levels by doubling inulin infusion rate did not affect the observed value for GFR.

The infusion and traditional values for PAH clearance showed poor agreement presumably due to extrarenal excretion of PAH. The infusion values averaged 20.7% above the traditional values and individual results varied by as much as 66.5%.

The estimation of GFR by inulin infusion represents a simple, but accurate and reproducible method potentially suitable to clinical practice. It requires only a constant infusion pump and 2 blood samples and eliminates the pitfalls of urine collections.

NEPHROLOGY

Second Session

RENAL RESPONSE TO ACID LOADING IN THE DEVELOPING LAMB FETUS, INTACT IN UTERO. Salha S. Daniel, Robert Baratz, Edward Bowe, Ming Yeh, Roger Lallemand, Allen I. Hyman, and L. Stanley James. Division of Perinatology, College of Physicians and Surgeons, Columbia University, New York, New York.

Catheters were implanted at hysterotomy into an artery and vein, the bladder (via the urachus) and the amniotic cavity of 4 fetal lambs 100-120 days gestation. Three or more days after surgery when the acid-base state of both mother and fetus were normal, 100 ml of M/4 lactic acid, osmolality 300 m osm/kg, was infused into the fetal vein over a 90 minute period. Blood samples were taken periodically and urine was collected before, during and for three hours after the infusion. Blood pH fell from 7.27 to 7.14 during the infusion and rose to 7.32 three hours after. During the same period urine pH fell from 6.69 to 6.16 and then rose to 6.50. Blood lactate increased from 2.2 to 13.3 mEq/L and was still 8 mEq/L at the end of the three hour period. Corresponding urine values were 1.1, 16.0 and 13.5 mM/L. However, the highest urine concentration occurred during the 1st and 2nd hour after the infusion reaching 2.13 mM/L. The lactic acid infusion caused a diuresis, urine flow increasing from 0.15 to 0.08 ml/min, returning to control levels at the end of 3 hours. Although the highest lactate concentration in the urine occurred in the post infusion period, maximum lactate excretion of 8.5 μM/min was observed during the infusion when diuresis was occurring. Net acid excretion during the period of observation amounted to only half of the acid load. These experiments indicate that the fetal kidney is significantly able to contribute to fetal acid base homeostasis by excreting a large portion of acid load.

RELATIONSHIPS BETWEEN PTH, cAMP AND RENAL TUBULAR REABSORPTION OF SOLUTES. F. Glorieux, R. McInnes & C. Scriver. McGill University-Montreal Children's Hospital Research Institute, Montreal, Canada.

Renal tubular reabsorption of phosphate (Pi) and amino acids (AA) is impaired in chronic secondary hyperparathyroidism and in about 1/3 of cases of primary hyperparathyroidism. Suppression of PTH hyperactivity ablates the tubular dysfunction. We examined the effect of purified bovine PTH infusion upon renal excretion of cyclic 3',5'-adenosine monophosphate (cAMP), Pi and AA, to discern the nature of transport inhibition by PTH and to investigate whether Pi and AA share a common component of reabsorptive transport in kidney. The latter question arises since Pi infusion depresses renal tubular transport of AA. Studies were performed in 30-minute periods before and after I.V. infusion of 200-400 units of bovine PTH. The renal clearance of creatinine, Pi and AA were measured by conventional methods, at high urine flow rates in 4 normal subjects; 3 male X-linked hypophosphatemic patients and 1 pseudohypoparathyroid patient; cAMP was measured by a muscle kinase method (courtesy of Dr. A. Tenenhouse).

Subjects	Urinary cAMP	Renal Reabsorption (Pi)	(AA)
Normal	↑	↓	0
X-linked HP	↑	0	0
PHP	0	0	0

(0=no change, ↑=increase, ↓=decrease after PTH vs control periods).

The findings confirm that cAMP-dependent inhibition of Pi transport is defective in X-linked hypophosphatemia, whereas the PTH-induced cAMP response is blocked in PHP; it is also apparent that the AA transport response to acute PTH exposure is dissociated from the Pi response.

RENIN-ANGIOTENSIN SYSTEM IN THE FETAL SHEEP. Fred G. Smith, Jr., Richard A. Bashore, Luciano Barajas and Andrei N. Lupu. Depts. of Pediatrics, Ob-Gyn, Zoology and Physiology, UCLA School of Medicine, Los Angeles, California.

It has been well documented that glomerular filtration rate (GFR) and renal blood flow (RBF) are decreased and renal vascular resistance is increased in newborn infants. More recently it has been demonstrated that both GFR and RBF are also decreased in the animal fetus.

In order to investigate the relationship of the renin-angiotensin system to decreased renal function in the fetus, plasma renin activity (PRA) was measured simultaneously in the intact fetal lamb and ewe. (Method of Boucher) Six lamb fetuses with gestational ages between 80 and 135 days (Term - 145 days) were delivered by caesarean section under low spinal anesthesia with precautions to preserve umbilical blood flow. Arterial blood was obtained immediately on delivery from both the fetus and ewe.

The mean PRA in 6 lamb fetuses (487 ng/100 ml, range 312-665) was greater than that of the ewes (158 ng/100 ml, range 30-250). The highest PRA were in fetuses of low gestational ages. Histologic and electronmicroscopic studies of fetal juxta-glomerular areas revealed the presence of renin granules in both the fetus and ewe. The presence of an already well-developed renin-angiotensin system in the fetus may indicate its participation in control of fetal urine composition through its direct or indirect effect on renal hemodynamics and Na^+ excretion.

METABOLIC BASIS OF FUROSEMIDE INHIBITION OF RENAL SODIUM REABSORPTION Takashi Yoshida and Jack Metcoff, Dept. Ped., CMH, Univ. Oklahoma, Okla City

The action of Na^+,K^+-activated ATP-ase has been considered a major mechanism for active transport of Na across cell membranes. Concrete evidence of the ATP-ase involvement in renal sodium reabsorption(R_{Na}) is lacking. Furosemide(F) injection into rats(20 mg/Kg) induced a marked natriuresis. In kidneys of the F injected rats, there were marked increases in the contents of ATP and ADP, and decrease in AMP content. Inhibition of glycolysis in the F injected rat's kidney was evidenced by decreased levels of glycolytic intermediates below triose phosphate. A cross-over point analysis indicated the step catalyzed by glyceraldehydephosphate dehydrogenase(GAPDH) to be the site of F inhibition. Kinetic analyses showed that F is an allosteric inhibitor of GAPDH. F inhibited GAPDH non-competitively with respect to NAD. Increase of ATP content in the F injected rat's kidney was suggestive of inhibition of ATP utilization by Na^+,K^+-ATP-ase. But when tested in vitro, F(10^{-4}M) did not inhibit ATP-ase activity. On the other hand, adenylate kinase(AK) activity was inhibited by F in a dose-dependent manner. This may be related to the increased ADP level in the F injected rat's kidney. Effect of F on ATP-ase in vivo may be different from that in vitro. It is possible to reconcile the hypothesis that ATP-ase is needed to generate energy for R_{Na}, and our observation that F did not affect ATP-ase in vitro although F did block R_{Na}. A possible cooperative interaction between AK($2ADP \rightleftharpoons ATP + AMP$) and ATP-ase ($ATP \rightleftharpoons ADP + P_i$) could give the relationship: $K = [P_i] \times [AMP]/[ADP]$. From this equation, when P_i is increased, either decreased AMP or increased ADP would occur. In the F injected rat's kidney, increased ADP and decreased AMP contents were observed. The increased ATP content could be secondary due to the increased ADP which is an inhibitor of ATP-ase. Although the P_i level in subcellular compartment was not determined, it is possible that inhibition of GAPDH step would limit P_i utilization and accumulated P_i also is inhibitory to ATP-ase activity. Thus, we speculate that inhibition of GAPDH and AK by F might indirectly inhibit ATP-ase in vivo, without an evident effect, in vitro. (Supported by a grant from Hoechst Pharmac. Co.)

SUPERFICIAL NEPHRON AND TOTAL KIDNEY GLOMERULAR FILTRATION RATE DURING DEVELOPMENT. Adrian Spitzer and Matthias Brandis, (Intr. by Chester M. Edelmann, Jr.). Albert Einstein College of Medicine, Department of Pediatrics and the Rose F. Kennedy Center, Bronx, N.Y.

It is well documented that at birth the deep nephrons are more mature than the superficial ones. This seems to reflect the centrifugal pattern of renal organogenesis. However, the individual characteristics of post-natal maturation of these distinct populations of nephrons has not been investigated. In the present study micropuncture and standard clearance techniques were employed for measurement of single nephron glomerular filtration rate and total kidney glomerular filtration rate in 33 guinea-pigs ranging in age from 2 to 32 days and in weight from 81 to 267 gm. The superficial nephron glomerular filtration rate (SNGFR) increased from 1.0 nl/min (±0.5, S.D. 12 obs.) at 2 days to 11.8 (±7.9, S.D., 27 obs.) by 4 weeks of age. Total kidney glomerular filtration rate (TKGFR) rose during the same period from 0.2 ml/min/kidney (±0.1, S.D., 11 obs.) to 0.7 (±0.3, S.D., 12 obs.). The rate of increase in SNGFR lagged behind TKGFR up to about 18 days of age and significantly surpassed the rate of increase in TKGFR during the rest of the observation period. As a result, the ratio of SNGFR/TKGFR was 5.3 at 2 days of age, 4.1 at 18, and 16.6 at 4 weeks. It appears, therefore, that the increase in GFR observed immediately after birth is the result of the increase in the functional capacity of the more mature, juxtamedullary nephrons, whereas the subsequent rise is the consequence of maturation in the cortical units. The very last to reach full functional capacity are, probably, the superficial nephrons.

RENAL HANDLING OF GLUCOSE IN THE DEVELOPING CANINE KIDNEY. Billy S. Arant, Jr., Martin A. Nash, and Chester M. Edelmann, Jr. A. Einstein Col. Med., Dept. Ped., Bronx, N.Y.

The original report of a low ratio of TmG:Cin in premature infants suggested a state of glomerular hyperperfusion. Recent data, however, have shown no change in TmG:Cin in children 2.5 weeks to 15 years of age, and no difference from values obtained in adults. Since no comparable data are available in experimental animals, and since the glucose titration curve has not been investigated developmentally, the present study was designed to investigate glomerulo-tubular balance, nephron heterogeneity, and the interrelationship between tubular reabsorption of glucose and sodium in the developing canine kidney. Glucose titration curves, with blood glucose concentrations ranging from normal to at least 1200 mg%, are being performed in mongrel puppies from birth to 8 weeks of age. Urinary and blood glucose concentration is determined by a glucose oxidase method. Completed to date are studies in 5 puppies, 10 to 35 days of age, and in 2 mongrel bitches. No differences related to age, weight, or body surface area were found in this small group. Renal thresholds for glucose were similar in all animals, 216±18.5 mg% (mean ± SD) in the puppies, and 220 and 230 mg% in the adult animals. TmG:Cin was the same in the puppies (2.80±0.21) as in the adults (2.50 and 2.62). At very high levels of plasma glucose, GFR decreased, a phenomenon previously found in adult dogs. Changes in rates of glomerular filtration, reabsorption of sodium, and reabsorption of glucose were directionally similar. At lowered levels of fractional sodium reabsorption (78-89%) TmG was decreased slightly from values obtained when sodium was reabsorbed maximally (>99%). These preliminary data suggest that the renal handling of glucose in puppies is qualitatively and quantitatively similar to that in the adult. Thus the theory of glomerular preponderance in the immature kidney, which originated from this laboratory, is not supported.

FAMILIAL NEPHRITIS: GENETIC HETEROGENEITY AND PATHOLOGY. Donald Gribetz, Peter Hathaway, Jacob Churg, Leonard Kasen, Seymour Cohen and Lotte Strauss. Mount Sinai School of Medicine, Depts. of Pediatrics and Pathology, New York.

Members of eight families with familial nephritis were studied in an effort to shed light on the poorly understood pathogenesis, pathology and genetics of this syndrome.

Pathological studies revealed no specific lesions on light microscopy. Electron microscopy, however, revealed the presence of a distinctive glomeruler lesion in some of the families. When present this consisted of a thickening and splitting of the basement membrane into several layers. Interspersed were clear spaces of variable size and shape containing dense particles.

This lesion was present in six children biopsied from four families and absent in nine children from four other families. In six of the families, more than one member was biopsied. In the two families "positive" for the lesion, each of the two members biopsied was positive; in the four "negative" families, each of the nine members biopsied was negative. No families have been found in which there have been clinically affected individuals of both pathologic types. No matter what frequency we accept for the occurence of this e.m. finding, the familial distribution is significantly different, at the 2% level, from that which would be expected if the distribution were random.

It thus appears as if this newly described electron microscopic lesion in the glomeruli of patients with familial nephritis is specific for the syndrome when present, and is itself probably inherited as a mendelian trait. Moreover, these two types of pathology seem to define a genetic heterogeneity in this poorly understood syndrome.

THE EFFECTS OF STRESS ON INTRARENAL DISTRIBUTION OF BLOOD FLOW IN INFANT PRIMATES. Eddie S. Moore, Maurina B. Galvez, John B. Paton, David E. Fisher and Richard E. Behrman. Univ. of Ill. Coll. of Med., Dept. of Ped., Chicago.

The purpose of this study was to determine the pattern of distribution of intrarenal blood flow in resting infant primates and to measure changes in this distribution in response to stress. Studies were performed in 22 infant macaca speciosa monkeys at 3 days of age. Cardiac output (C.O.) and intrarenal distribution of renal blood flow (RBF) were measured by injection of 50 μradiolabeled carbonized microspheres into the left ventricle. After catheters were placed in the left ventricle, aorta and inferior vena cava via the femoral vessels, the infant monkey was allowed to recover overnight in an incubator. On the day of study, the infant was stimulated as little as possible before resting C.O. and intrarenal distribution of RBF were determined. The infant was then severly stressed by intermittant positive-pressure ventilation. Changes in C.O. and distribution of intrarenal flows were determined by 2nd and 3rd injections of different labeled microspheres during and after ventilation. The infants were then sacrificed and the kidneys dissected into outer cortical (O.C.) and inner cortical (I.C.) segments for counting of radioactivity. During the resting state the total RBF was 2.4cc/min/gm of kidney which was 12.6% of the cardiac output. The O.C. and I.C. flows in the resting state were 5.6 and 2.5cc/min/gm respectively. The O.C./I.C. was 2.24. After stress the O.C. and I.C. flows were 1.10 and 1.70cc/min/gm respectively. The O.C./I.C. after stress was 0.65 and the total RBF fell to 0.9cc/min/gm.

These studies demonstrate that the pattern of intrarenal distribution of RBF in resting minimally stimulated 3 day old infant monkeys is the same as in adults with a preponderance of O.C. flow over I.C. flow. This intrarenal distribution pattern is reversed in response to stress as has been described in numerous adult experiments ("Trueta Phenomenon").

HEMOLYTIC-UREMIC SYNDROME: TEN YEARS EXPERIENCE WITH NON-HEPARINIZED PATIENTS. Bruce M. Tune (intr. by Robert O. Christiansen), Stanford University School of Medicine, Department of Pediatrics, Stanford, California.

During the years 1960-1969, 27 children (14 male, 13 female) were seen at the Stanford University Hospital with the hemolytic-uremic syndrome. While the hematologic abnormalities were comparable to those found by Gianantonio, et al in Buenos Aires (J.Pediat. 64:478, 1964), 3 major differences were seen in our population: 1) older age, averaging 4 5/12 years at Stanford vs 1 1/12 in Buenos Aires; 2) more prolonged (3 to 16 vs 1 to 3 days) and more frequently severe prodrome (e.g. 18% vs 3% initially hospitalized with a diagnosis of "acute abdomen"); 3) shorter duration of oligo-anuria, average 6.3 days (0-18) vs 12.2 (3-48). Three patients died in the acute phase, 2 of the 5 seen in 1960-1961 before peritoneal dialysis was used and 1 of the subsequent 22. Of the 24 survivors, 21 patients have been followed from 2 to 10 years (average 5 years). Nineteen patients have recovered completely, with normal blood pressures, disappearance of proteinuria and hematuria, and normal creatinine clearances of 90 to 142 ml/min/1.73M^2 (average 114). Two patients developed chronic renal insufficiency after recovery from the acute syndrome; one progressed to end-stage within a year and the other has remained stable for 4½ years. None of these patients received heparin therapy. This frequency of chronic residual renal insufficiency (9.5%) contrasts with the 30% seen by Gianantonio, et al (J.Pediat. 72:757, 1968). It is concluded that the hemolytic-uremic syndrome as seen in this geographic area has a different natural history and more benign long term prognosis than is seen in Buenos Aires. Any conclusions as to the efficacy of heparin therapy will have to be interpreted in the light of these geographic differences.

THE NATURAL HISTORY OF MEMBRANOUS NEPHROPATHY IN CHILDREN. Hermann Olbing, Boyce Bennett, Jay Bernstein, Adrian Spitzer, and Ira Greifer. Albert Einstein College of Medicine, Dept. Ped. & Path., Bronx, N.Y.

It is the prevailing opinion that despite transitory clinical remission, histological lesions in patients with membranous nephropathy (MN) do not improve. The study of nine children with MN reported here demonstrates, however, that clinical remission can be accompanied by marked morphological improvement, as judged by light and electron microscopy. Over an 8 year period, MN was diagnosed in 5 boys and 4 girls out of 199 children biopsied for idiopathic proteinuria with or without a nephrotic syndrome (NS). Eight had NS; all had hematuria; their ages ranged from 2 to 15 years. Typical spikes (PASM) indicating subepithelial deposits were shown in all. Three of the 4 patients younger than 9 years at clinical onset have been in complete remission for 1/2, 3 and 5 years. Remissions developed in two of them during conventional treatment with prednisone. The third failed to respond to prednisone alone, but had a complete remission with prednisone plus azathioprine. One of these three children had two relapses which responded quickly to retreatment; the other two have not relapsed. In two of these patients, whose renal morphology was unchanged one year after initial biopsy, repeat examination 2-3 years later demonstrated resorption of subepithelial deposits and near normalization of the basement membrane. The fourth patient below the age of 9 remains proteinuric 4 years after initial therapy, but still has normal clearances. Of the 5 children older than 10 years at clinical onset, only 4 have been followed long enough for re-evaluation; none has shown clinical or histological improvement. One has moderate and two severe renal failure. The fourth child has normal function, but shows progression on biopsy. The alleged uniformly poor outcome of patients with MN might result from the practice of selecting for biopsy only those who fail to respond to treatment or relapse frequently. As shown by the present study, MN need not have an ominous prognosis, particularly in younger children.

RENAL TUBULAR TRANSPORT OF IMINOACIDS AND GLYCINE. Ingeborg Krieger. Children's Hospital of Michigan, Detroit.

A mentally retarded male infant presented first at 3 months of age with hydroxyprolinuria. Aminoacids by column chromatography and hydroxyproline (hypro) by a chemical method were restudied at 9 months of age, when the patient showed persistent diet dependent elevation of urinary hypro (0.19 μmol/ml) at normal plasma levels; endogenous clearance was 8.0 ml/min/1.73 (normal 0). No hypro was excreted on a low hypro diet and during the night. In contrast to reported cases of iminoglycinuria there was no associated prolinuria. Urinary glycine was also normal. Endogenous clearance was slightly elevated at 9 months, 11.2 ml/min/1.73 (normal up to 8.6), rising to 26.3 ml/min/1.73 at 16 months, although 24 hour glycine excretion remained not diagnostic. Gelatin loading exposed the associated glycinuria (6.90 μmol/ml). One 24 hour urine examination of each parent revealed mild glycinuria in the mother. Gelatin loading did not produce prolinuria in the patient although plasma proline approached levels at which normal individuals begin to excrete proline. Prolinuria was to be expected if the associated hypro load had been competing at a tubular absorption site.

VALUES OF PATIENT AND OF 3 NORMAL CONTROL INFANTS (in brackets)

		Plasma μmol/ml	Urine μmol/ml	Clearance/1.73
Hypro:	Gelatin load	0.255 (0.156)	3.50 (0.20)	18.34 (0.50)
	after meals	0.022	0.19	24.22
Pro:	Gelatin load	0.601 (0.590)	0.55 (0)	1.21 (0)
	after meals	0.308	0	0
Gly:	Gelatin load	0.900 (0.680)	6.90 (0.61)	10.20 (0.56)
	after meals	0.223	1.51	19.13

This patient appears to have a new defect of a tubular transport mechanism which is not shared with proline, confirming the suspected heterogeneity of the transport system for iminoacids and glycine.

CONGENITALLY SHORT URETEROVESICAL JUNCTION CAUSING PRIMARY REFLUX -- A COMMON FAMILIAL AND HEREDITARY TRAIT.
Robert H. Burger, F. F. Thompson Hosp., Dept. of Surgery (Urology), Canandaigua, New York. (Intr. by Gilbert B. Forbes)

Twenty-three families where primary reflux was present in more than one first-degree relative have already been reported in the literature.

The author has found seven more families in which two or more first-degree relatives had primary vesicoureteral reflux (20 refluxers in 7 families). In five of the seven families, both parents and all siblings were investigated cystographically and cystoscopically. In four families the abnormal trait was transmitted from mother to child, and in five of the families more than one sibling refluxed, indicating a definite familial and hereditary transmission of the congenitally short intravesical ureter which permits reflux. Thorough investigation of first-degree relatives of any refluxing patient with urologic symptoms, pyuria, positive urine cultures or suggestive urologic history uncovered ten relatives with reflux who ordinarily would not have been investigated. Three patients were diagnosed only because the author investigated all first-degree relatives in the family urologically when there were already two refluxers in that family. Pedigree analysis indicates that the trait is either a dominant with incomplete penetrance or, more likely, polygenic in nature.

It is strongly suggested that when a refluxer is diagnosed in a family a complete investigation be made on first-degree family members to uncover any urologic symptoms or signs. If there is any suggestion of this, a cystogram and cystoscopy should be performed. If two members of a family already are known to reflux, cystography and cystoscopy is recommended on all close family members with or without evidence of urologic disease.

A NEW SYNDROME OF RENAL SALT WASTING. Robert M. Ehrlich and J. William Balfe. (Intr. by John D. Bailey).

Children with salt wasting due to transient renal tubular resistance to aldosterone (A) or defects in A biosynthesis have been described. A newborn girl with vomiting, dehydration, hyponatremia (120 mEq/L) and hyperkalemia (5.9 mEq/L) was studied. Blood pressure, kidney function, IVP, sweat chlorides, urinary 17 ketosteroids, amino acids, ACTH stimulation, cortisol diurnal variation and red cell sodium transport were normal. Sodium balance studies indicate large urinary losses with low A and no response to DOCA. (see table).

AGE	DIETARY Na	SERUM Na	SERUM K	PLASMA ALD.	PLASMA RENIN ACTIVITY	URINE Na	URINE K	URINE ALD.	DOCA
	mEq/kg/24h	mEq/L		mug%	(N=<10)	mEq/24h		mug/24h (N=2-26)	mg/24h
8w	9.5	130	6.2	8.2	76			1	
	10.7	131	7.5			37	10		2
	10.5	131	5.6			36	9		3
1y	9.8	131	5.8	**	66	73	27	1	
	8	126	5.9	**	127.5	40	26	1	
	9	128	6.6			78	42		5

Further plasma A** and urinary precursors of A are being measured. At 18 months she is thriving but requires 5 gm. of sodium chloride per day. The association of renal tubular resistance to Doca, low urinary A with elevated plasma renin appears to be a previously undescribed clinical condition.

NEPHROLOGY

Read by Title

CHILDHOOD POLYCYSTIC DISEASE OF KIDNEYS AND LIVER: ROENTGEN SIMILARITY TO MEDULLARY SPONGE KIDNEY AND GENETIC IMPLICATIONS. By Luis A. Cabal, Lester Weiss, and William A. Reynolds; Departments of Pediatrics and Radiology, Henry Ford Hospital, Detroit, Michigan.

Childhood polycystic disease of kidney and liver was found in six members of a sibship of eight. Their ages ranged from six to twenty-six years. Liver biopsy from two and kidney biopsy from one of the family members had the typical pathology found in patients with polycystic disease of kidneys and liver. The proband, who had trisomy 21, was severely affected. He had portal hypertension, bleeding esophogeal varices, hypersplenism, and ascites. None of the other affected siblings had hepatomegaly, abnormal liver function studies, roentgen evidence of esophogeal varices, or evidence of abnormal renal function. The intrafamililial uniformity of the clinical picture (with the exception of the proband with trisomy 21) is consistent with the concept of genetic heterogeneity in childhood polycystic disease of kidneys and liver. The severity of the liver disease in the patient with trisomy 21 could be explained by the gene locus for polycystic kidneys being on chromosome 21 or by a greater suceptibility of patients with Down's syndrome to a variety of diseases. This family is unusual in that several asymptomatic adults are affected.

Four affected members had abnormal technetium 99 liver scans. The roentgen appearance of the kidneys in the affected individuals was indistinguishible from renal tubular ectasia or medullary sponge kidney. In only one patient were cortical cysts evident radiographically. Medullary sponge kidney is thought to be a relatively benign nonfamilial condition; therefore, the families of patients with the roentgen findings of medullary sponge kidneys are not usually studied. Excretory urograms from siblings of patients diagnosed as having medullary sponge kidney might well demonstrate additional adults with recessively inherited polycystic kidneys and liver.

BULLOUS PEMPHIGOID AND MEMBRANOUS GLOMERULOPATHY. Samuel P. Gotoff, Nancy B. Esterly, Somsak Lolekha, Eddie S. Moore, Roger D. Smith, and Nancy L. Furey. Abraham Lincoln Sch. of Med., U. of Ill. and Northwestern Med. Sch., Chicago.

Two rare diseases with immunologic features were noted in a preadolescent child. Bullous pemphigoid is a chronic blistering disorder with fixed and circulating antibodies to the skin basement membrane zone (SBM). Membranous glomerulopathy presents with the nephrotic syndrome and is characterized by renal glomerular basement membrane (GBM) thickening due to epimembranous deposits as observed by electron microscopy (EM) which contain IgG and β1c identified by immunofluorescent staining (FA).

A 13 year old girl presented with recurrent nephrotic syndrome and bullous lesions of the skin and mouth. Proteinuria and rash had persisted despite therapy with corticosteroids. On admission, she was markedly cushingoid with anemia, hypoproteinemia and severe proteinuria. Renal function was normal. Skin biopsy revealed extensive epidermal-dermal separation and a dense mononuclear cell infiltrate within the dermis. Renal biopsy showed diffuse thickening of the GBM, and EM disclosed continuous and discontinuous epimembranous deposits. FA of the skin demonstrated IgG and β1c in a linear pattern along the epidermal BM. Similar staining of the kidney biopsy revealed linear deposition of IgG and β1c along the GBM. Serum from the patient contained IgG which, by indirect FA, reacted with SBM but not with GBM. Treatment with 6-MP and prednisone resulted in a profound decrease in the anti-SBM titer from 1:1280 to 1:40 but no clinical improvement. At autopsy, renal vein thrombosis and a pulmonary infarction were found. Localization of IgG and β1c were limited to the skin and renal glomerulus and were unchanged.

The findings suggest that both the cutaneous and renal lesions were mediated by an immunologic mechanism. The circulating antibody was specific for skin but not kidney BM. Bullous pemphigoid may be an autoimmune disease mediated by antibody directed to SBM whereas membranous glomerulopathy is considered an immune complex disorder with the kidney passively involved. (Supported by USPHS grant AM 10318.)

BARTTER'S SYNDROME: EVIDENCE FOR PATHOGENESIS. Ralph Cash, Sheldon Brenner, Avinash Chawla and Larry Fleischmann, Children's Hosp. of Michigan, Detroit.

Male infant with Bartter's Syndrome, diagnosed at 4 hrs. of age, has been followed for the first year of life. Electrolyte values in first 2 weeks of life suggested renal salt loss as the precipitating event (S.P.R. 1971, pg. 212). Effect of varied NaCl intake and volume expansion with salt-poor albumin on plasma renin activity (PRA), aldosterone excretion (AE) and renal tubular sodium rejection (NaR) was studied serially. Renal biopsy at 8 weeks was normal but juxtaglomerular hyperplasia was identified on repeat biopsy at 8 months.

	PRA (N:< 0.3ng)	AE(24hr) (N:< 22ug/1.73M^2)	NaR (N:< 1%)
Normal Diet	2.2	32	3.0
High Salt Diet	0.37	4	8.1
Volume Expansion	0.17	12	2.0

Confirmation of chronically contracted vascular volume was obtained repeatedly utilizing radioisotopic techniques. PRA and AE responded appropriately but incompletely to Na^+ load at 2 weeks of age. Insensitivity to pressor effect of infused norepinephrine was corrected by volume expansion. Excessive renal tubular sodium rejection was confirmed but attempts to isolate a natriuretic factor by the method of Bricker and Klar were unsuccessful. Expansion of blood volume resulted in profound hyponatremia without eliciting a rise in PRA, suggesting that volume depletion was the greater stimulus to renin release than sodium depletion per se. These observations support the theory of renal salt loss and contracted vascular volume as the pathophysiologic defect in Bartter's Syndrome.

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Cryoprotein with anti-streptococcal plasma membrane antibody activity in acute glomerulonephritis. William R. Griswold and Rawle M. McIntosh. Department of Pediatrics, Columbia University, New York, New York.

In previous communications (J. Lab. Clin. Med. 75: 566, 1970, Int. Arch. Allerg. Appl. Immunol. 41: 700, 1971) we have demonstrated cryoprecipitates with biologic properties of immune complexes in acute glomerulonephritis (AGN). It has been suggested that streptococcal plasma membrane is the specific antigen in the pathogenesis of AGN and also that it cross reacts with a glomerular basement membrane antigen. However we have been unable to demonstrate streptococcal antigens or streptococcal antibody activity in cryoprecipitates. This study further characterizes cryoprecipitates in AGN and examines the role of the streptococcus in this phenomenon.

Cryoproteins were isolated from a patient with AGN and characterized for globulin composition as previously described. Antibody activity to plasma membrane and plasma membrane content of the cryoprotein, and supernatant serum after cryoprecipitation were studied. The cryoprecipitate contained IgG, IgM and IgA. Anti-plasma membrane activity was detected in the cryoprecipitate but not in the supernatant serum. No streptococcal antigens were found in the cryoprecipitate. Immunofluorescent staining of normal human glomeruli with cryoprecipitate containing anti-plasma membrane antibody was negative. The failure to detect plasma membrane in the cryoprecipitate may be due to antigen saturation.

The absence of plasma membrane antibody activity in the serum after cryoprecipitation and its presence in the cryoprecipitate suggests that the plasma membrane is involved in the cryoprecipitation phenomenon. The absence of fixation to glomerular basement membrane is evidence against the cross-reactive antibody hypothesis. These studies lend further support to the immunopathologic significance of cryoprecipitates in glomerulonephritis.

CLINICAL ASSESSMENT OF RENAL BLOOD FLOW IN CHILDREN WITH XENON133. Alan B. Gruskin, Victor H. Auerbach and Iain F.S. Black. Dept. Ped. Temple Univ. Sch. Med., St. Christopher's Hosp. Child., Phila., Pa.

We shall report a new system developed to record and analyze radioactive washout curves in general,and its application in determining renal blood flow (RBF) and fractional RBF in children. ^{133}Xe is injected into the renal artery, and the radioactivity detected by a NaI crystal placed over the kidney is recorded continuously for 30 minutes,using a Packard nuclear spectrometer outputted to a Cipher magnetic tape recorder capable of recording 50,000 ± 1% pulses/sec. The resultant data are digitalized and transferred to a Hewlett-Packard multichannel analyzer at a rate of 1 channel/sec. An H-P computer-calculator is programmed to plot the natural logarithm of the count rate against time. The proximal limit of the terminal component of the washout curve is ascertained by visual inspection. Two sequential least squares regression lines are computed. The first utilizes all data points, the second rejects points more than 1.75 S.D. away from the first line. The zero time intercept is obtained. The regression line is subtracted point by point from the original data. A new curve is plotted. Sequential repetition of this process is performed until no further components can be determined. RBF and fractional RBF to outer (O.C.) and inner (I.C.) cortex are obtained from appropriate slopes and intercepts by standard methods. The data obtained in our initial four studies demonstrate both the variable flow patterns seen in children with different problems and the potential usefulness of this technique as a diagnostic and investigative method for measuring RBF at the time of aortography in children.

Age	Diagnosis	Flow ml/100gm/kidney		% Total Flow	
		O.C.	I.C.	O.C.	I.C.
8	normal kidney	342	62	87	7
7	post op. tetralogy	279	58	71	16
9	congestive failure	91	21	52	20
6	subaortic stenosis	143		44	

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PROXIMAL RTA IN SUBACUTE NECROTIZING ENCEPHALOMYELITIS ASSOCIATED WITH DECREASED PYRUVATE CARBOXYLASE ACTIVITY. Alan B. Gruskin, Mulchand S. Patel, Michael Linshaw and Warren Grover (Intr. by V.H. Auerbach) Dept. Ped. and Biochem. Temple Univ. Sch. Med., St. Christopher's Hosp. Child., Phila., Pa.

Isolated proximal renal tubular acidosis (RTA) was found in two infants having lactic acidosis associated with subacute necrotizing encephalomyelitis. Reduced renal thresholds(17.5-18.5 mM/L) were demonstrated, in conjunction with the ability to excrete normal quantities of acid. One patient underwent the following studies. With the determination of a bicarbonate titration curve the tubular reabsorption of bicarbonate fell from 1.8-1.9 to less than 1.0 mM/100ml GFR as serum bicarbonate increased from 14 to 34mM/L. Simultaneously, tubular reabsorption of sodium and phosphate progressively fell; and lactate and urate clearances increased from control levels as greater volumes of bicarbonate containing solutions were administered, resulting in a 10% increase in chloride space. These changes can be attributed to the renal effect of volume expansion. A marked increase in plasma lactate in the patient indicated an impairment in the metabolism of pyruvate. As ATP is generated in the renal cortex by metabolism of pyruvate, the kidney would generate less energy. The diminished supply of energy might then be reflected in an inability to reabsorb normal quantities of filtered sodium bicarbonate. At autopsy,the activity of hepatic and renal pyruvate carboxylase was diminished when compared to controls. Venous lactate increased to values twice that seen in another individual when performing a similar study. The abnormal elevation in the patient's venous lactate may reflect the impairment in hepatic and renal gluconeogenesis Moreover, since the excretion of ammonium in response to acidosis was within expected quantities, it may be suggested that the metabolism of glutamate, the principle precursor of ammonium, was not affected.

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RENIN HYPERACTIVITY IN INFANTILE RENOVASCULAR HYPERTENSION. K. Mary Hewking, W. Joseph Rahill and Agostino Molteni (Intr. by Sumner Yaffe), State University of New York, Depts. of Pediatrics and Pathology, Buffalo

Two asymptomatic infants, ages 4 (M) and 6 (F) months, were found to have severe arterial hypertension associated with stenoses of the main renal artery. Other causes of hypertension were excluded. Extreme elevations of peripheral venous renin were present (>30 nG/ml and 22 nG/ml, normal <2.5 nG/ml, 5 infants). Renin hyperactivity in case 1 fell to normal after uninephrectomy but mild hypertension remained. In case 2 peripheral renin remained high after uninephrectomy but renin fell to normal and hypertension improved after re-vascularization of the remaining ischemic kidney. After 2 months blood pressure rose severely and was not controlled despite medical therapy; peripheral renin also rose (6-11 nG/ml). Repeat angiography showed good renal perfusion in the main vessel (spleno-renal anastomosis) but mild irregularity of the smaller intrarenal arteries.

Glomerular filtration rate (case 1, 80% normal, 4 1/2 mo; case 2, 65% normal, 13 mo) fell gradually (case 1, 68% normal, 11 mo; case 2, 40% normal, 31 mo). Renin activity in renal cortex was high (60 nG/mg, normal, <5 nG/mg 2 infants) and increased juxta-glomerular granularity present in case 2.

Both infants had associated extrarenal arterial disease (case 1 irregularity of distal aorta and iliac arteries; case 2 absent superior mesenteric artery). In infants with renovascular hypertension, extrarenovascular malformations occur often (literature review, 5/10) and bilateral renal arterial disease is frequent (5/10). Without surgery prognosis is poor (4/4 died). 5/6 improved after surgical correction; 3 of these were normotensive after >1 year follow-up. No consistent histopathology of renal vessels was found and no etiology was established in all 10 cases.

Peripheral renin hyperactivity correlates well with severe hypertension in infantile renovascular ischemia. Determination of peripheral renin activity is helpful in diagnosis and follow-up of these cases.

Acute diffuse proliferative glomerulonephritis following meningoccal infection: A new antigen-antibody cause of acute nephritis. John T. Herrin, Robert B. Colvin, and Donald R. Dibonna. Introd. by John D. Crawford. Harvard Med. Sch., Children's Service and Departments of Pathology and Medicine, Massachusetts Gen. Hosp., Boston.

Although segmental lesions have been described in meningoccal sepsis, this organism is not one of those implicated as a cause of diffuse proliferative glomerulonephritis.We wish to report the findings and clinical course of a 13 year old boy with meningoccal sepsis who developed acute diffuse glomerulonephritis. He presented with meningitis and septicemia and developed gross hematuria with red cell casts, mild azotemia, and hypocomplementemia. Renal biopsy findings were indistinguishable from post streptococcal glomerulonephritis, but culture and antibody studies in both patient and his immediate family were negative for streptococcus. His clinical course was characterized by prolonged hypocomplementemia and a persistent active urinary sediment for some 6 months before gradual return to normal.

Histological studies showed diffuse proliferative glomerulonephritis on light microscopy. Electron microscopy showed subepithelial deposits resembling antigen-antibody complexes and occasional areas of disruption of basement membrane.

ON THE PREPONDERANCE OF MALES IN THE NEPHROTIC SYNDROME (N.S.) OF CHILDHOOD Walter Heymann and Sudesh P. Makker Case Western Reserve Univ. Sch. of Med., Univ. Hosps. of Cleveland, Dept. of Ped., Cleveland, Ohio

Surveying a material of 148 cases of children with the idiopathic form of the N.S. seen during the last ten years, a ratio of males to females of 1.9/1.0 was again established. This ratio stays reasonably constant until age 13 years. It then decreases over the next few years to adult levels where no preponderance of males is noted.

From biopsied material (186 cases) it becomes evident that the male predominance applies only to foot process disease (F.P.D.). In adults the ratio for F.P.D. is, however, only 1.01/1.0 (109 cases). The preponderance of males thus only applies to childhood nephrosis. It points toward an endocrine factor, but remains difficult to explain as yet. The difference in sex distribution supports again the also otherwise well supported concept that F.P.D. and "nephrosis with nephritis" are probably two different entities.

UNILATERAL RENAL AGENESIS: COMMON, SERIOUS, ? HEREDITARY Lewis B. Holmes, Children's Service, Massachusetts Gen. Hosp., Boston (Introduction by J. W. Littlefield)

The incidence of unilateral renal agenesis (URA) is estimated as 1 in 600 newborns (Pediatrics 47:97,1971), making it one of the most common malformations. Yet it is not known if it is hereditary or if there is either phenotypic or genetic heterogeneity among the affected children. To establish this we have evaluated 60 affected children. 45 (23F, 22M) were ascertained by clinical studies at ages 1 week to 18 years, av. 5.4 years. Half had significant abnormalities of their single remaining kidney: hydronephrosis (15), dysplasia or ectopia (6) and pyelonephritis (3).

Inheritance of URA is suggested by the chance finding of asymptomatic affected siblings in two families. In family A two children had URA and hydronphrosis of the other kidney and a third had hydronephrosis of both kidneys. In family B two siblings had URA proven at autopsy. A specific mode of inheritance can be postulated only when prospective studies of a large number of asymptomatic family members have been completed.

Half of these 60 children had associated congenital malformations. Four different phenotypes were evident: 1) Absence of half of the bladder trigone and ureter and ipsilateral Mullerian or Wolffian duct anomalies, such as absent testis, ovary, uterus and vagina (19 pts.); 2) imperforate anus, vertebral and preaxial forearm anomalies and hypoplasia of the bony pelvis and one leg, (6 pts.); 3) cloacal exstrophy with facial, spine and limb deformities (2 newborns); and 4) persistence of uterus and vagina in male (1 pt.). The second of these phenotypes is possibly hereditary (J. Ped. 79:1033,1971). This phenotype is very similar to an autosomal malformation (Danforth short tail, Sd) in the mouse, in which the abnormal ureter does not induce kidney development.

MALIGNANT LYMPHOMATOUS DISEASE AND NEPHROTIC SYNDROME. L.R. Hyman, P.M. Burkholder, P.A. Joo, and W.E. Segar, Univ. of Wis., Univ. Hosp., Depts. of Ped. and Path., Madison.

The occasional association of nephrotic syndrome and malignant lymphoma has been observed. We have studied the kidney of two children with malignant lymphomas and associated nephrotic syndrome by light, immunofluorescence, and electron microscopy. In both cases, a clinical remission followed cyclophosphamide therapy. Remission persists after discontinuance of therapy. A 6-year-old child with stage III-A Hodgkin's disease developed recurrent nephrotic syndrome and Herpes Zoster skin infections. A kidney biopsy obtained at the staging procedure showed a minimal change glomerulonephropathy with no immunoglobulin deposition and only local glomerular epithelial foot process "fusion". A second renal biopsy obtained 2 years later showed a diffuse glomerulitis with limited glomerular deposition of IgG, IgM, and C_4. Electron microscopy showed rare, local subendothelial and intramembranous electron dense deposits along glomerular capillary walls with moderate increase in mesangial matrix and cells. The second patient is an 11-year-old boy with Burkitt's lymphoma, stage II-A. Hypertension, protenuria and an elevated antibody titer to E.B. virus were noted 5 months after tumor therapy. A renal biopsy showed a mixed membranous and proliferative type of glomerulonephritis. There were local deposits of IgG, IgM, and C_4 in glomerular tufts. Ultrastructurally there was marked thickening and expansion of mesangial matrix and extensive subendothelial "edematous" alteration of glomerular basement membrane. The findings of nephrotic syndrome, proliferative glomerulonephritis, glomerular deposits of immunoglobulins, and electron dense deposits or subendothelial "edematous" alteration along glomerular capillary basement membranes in malignant lymphomatous disease suggests a relationship between the lymphoma and renal disease. It is postulated that the glomerulonephritis may be of immunologic etiology involving tumor specific antigens or persistant oncogenic or passenger viral antigens.

NONOBSTRUCTIVE HYDRONEPHROSIS AND HYDROURETERS DUE TO GENERALIZED PERITONITIS Sudesh P. Makker, Robert J. Izant, Jr., Arthur S. Tucker, and Walter Heymann (Intro. by Warren E. Grupe) Case Western Reserve Univ. Sch. of Med., Univ. Hosps. of Cleveland, Depts. of Ped., Surg. and Rad., Cleveland, Ohio

Three cases of generalized peritonitis, two due to ruptured appendix and one due to primary peritonitis, are presented. All three cases were found to have associated mild to severe hydronephrosis and hydroureters. The hydronephrosis and hydroureters were of the nonobstructive type and disappeared spontaneously within four to twenty months after the onset. The presence and clinical importance of this association is stressed. A hypothesis is suggested that in analogy to paralytic ileus, the kidney pelvis and ureter may participate in impaired peristalsis associated with peritonitis.

THE EFFECT OF ACUTE SALT DEPLETION ON THE EARLY RESPONSE TO COMPENSATORY HYPERTROPHY IN THE RAT. Ellin Lieberman, Cyril Chantler, Jean L. Harrah and Malcolm A. Holliday. Univ. of California, San Francisco and San Francisco General Hospital, Dept. of Ped., San Francisco; Univ. of So. California and Childrens Hospital of Los Angeles, Dept. of Ped., Los Angeles; Guy's Hospital, Dept. of Ped., London.

Uninephrectomy is followed by an increase in function within 1-2 hours and by increases in ribonucleic acid (RNA) and protein synthesis within 6 hours, such that total RNA and protein or dry kidney weight (DKW) are increased by 15-20% 48 hours postnephrectomy. We have postulated that the increase in RNA and DKW may be dependent upon the early functional response. We sought to test this hypothesis by comparing RNA and DKW increases in rat kidney 48 hours after nephrectomy in normal rats and in rats depleted of salt so as to reduce the functional response. A left nephrectomy was done on 6 control rats, which were then dialyzed against 0.15 M NaCl and maintained for 40-48 hours. GFR was determined and the remaining kidney obtained. RNA and DKW of the remaining (right) kidney was expressed as per cent of the value found in the first (left) kidney. A left nephrectomy was done on 12 rats which were then dialyzed against 7.5% glucose in water and maintained on a salt-free diet to induce salt depletion. Weight loss was 3% in the control rats and 13% in the salt-depleted rats. GFR was measured following saline reexpansion and was less in the salt-depleted rats than in the controls. The increase in kidney RNA was 123±7% and in DKW 115±2% in the control rats following uninephrectomy. The increase in RNA was 124±7% and in DKW 107±6% in the salt-depleted rats. The blunting of the functional response to uninephrectomy was not associated with a decrease in RNA response but was associated with a blunting of the increase in DKW ($p < .001$). Whether RNA would be affected by greater depression of function or whether DKW increase was merely delayed cannot yet be ascertained. The data are consistent with a link between functional and structural responses by the kidney undergoing hypertrophy.

EFFECTS OF SODIUM CONCENTRATION ON BASELINE SODIUM TRANSPORT AND VASOPRESSIN-INDUCED SODIUM TRANSPORT IN THE ISOLATED TOAD BLADDER Stanley A. Mendoza (Intr. by Jerry A. Schneider). Univ. of Calif. San Diego, Sch. of Med., Dept. of Ped., La Jolla, Calif. 92037

The previous demonstration that baseline sodium transport and the increase in sodium transport of the toad bladder due to vasopressin (VP) are affected differently by a number of metabolic inhibitors or by alterations in the potassium concentration of the serosal bathing medium suggested that the two processes might occur through different mechanisms. This hypothesis was tested further by varying sodium concentration ([Na]) and measuring baseline and VP-induced sodium transport. Short-circuit current (SCC) was used as a measure of net Na transport. Mucosal and serosal [Na] were varied from 15-115mM and the solutions were kept isotonic by the addition of either Tris-HCl or sucrose.

Effect of isotonic replacement of Na by sucrose

[Na]	On baseline SCC	On SCC response to VP	P
90mM	19±7% inhibition	21±15% stimulation	<.025
70mM	41±4% inhibition	12±8% inhibition	<.01
50mM	70±5% inhibition	18±25% inhibition	<.01
30mM	91±2% inhibition	80±3% inhibition	<.025
15mM	96±1% inhibition	92±3% inhibition	>.1

Similar results were obtained when Tris-HCl was used to replace [Na] or when 10mM cyclic AMP or 10mM theophylline was used instead of VP. These data support the hypothesis that two parallel and different pathways for sodium transport exist in the toad bladder.

BACILLURIA AND THE NEPHROTIC SYNDROME. Melinda I. McVicar, Anthony Policastro and Anthony D. Nicastri. Depts. of Pediatrics and Surgical Pathology, Downstate Medical Center, Brooklyn, New York. (Intr. by Jonathan T. Lanman).

The frequency of bacilluria and its relationship to the clinical course of 30 children with the nephrotic syndrome (N.S.=serum albumin < 2.5 gm%, serum cholesterol > 250 mg% and proteinuria > 1 gm/24 hr.) was investigated. Confirmed bacilluria was diagnosed when 2 consecutive clean midstream urine specimens grew out more than 10^5 organisms per ml. Seven episodes of confirmed bacilluria were diagnosed in 5 patients during the 4 years of the study. The frequency of cultures per patient per month ranged from 0.44 to 1.2 with a mean of 0.7. The follow-up period ranged from 5 to 48 months with a mean of 26.4 months and a median of 26 months. Renal biopsy was performed on all patients and classification was made according to histologic and clinical findings similar to those suggested for the International Collaborative Study of Kidney Disease in Children. The histologic classification of the 5 patients with confirmed bacilluria was: 3 minimal changes, 1 focal sclerosis, 1 chronic glomerulonephritis. The clinical status at the time of onset of confirmed bacilluria in each of the 7 episodes was: 3 patients in remission and 4 nephrotic. The severity of the disease (Non-responders and frequent relapsers versus infrequent relapsers) could not be significantly correlated despite the fact that 4 out of the 5 patients with confirmed bacilluria had severe disease. The correlation was poor because 7 of the 13 patients whose cultures were always sterile also had severe disease. Proteus mirabilis was grown from 10 of the 18 positive cultures. This unusual finding may be related to the increased urinary concentration of urea frequently found among nephrotics and which favors the growth of proteus mirabilis while inhibiting E. coli.

LOWE'S SYNDROME: A multi-systemic transport defect. J.G. Mongeau, J. Robillard, C. Morin, L. Dallaire, P. Massicotte. (Intr. by J.R. Ducharme) Dept. Pediatrics, University of Montreal, Ste Justine Hosp., Montreal, Can.

Lowe gave the description of this syndrome as the one of a male with mental retardation, hypotonia and ocular defect, with rickets and a renal tubular defect characterized by glycosuria, aminoaciduria and an abnormal ammoniogenesis. Jejunal mucosa of two patients with Lowe's Syndrome (L.S.) was found by others to show a partial defect in lysine and arginine transport.

The purpose of the present work is to study in greater details the transport of carbohydrates and aminoacids in the intestine, and to compare this defect with the one observed in the tubule.

A 2 year old boy suffering from a typical L.S. was studied and the following renal function tests were done: glomerular filtration rate (GFR), Tm of bicarbonates (TmB) and of glucose (TmG), titrable acidity (TA), and ammonium excretion (NH_4) after NH_4Cl loading test and aminoacid clearances. Intestinal transport was studied by oral glucose tolerance (OGTT), xylose loading (XL) phenylalanine loading (PL), and also by the incubation of jejunal mucosa with C_{14}lyse ($C_{14}L$) C_{14}phenylalanine ($C_{14}P$) in order to study the intestinal uptake of these aminoacids as expressed by their distribution ratios (D.R.). The results are the following:

	GFR ml/m	TmB mM%	TmG mg/m	TA µeq/min	NH_4 µeq/min	OGTT	XL	PL	$C_{14}L$ DR	$C_{14}P$ DR
*L.S.	106	17	195	102	40	flat	flat	flat	8.7	24.5
Normal	120	28	375	52	73	N	N	N	9.8	39.7

These results definitely suggest a renal and intestinal common defect in the transport of carbohydrates and aminoacids.

SUBTOTAL PARATHYROIDECTOMY FOR PROGRESSIVE RENAL OSTEODYSTROPHY IN CHILDREN
Eddie S. Moore, Maurina B. Galvez, Hugh V. Firor, and Lynne L. Levitsky. Depts. of Pediatrics and Surgery, Univ. of Ill. Coll. of Med., Chicago, Ill.
(Intr. by George Honig)

The incidence of renal osteodystrophy as a complication of chronic renal failure is apparently increasing since the advent of chronic hemodialysis. Subtotal parathyroidectomy has been widely used in the treatment of renal osteodystrophy in adults but few cases have been reported of this procedure in children. Of 35 children with chronic irreversible renal failure followed in our clinics, 14 have developed bone disease. The major clinical finding was progressive disabling bone deformities of the knees and ankles. Bone pain was transient and mild. Serum calcium levels were low or normal prior to the apparance of x-ray or clinical signs. Only 2 children had a persistent elevation of serum phorphorus above 4 mgm%. Therapy with Vitamin D and amphogel resulted in normal serum calcium levels but healing did not occur. In 3 patients bone disease progressed inspite of chronic hemodialysis therapy. Four of these children received renal homografts and complete healing of bone disease occurred when the transplant was successful. Three other children are awaiting early renal transplantation. In 7 children an early renal transplant was not available and they underwent subtotal parathroidectomy. These 7 children ranges in age from 6 to 12 years (mean 9.3) and have been followed from 1 to 13 months post-surgery. There were no surgical complications. Serum calcium fell to low values after surgery and all of the children had a positive Chevostek's sign. There were no other manifestations of hypocalcemia. Vitamin D therapy was used in the treatment of post-surgery hypocalcemia in children who were not on hemodialysis. X-ray evidence of recalcification was present within 6 weeks. Bone pain ceased and there was complete healing of pathologic fractures. This study suggests that when early renal transplantation cannot be done, progressive symptomatic and disabling renal osteodystrophy in children can be effectively treated with subtotal parathyroidectomy.

ADJUSTMENT OF RENAL FUNCTION AT BIRTH.
W. Joseph Rahill and S. Subramanian, State University of New York, Depts. of Pediatrics and Surgery, Buffalo

To determine whether significant changes in renal function occur at birth we studied 12 purebred beagle fetuses and puppies near term. Each animal was studied before (3 periods) and after (3 periods) delivery by Cesarean section. During measurements of renal clearances the fetal head and chest were in utero submerged in amniotic fluid; the pelvis and hind legs were exposed. Maternal arterial acid-base equilibrium was maintained at preanesthetic levels. No physical evidence of fetal or neonatal cardiorespiratory or skeletal muscular depression was observed. Rectal temperature of the fetuses and puppies varied between 36° and 38° C.

In 11 fetuses mean arterial pressure was 42 mm Hg (sem 6.4), heart rate 172/min (sem 7.6), arterial pH 7.14 (sem .05), pCO_2 68 mm Hg (sem 9.1), pO_2 18 mm Hg (sem 1.7) and hematocrit 56 (sem 2.2). In 9 pups no consistent rise in arterial pressure occurred within 1 hour after birth. No significant change in urine flow, inulin clearance (F 0.399 ml/min, sem .064; P 0.331 ml/min, sem .043), C_{IN}/C_{PAH} (F 0.376, sem .040; P 0.411, sem .031, n = 12), sodium clearance (F .044 ml/min, sem .019; P .052 ml/min, sem .009), or potassium excretion (F 0.772 µEq/min, sem .161; P 0.687 µEq/min, sem .116) occurred after delivery with the exception of a transient rise in urine flow after delivery (F .029 ml/min, sem .006; P .055 ml/min, sem .010). Both PAH clearance (F 1.19 ml/min, sem 0.21; P 0.888 ml/min, sem .156, $p < .01$) and fraction of filtered sodium reabsorbed (F .92, sem .02; P .82, sem .04, $p < .02$) fell significantly within 2 hours after delivery.

These results show that no immediate increases in these renal functions occur after Cesarean birth in the dog. Unless PAH extraction fell considerably after birth renal plasma flow did not rise after birth. The primary effect of birth on renal function is probably one of transient renal hypoxia.

Supported by Heart Ass. WNY and by NIH.

CYTOXAN IN STEROID DEPENDENT NEPHROSIS.
George A. Richard, R. Dixon Walker. Dept. Ped. and Urology, Univ. Fla. Col. Med., Gainesville. (Intr. by Owen M. Rennert)

During the past five years seventy (70) children have presented to us with the nephrotic syndrome. Of these, thirty-nine (39) have had steroid dependent nephrosis with biopsy proven minimal glomerular changes, normal renal function, and normal $Beta_1C$ levels.

During the past two years, twenty-three (23) of these children with steroid dependent nephrosis have been treated with Cytoxan in order to avoid the increasing side effects of prednisone therapy. The prednisone side effects have included diabetes mellitus (2), cataracts (5), increased blood pressure (4), retarded growth (5) and a chronic cushingoid appearance (20). Cytoxan was given daily (2 mg./kg.) for two months following the induction of a remission with prednisone (2 mg./kg.). These children have been followed a total of 138 patient months post Cytoxan therapy. There have been no instances of significant Cytoxan toxicity.

Six children (6/23) have had a total of 8 relapses. Each relapse has responded to an additional course of Cytoxan, and currently all of the Cytoxan treated children are doing well on no medication. The majority of prednisone side effects have resolved.

In summary, Cytoxan given for two months following a prednisone induced remission of the nephrotic syndrome appears to be of considerable benefit to children with steroid dependent nephrosis.

RENAL INTERACTION OF CHLOROTHIAZIDE, AMINOPHYLLINE AND ISOPROTERENOL IN NEPHROGENIC DIABETES INSIPIDUS
George A. Richard, W. B. Weil. Dept. Ped. Univ. Fla. Col. Med., Gainesville and Dept. Human Develop., Mich. St. Univ., East Lansing.
(Intr. by Owen M. Rennert)

This study was prompted by the evidence that vasopressin, aminophylline and isoproterenol favor the accumulation of cyclic AMP by different pathways (J. Clin. Invest. 41:702, 1962). In addition, work in Beagle dogs (Int. Sympos. of Pharm., 1967) demonstrated that aminophylline has an action similar to vasopressin to decrease free water clearance. We studied the effect of chlorothiazide, aminophylline and isoproterenol on free water clearance in three brothers with Nephrogenic Diabetes Insipidus. Standard methods demonstrated normal Inulin and PAH Clearances in three cooperative, unanesthetized, well hydrated boys. For one week each boy was maintained on his usual low solute diet and prior chlorothiazide therapy. Free water clearance increased significantly in each boy following a single I.V. infusion of 4 mg./kg. of aminophylline and also following a seven day course of 12 mg./kg./day of oral aminophylline. There was only a slight increase in Inulin and PAH Clearances during the acute course of aminophylline. In addition, each boy's average daily urine volume increased 15% during the week of combined chlorothiazide and aminophylline therapy. After the week's course of combined therapy, an I.V. infusion of 0.2 µg./min. of isoproterenol produced a significant decrease in free water clearance associated with a marked decrease in PAH clearance and a slight decrease in inulin clearance.

These data demonstrate that although these agents have a physiologic effect neither acute nor chronic aminophylline therapy (increased free water clearance) nor isoproterenol therapy (decreased PAH clearance) would benefit *children with Nephrogenic Diabetes Insipidus.*

NEUROLOGY

NEUROTOXIC EFFECTS OF LEAD IN THE CHICK EMBRYO.
Joseph Kochen and Asao Hirano, Albert Einstein College of Medicine, Montefiore Hospital and Medical Center, Departments of Pediatrics and Pathology, New York. (Intr. by Laurence Finberg)

The relationship of lead to brain damage in early childhood is well known. The transfer of lead across the placenta has been confirmed by the presence of lead in fetal tissues and cord blood. However, the extent of lead exposure which may be toxic to the human fetus remains unknown.

The injection of 25µg of lead into the yolk sacs of 4-day-old chick embryos results in the development of hemorrhagic foci in the central nervous system within 48 hours. In the most severely affected embryos, death occurs with massive bleeding into the ventricles. No indications of a generalized bleeding tendency are present. By the 18th day, many of the embryos have developed a large fluid-filled cyst which has herniated through the midline occipital region of the cranium. Staining of bone shows absence of fusion and lateral displacement of occipital bones to a degree proportional to the size of the cyst. Microscopically, the ventral wall of the cyst is lined by ependyma and choroid plexus. The dorsum of the cyst consists of an extension of the meninges contiguous with subcutaneous tissue and skin. The lateral walls of the cyst show a progressive depletion of neural tissue from the base to the roof of the cyst. Morphologically, the cyst appears to be a massive expansion and protrusion of the fourth ventricle and subarachnoid space. The close similarity of these findings to congenital closing defects, such as meningoencephalocele suggests the possibility that a similar etiology may be responsible for certain central nervous system malformations in the human fetus. (Aided by a grant from the United Cerebral Palsy Research and Educational Foundation).

INDEPENDENCE OF BLOOD AND BRAIN GLUCOSE LEVELS: DECREASED BRAIN GLUCOSE WITH ELEVATED PLASMA GLUCOSE.
Jean Holowach Thurston, Maria Ikossi and Wendel R. Pierce. (Intr. by Philip R. Dodge, Wash. Univ. School of Medicine, Dept. of Pediatrics, St. Louis, Missouri.)

Hypoglycemia is a potentially serious and not uncommon condition in infants and children. Although it is generally accepted that decreased blood glucose levels are associated with reduction in brain glucose concentration, the possibility of reduced brain glucose levels with normal or even elevated blood glucose levels has seldom been considered. Research in our laboratory has revealed that blood glucose levels are not a consistent reflection of brain glucose levels. Anoxia was produced in 40 mice less than 12 hours of age by exposure to N_2 at 37°C (pO_2 less than 5 mm of Hg). Brain glucose levels fell from the normal value of 0.60 ± 0.14 m-moles/kg in zero time animals to 0.22 ± 0.04 m-moles/kg after six minutes of anoxia. In the livers of the same animals there was a fourfold increase in glucose concentration, from 2.61 ± 0.28 m-moles/kg to 10.45 ± 0.45. In 22 other animals of the same age plasma glucose levels increased from 3.04 ± 0.03 mM to 5.56 ± 1.09 mM during this interval of anoxia. Paradoxic values of glucose in blood and brain of mice are not unique to cerebral anoxia. We have seen them in aspirin poisoning (J. Clin. Invest. 49, 2139, 1970) and after chronic hydrocortisone treatment (J. Neurochem. 16, 107, 1969). In conclusion, in evaluating blood glucose levels it is important to consider that these values are not necessarily an accurate reflection of values present in the brain.

THE ROLE OF HYPOXIA IN THE DEVELOPMENT OF NUCLEAR JAUNDICE IN BILIRUBIN ENCEPHALOPATHY, Arthur L. Rose. (Intr. by Dr. Henry Barnett), Albert Einstein Coll. of Med., Dept. of Neurol. and Ped., Bronx, New York 10461

This study was undertaken in an attempt to clarify the mechanism and significance of selective nuclear jaundice in bilirubin encephalopathy. Seventy-two 14-16 day old homozygous Gunn rats (serum bilirubin 7-14 mgs%). were used. Group I. Thirty-eight rats treated with 100-200 mgs/kg sulfadimethoxine s.c. developed acute neurological signs and often terminal hypoxia. Their brains, examined after 4-100 hours' survival showed macroscopic nuclear jaundice in 33%. Mean serum bilirubin reduction was 4 mgs%. Group II. Twelve rats were asphyxiated in 100% N_2 for 4-8 minutes, resuscitated, given sulfadimethoxine 100-200 mgs. s.c. and killed 2-9 hours later. Nuclear jaundice was present in 82%. Mean serum bilirubin reduction was 5.2 mgs.%. Group III. Twelve jaundiced controls were sacrificed(6 with and 6 without sulfadimethoxine treatment) avoiding hypoxia. None of their brains showed nuclear jaundice. Group IV. Ten rats were asphyxiated as above and injected with 1% Trypan Blue (6) 10 mls/kg or 2% Evans Blue 2.5 mls/kg (4) i.p. and killed 4-19 hours later. No gross or microscopic blue or orange staining was present.

The microscopic pathology was the same in all 4 groups and consisted of selective neuronal degeneration with accumulation of glycogen in mitochondria and in the endoplasmic reticulum,in the cerebellum, post-lat. thalamus, inf. colliculi, globus pallidus and brain stem tegmentum (H. Schutta and L. Johnson, 1967; A. Rose and A. Johnson, 1972). Nuclear jaundice occurred in these areas of pre-existing degeneration but only in Groups I and II. It was concluded that bilirubin acts as an intracellular tracer marking areas of pre-existing neuronal damage and that its uptake by neurons is markedly increased by hypoxia. (Supported by NINDS 1 R01 NS 09064-01).

DIFFUSE BRAIN DAMAGE, MICROCEPHALY, INTRACRANIAL CALCIFICATIONS, AND "OWL EYE" INCLUSION BODIES ASSOCIATED WITH INTRAUTERINE INFECTION WITH HERPES SIMPLEX VIRUS, TYPE 1. Alfred L. Florman, Anne A. Gershon, Piers R. Blackett, and Andre J. Nahmias. New York Univ. Sch. of Med., Roosevelt Hospital, New York City and Emory Univ. Sch. of Med., Atlanta, Georgia.

A "small for dates" male infant developed respiratory difficulty and increased muscle tone within the first 24 hours of life. At 1 week the IgM level was 86 mg%. By 4 weeks there were obvious microcephaly, intracranial calcifications and cells with "owl eye" inclusion bodies in the urine. No skin vesicles were ever present. At 3 months low titer CF antibody for cytomegalovirus (CMV) was found in both mother and baby but it was not subsequently found in the baby's serum. However, at 2 months herpes simplex virus Type 1, not CMV, was isolated from the baby's CSF and urine. At 3 months, herpesvirus was recovered again from the urine, but not from the CSF. Specific herpesvirus antibodies were demonstrated only by indirect immunofluorescence. Until 8 months it was only IgM herpesvirus antibody. At 8 months it was found in both the IgM and IgG fractions. Up to 1 year, no herpesvirus CF or neutralizing antibodies (NA) have been found. Failure to produce CF and NA after intrauterine infection is unusual, but has been reported in a few instances of congenital rubella. Clinically the child has done poorly. He is markedly retarded, has increased muscle tone and recurrent seizures.

Most instances of herpes simplex virus infection in newborns are acquired during delivery and are due to Type 2 strains. This child probably acquired his Type 1 infection sometime before delivery and the teratogenic effects - brain damage, microcephaly, intracranial calcifications and inclusion bodies - were strikingly like those usually associated with cytomegalovirus infection. Two similar instances have been reported, and from one a herpes virus Type 2 was recovered. The present case suggests that fetal age at the time of infection may be as significant a determinant of pathology as the infecting agent and re-emphasizes the need for viral isolation studies to confirm etiology.

RETARDATION OF BRAIN GROWTH BY NEONATAL SEIZURES. Claude G. Wasterlain, M. D. and Fred Plum, M. D. Cornell Univ. Med. Col., Dept. of Neurology, New York 10021 (Intr. by W. W. McCrory)

Human neonatal seizures are associated with a poor prognosis for intellectual development. We investigated the influence of epileptic seizures on brain and body growth at critical stages of development by subjecting young rats to one daily electroconvulsive shock (ES). Littermates were paired at birth according to weight and sex and were weighed every other day thereafter. One member of each pair received ES, the other member was handled in a similar fashion but not shocked. If one animal of the pair died, its companion was eliminated from the experiment. Group I newborn rats (5 litters, 44 rats) had ES seizures from day 2 to 11 of life. Group II (5 litters, 44 rats) were shocked from day 8 to 17 of life, while group III (5 litters, 48 animals) received daily ES from day 19 to 28 of life. In group I, 7 of 18 experimental animals and none of the controls died before 30 days of age. In group II, 1/18 experimentals and 0/18 controls died, while in group III 0/24 experimentals and 1/24 controls died. At 30 days of age, all animals were sacrificed. All experimental groups showed a significant reduction of body weight over paired controls. Brain weight was reduced by 14% of mean control brain weight in group I ($p<0.01$), by 8% of control brain weight in group II ($p<0.01$) and was not significantly different from controls in group III, although convulsions appeared more vigorous in older animals. The brain weight/body weight ratio was significantly lower in rats with early convulsions than in nonconvulsing littermates ($p<.025$ for groups I and II), while in group III, there was no significant difference between control and treated rats. When all rats shocked during active brain growth (groups I and II) were compared to those shocked after myelination (group III) there was little difference in body weight (early ECS 53.93 gms, late ECS 52.93 gms) suggesting comparable nutritional status in the two groups, but brain weight and brain/body ratio were smaller in the "early ES" group ($p<0.001$). These findings imply that during its period of rapid growth the rat's brain is selectively vulnerable to relatively mild electroconvulsive seizures which leave the brain of older rats undamaged. The mechanism and specificity of this effect are being investigated.

ELECTROPHORETIC DEMONSTRATION OF THE ENZYME DEFECT IN METACHROMATIC LEUKODYSTROPHY. Mario C. Rattazzi, James S. Marks and Ronald G. Davidson, Dept. Ped., Div. Hum. Genet., SUNYAB, Buffalo, N.Y.

Metachromatic Leukodystrophy (MLD) is a degenerative neurological disease characterized by an autosomal recessive mode of inheritance and accumulation of cerebroside sulphate in the nervous system and other tissues. Homozygous affected patients have marked deficiency of arylsulphatase A, one of the three forms (A,B,C) of this lysosomal enzyme. The deficiency has been detected in several tissues and cells, but no method for visualization of arylsulphatase activity from extracts of relatively small amounts of cells was available. This report describes a sensitive electrophoretic method which allows for the visualization of the three arylsulphatase types from a variety of tissues and cells including cultured skin fibroblasts and amniotic fluid cells. The electrophoresis is performed for two hours at room temperature using cellulose acetate gel ("Cellogel") and a 0.036M barbital-acetate buffer, pH 7.3. Bright fluorescent bands of enzyme activity can be seen under U.V. light after incubation of the gels for one hour at 37°C with a 5mM solution of purified 4-methyl umbelliferone sulphate in 0.5M acetate buffer, pH 5.4. The identity of the enzyme bands has been established by specific inhibition, pH optima and differential sedimentation studies. Direct quantitation of the separated bands can be readily performed.

A family in which two children suffer from MLD has been studied. Absence of the arylsulphatase A band could be demonstrated in preparations of cultured skin fibroblasts from the two patients while decreased fluorescence of that band was evident in preparations from their parents. In an additional family, a pregnancy has been monitored by amniocentesis and electrophoresis of extracts of cultured amniotic fluid cells: a clear arylsulphatase A band was present. This sensitive technique is useful for pre- and post-natal diagnosis of MLD and allows for the study of electrophoretic heterogeneity of arylsulphatases using cellular material easily obtained from living individuals.

THYMIDINE KINASE ACTIVITY IN CEREBROSPINAL FLUID OF HERPESVIRUS HOMINIS INFECTED RABBITS. Milo D. Hilty, Donald C. Thomas, Ralph E. Haynes, Henry G. Cramblett. Ohio State Univ., Col. of Med., Children's Hosp., Dept. of Ped., Columbus, Ohio.

The diagnosis of Herpesvirus hominis (HVH) encephalitis is made with certainty only when the virus is isolated from brain tissue or cerebrospinal fluid (CSF). Most premortem HVH isolations have been from brain biopsy specimens; HVH has been recovered from CSF only three times. The present methods for making an early diagnosis are not efficient and improved techniques are needed. Recent studies indicate that thymidine (TdR) kinase is induced during the course of HVH replication in cell culture. The in vivo induction of TdR kinase by HVH has not been reported in any animal system. The rabbit model of HVH encephalitis was used to determine if TdR kinase could be detected in CSF. The rabbits were infected by corneal inoculation of HVH which had been recovered from brain biopsy material of a patient with HVH encephalitis. Rabbits developed encephalitis 5-7 days after inoculation, and CSF was collected by cisternal tap at 7-11 days. Thymidine kinase activity was determined using a chromatographic disc technique. Significant levels of TdR kinase was detected in CSF of infected rabbits and not in controls. Attempts to determine the source of the TdR kinase activity is being investigated utilizing acrylamide gel electrophoresis, pH optimum, and heat stability.

MUCOSULFATIDOSIS: BIOCHEMICAL AND ULTRASTRUCTURAL OBSERVATIONS. George Hug, Shirley W. Soukup, William K. Schubert, Kevin Bove, and Linda Walling. The Children's Hospital Research Foundation, Cincinnati, Ohio.

A three year study has been made of a girl, now 5 years of age, who has mucosulfatidosis. This included biochemical, light and electron microscopic analysis of biopsy specimens of liver, brain, kidney and bone marrow, as well as fibroblast cultures. Originally, Hurler's disease was suspected because of her facial appearance and marked Alder-Reilly granulation of leukocytes, although there never was corneal cloudiness. The clinical course, however, resembled metachromatic leucodystrophy (MLD) leading to spasticity and cerebral degeneration. The urine lacked excess mucopolysaccharide, and was deficient in activity of arylsulfatase A similar to MLD. Histochemical analysis of tissue biopsy specimens indicated sulfatide accumulation in brain, peripheral nerve and renal tubules and mucopolysaccharide accumulation in myeloid precursors. Liver, kidney and fibroblast cultures were deficient in activity of arylsulfatase A, B, and C; the activity of 6 other lysosomal enzymes was normal or increased; the activity of hepatic α- and β-galactosidase was marginally low ($p < 0.05$). Electron microscopy revealed "Zebra" bodies in the brain and large membrane surrounded vacuoles in hepatocytes and bone marrow cells, i.e., observations identical with those of Hurler's disease but dissimilar to those of MLD. Staining of fibroblast cultures showed granules positive for aldehyde fuchsin and alcian blue similar to cultures of mucopolysaccharidoses, and unlike those of MLD. ^{35}S uptake by cultured fibroblasts of mucosulfatidosis was twice the normal rate and comparable to mucopolysaccharidosis. The overlap of clinical, biochemical and morphological findings between MLD, Hurler's disease and mucosulfatidosis suggests the observed acid hydrolase deficiencies may not be the primary lesion in these lysosomal diseases.

(Supported by Grants HD-05221, AM-13903, and RR-123)

HOMOCYSTINURIA PRESENTING AS REVERSIBLE "SCHIZOPHRENIA." A NEW DEFECT IN METHIONINE METABOLISM WITH REDUCED METHYLENE-TETRAHYDROFOLATE-REDUCTASE ACTIVITY.
FREEMAN, J.M., FINKELSTEIN, J.D., MUDD, S.H., AND UHLENDORF, B.W. JOHNS HOPKINS UNIV. SCH. OF MED. DEPTS. NEUROLOGY AND PED., V.A. HOSP., WASH., D.C., AND NATL. INST. OF MENTAL HEALTH, AND DIV. OF BIOLOGIC STANDARDS, NIH.

A 15 year old mildly retarded Negro female admitted with a two year history of progressive withdrawal, hallucinations, delusions, and catatonia unresponsive to psychotherapy had homocystinuria without elevation of plasma methionine. Psychotic symptoms disappeared gradually, concomitant with administration of pyridoxine and folic acid, but recurred when the patient discontinued medication for nine months. Readministration of these drugs was again associated with remission of symptoms. A mildly retarded but non-psychotic sister also had homocystinuria. Both children lacked the clinical manifestations usually associated with cystathionine synthase deficiency. The patients were able to convert a large oral load of methionine to inorganic sulfate, indicating adequate in vivo cystathionine synthase activity. Normal specific activities of cystathionine synthase and of the enzymes methylating homocysteine were found in liver biopsy material and cultured fibroblasts. Fibroblasts grew in a basal culture medium containing methionine, but not one in which homocystine replaced methionine. This suggested a lack of normal capacity to form methionine from homocystine, and a possible deficiency in synthesis of N^5-methyltetrahydrofolate. A decrease in the activity of methylene-tetrahydrofolate-reductase, the enzyme synthesizing N^5-methyltetrahydrofolate was demonstrated. Homocystinuria without increased levels of methionine may suggest the diagnosis of this new enzymatic defect.

CEREBRAL VENTRICULAR FLUID PRESSURE RECORDINGS DURING DRUG THERAPY. Patricia W. Hayden*. University of Washington Medical School, Seattle, Washington. (Intr. by David B. Shurtleff).

Continuous isovolumetric ventricular fluid pressure (VFP) recordings from hydrocephalic dogs, cat, rabbit and man demonstrate similarities in the cardiorespiratory, Valsalva, rebreathing and mean pressure responses between species. 93 studies, 81 during chemical therapy, some with water and salt restriction and replacement, have shown the following mean pressure responses: Sedatives (droperidol, fentanyl and pentabarbitol) caused transient increases of 28-40% in VFP. Chlorthiazide and isodril caused no discernable effect and acetazolamide an increase of 27 to 59%. Isosorbide reduced VFP 36-49% in animals and 30-80% in humans. Water restriction during isosorbide therapy intensified reduction in VFP and was associated with loss of body weight and no discernable alteration of rebound on cessation of drug. Rehydration elevated VFP and intensified rebound. With ad libitum water available during isosorbide administration no weight loss occurred and rebound was less than with rehydration following water restriction. Salt restriction intensified VFP decrease in humans, prolongs the time for return of pressure to baseline and appears to minimize rebound.

NEUROLOGY

Read by Title

PHASE-FREQUENCY AVERAGING: A NEW WAY OF ANALYZING ELECTROPHYSIOLOGIC SIGNALS. Victor H. Auerbach, Dept. Ped., Temple Univ. Sch. of Med., & St. Christopher's Hosp. for Children, Phila., Pa.

Signal averaging in the time domain is useful for the amplification of a weak signal in the presence of random noise. With relatively clean signals, time averaging, whether performed by analog or digital means, can only produce interpretable results if phase relationships are kept constant by means of an externally derived synchronizing pulse. Thus, electroretinograms (ERGs), which are evoked responses, may be averaged in the time domain. Analysis of ERGs in the frequency domain produces, in addition, a spectrum of the harmonic content of the original signals. Electroencephalograms (EEGs), being seemingly random oscillations, when averaged in the time domain, yield only horizontal lines, corresponding to the average DC potential of the signals. Averaging EEGs in the frequency domain, nevertheless, permits the analysis of average harmonic content to be made.

A novel algorithm has been developed which allows computer analysis in the frequency domain to be carried out of either coherent (ERG) or incoherent (EEG) signals, using the Fourier transform and special ways of averaging phase angles. By independently averaging and retaining phase angles and harmonic amplitudes, one can reconstruct by reverse Fourier transformation a meaningful representation of the input data in the time domain. This representation will, in general, differ from the time average, depending on the degree of incoherence and random variations in time. The cross-correlation function and the average power spectrum are automatically obtainable. The method also yields statistical data, in the form of means and standard deviations for each of the harmonic amplitudes and phase angles, which should allow for comparisons to be made statistically of electrophysiologic data. Close scrutiny of these parameters during the progression of a given neurologic disease is now possible. (Supported in part by NIH Grants RR-5624, RR-75 and HE-12651 and the Penna. Lions' Eye Research Foundation.)

HYPOXIC INHIBITION OF CELL DIVISION IN NEONATAL RAT BRAIN. David Baum, Jo Anne Brasel, Myron Winick. Stanford University School of Medicine, Stanford, California and Cornell University Medical College, N.Y., N.Y.

Although severe hypoxia is a threat to the developing brain in infants with cardiopulmonary disease, the effects of oxygen difficiency on brain development are not fully understood. Since cellular division requires energy and ATP production is decreased by oxygen lack, brain cell division may be reduced by hypoxia. Therefore, the effect of hypoxia on brain cell division was investigated in ten-day-old rats, an age when this process is rapid in the rat's brain.

Similar litters of rat pups, with and without mothers, were given air or a mixture of 8% oxygen and 92% nitrogen for 24 hours. All pups were given ^{3}H-thymidine after 16 hours and decapitated 8 hours later. Uptake of ^{3}H-thymidine by the rat brains was used to estimate DNA synthesis and, indirectly, cell division. ^{3}H-uptake in air-breathing rats with mother was 8.57 $\pm$ 1.23 (cpm/mg DNA; mean $\pm$ S.D.) and without mother, 10.53 $\pm$ 1.09. In contrast, ^{3}H-uptake in hypoxic rats both with mother (5.08 $\pm$ 1.17) and without mother (4.40 $\pm$ 0.93) was significantly lower ($p < 0.001$). Because ^{3}H-uptake was lower in air-breathing pups with mother than without mother ($p < 0.01$), feeding may have had a role in these results. However, feeding does not appear to have a major influence on the effect of hypoxia in that ^{3}H-uptake was significantly lower ($p < 0.001$) with hypoxia (0.190 $\pm$ 0.035) than with air-breathing (0.313 $\pm$ 0.028) in motherless litters given ^{3}H-thymidine after 6 hours and decapitated 2 hours later.

These data suggest that severe hypoxia markedly depresses cellular division in brains of ten-day-old rats and should be taken into account when considering the developing brain in young hypoxic infants.

HEXACHLOROPHENE ASSOCIATED ENCEPHALOPATHY: Robert R. Chilcote, John A. Jupin, Howard H. Loughlin, August Curley, (Intr. by Robert J. Haggerty), Dept. of Pediatrics, Univ. of Rochester Sch. of Med., Rochester, N.Y.

Hexachlorophene (HCP) a chlorinated cyclic hydrocarbon with bacteriostatic properties against coagulase positive staphylococcus after prolonged contact, is used in a number of commercial products. The oral toxicity of HCP is well known and absorption through normal and damaged skin has recently been appreciated. Specific instances of toxicity resulting from dermal absorption have, however, lacked documentation. A 10 year old male who sustained a 25% partial thickness burn developed an encephalopathy characterized by alterations in consciousness, weakness, and hypothermia in the second week of convalescence. On the 14th post burn day, he expired from the effects of anoxia resulting from aspiration the previous day. His treatment had included 3x daily tub soaks to which a 3% HCP product had been added and repeated application of a spray consisting of diluted 3% HCP solution to areas of healing burns for several days prior to asphyxiation. Autopsy revealed satisfactorily healing burns, terminal pneumonia, and cerebral edema. Electron capture gas - liquid chromatography of methylated derivatives of ethanol-ether extracted tissue revealed HCP (in ppm), blood 2.2, brain 2.2, unburned skin 25, liver 4.4, muscle 2.4, kidney 2.2, and fat 6.0. The association of HCP as a possible etiologic agent is suggested by high tissue levels, similar toxicologic findings in experimental animals given HCP and humans exposed to chemically related compounds, and the absence of findings usually incriminated in late burn deaths. Fat storage suggests cumulative effects and complicates possible therapeutic interventions. Finberg has demonstrated blood levels as high as 0.6 ppm after five washings in a new born nursery. Further investigations are warranted to define the incidence of sublethal toxic syndromes in human usage of products containing HCP.

A PILOT STUDY OF SEROTONIN SCREENING OF NEONATES. Mary Coleman and N. Vildan Erkan (Intr. by Philip L. Calcagno). Georgetown University School of Medicine, Washington, D.C.

101 full-term normal newborn babies were tested to determine serotonin levels for a postulated new mental retardation screening test. The method is a micro modification of the spectrofluorometric determination of total 5-Hydroxyindoles in whole blood. 1.0 ml. of blood (for duplicate determinations) was collected by heel stick in a plastic tube containing heparin. 0.5 ml. of blood is diluted with 1.0 ml. distilled deionized water, mixed with 0.5 ml. of 10% $ZnSO_4$, shaken for 30 seconds, then 0.2 ml. 1 N. NaOH is added and shaken for 30 seconds. The mixture is centrifuged for 3 minutes at 16,000 R.P.M. 0.1 ml. concentrated fluorometric HCl is added to 1.0 ml. of clear supernatant, then read on spectrofluorometer. 57 males and 44 females were tested anywhere from 12 hours to 7 days of age. The values ranged from 11 to 54 nanograms/ml. The mode value was 22 nanograms/ml. A trend was seen with the serotonin level declining at 36-48 hours of age and then rising afterwards. The 3 patients with extreme values (the lowest and 2 highest) have evidence of central nervous system damage. The infant with the value of 11 nanograms/ml. was later diagnosed as having Down's Syndrome. The 2 infants having the highest values (48 and 54 nanograms/ml.) later developed spasticity documented by motion pictures of the neurological examinations. Since it is so important to draw a small amount of blood from the neonates, it seems as if this micro-method using whole blood will be a quick and accurate method that can be safely used for serotonin screening.

ROSEOLA INFANTUM AND ITS MODES OF CNS INVOLVEMENT
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Since its first description in 1910 roseola infantum (exanthema subitum) has been a clinically well defined, common febrile illness of infancy. An association with transient CNS signs has been noted since 1940. Only recently have scattered reports of disabling neurological sequelae appeared. A re-examination of university hospital records and a neurological office clientele yielded 82 unequivocally documented pediatric roseola cases. After reasonable exclusion of other antecedent noxious influences there remained 25 instances, where associated CNS signs could be related to roseola. A bulging fontanel, convulsions and hemiparesis were the most frequent transient accompaniments. Recurrent epileptic seizures, persistent hemiparesis, global or circumscribed psychomotor retardation occurred singly or in combination in 8 children, who could be followed from 3 to 9 years. Neurological signs were seen in most cases during the acute course of roseola, only in two instances were they delayed by 7 and 14 days. Any later sequelae were not encountered in a control group. The probable causal relationship between this common exanthema, generally regarded as benign, and permanent CNS afflictions is stressed. It is concluded, that roseola is associated with an encephalopathy of widely varying severity, which is usually but not always reversible. If neurological signs do not occur in the acute phase of the illness or within two weeks thereafter, a permanent deficit is extremely unlikely.

VELOCITY CURVES OF RABBIT BRAIN GROWTH
Shaul Harel, Kathy Watanabe and Richard J. Schain. UCLA Sch. of Med., Dept. of Ped., Los Angeles.

The period of maximal brain growth, called the "brain growth spurt," is thought to be a time of special vulnerability to adverse events affecting brain development. Previous studies in man and laboratory animals have shown that the timing of this period in relation to birth can be expressed as prenatal, perinatal or postnatal (Dobbing, 1968). The following constituents of regional areas of developing rabbit brain have been studied from 22 days of fetal life (1-10 days from delivery) to adulthood: wet weight, water content, protein, DNA, RNA, cholesterol, sulfatides and cerebroside content. With the use of velocity curves (growth increment/5 day interval as percent of adult value), it is possible to determine peak accumulation periods of the various constituents. The fastest period of whole brain growth, as expressed by brain wet weight, begins shortly before birth, reaches a maximum at 5 days of postnatal age, and ends at approximately 30 days. This brain growth spurt is terminated before occurrence of the peak of the body weight growth spurt. The rates of RNA and protein accumulation are maximal between 5 and 10 postnatal days. Total DNA, as an index of cell number, revealed that 15% of brain cells are present at birth. The DNA curve peaks between 10 and 15 days and then drops rapidly. The peaks of accumulation for cholesterol, cerebrosides and sulfatides, substances that are indices of myelination, occur later; cholesterol=18 days; sulfatides=45 days; cerebrosides=53 days. The height of the DNA peak for cerebellum indicates that this region has a more rapid rate of cell multiplication relative to the rest of the brain. The brain stem, by contrast, has a growth spurt of longer duration and more gradual deceleration. Our data indicates that, like the human newborn, the rabbit is a "perinatal brain developer" making it a useful model for investigation of perinatal factors affecting brain development.

ULTRASTRUCTURAL HEPATIC INFILTRATES IN SIBLINGS WITH REYE'S SYNDROME. Joseph R. Goodman and M. Michael Thaler (Intr. by M.M. Grumbach), Dept. of Ped., Univ. of California, San Francisco.

Acute encephalopathy with visceral fatty change (Reye's syndrome) is a relatively common, serious condition of unknown etiology. Previously undescribed ultrastructural changes were noted in the liver of 2 siblings in whom the disease occurred 16 months apart. Sib 1 (2-3/12 y/o) died after 3 days in coma. Treatment: 2 exchange transfusions, peritoneal dialysis and steroid hormones. Percutaneous liver biopsy 4 hours before death, and autopsy confirmed the diagnosis. Sib 2 (2-9/12 y/o) recovered after 5 days in coma. Treatment: 2 exchange transfusions, peritoneal dialysis and hemodialysis. Percutaneous liver biopsies (4), on the first and last days of coma, also 1 week and 1 month afterwards, confirmed the diagnosis.

The cytoplasm and nuclei of hepatocytes in both sibs had a granular appearance due to extensive deposits of discrete, round, uniformly staining bodies, ca 200 A in diameter, relatively translucent in comparison with ribosomes or glycogen granules. In approximately 15% of hepatocytes, these aggregates filled the cytoplasm, displacing other elements peripherally. Nuclear deposits appeared to spread centrifugally, leaving the nuclear membrane intact. The granular material disappeared during recovery, to be replaced by strikingly hypertrophied endoplasmic reticulum, numerous microbodies (peroxisomes), distended Golgi, and increasing amounts of glycogen. Mitochondria appeared reduced in number during coma, but were structurally unremarkable. Lipid shifted from hepatocytes to Kupffer cells during recovery.

These observations suggest that a non-crystalline, uniformly spherical material accumulates in the liver in Reye's syndrome, whose disappearance correlates with recovery.

CHEMICAL COMPOSITION OF THE BRAIN OF THE PRENATAL THYROIDECTOMIZED RHESUS MONKEY FETUS. Alan B. Holt, George R. Kerr, and Donald B. Cheek. Johns Hopkins Univ., School of Med., Dept. of Pediatrics, Baltimore, Md. and Harvard Univ., Dept. of Nutrition, Cambridge, Mass.

Six pregnant rhesus monkeys were injected with a single dose of I^{131} between day 70-90 of gestation (HT group). The same number of untreated pregnant rhesus monkeys served as normal controls. All fetuses were delivered by C-section on day 150 of gestation. The thyroid gland was absent in the fetuses of the HT group while their mothers had reduced thyroid function. The weight of the body, cerebrum, and cerebellum were not statistically different. The pattern of the chemical changes found in the HT group were similar in the cerebrum and cerebellum, the changes more severe in the cerebellum. RNA and protein contents were reduced with no statistical difference in the complement of DNA. The percentage of water was elevated with an expansion of the "chloride" space. The "non chloride" space (an index of neuronal volume) was reduced 9% and 20% for cerebrum and cerebellum respectively. Reduced amounts of cholesterol and lipid N-acetylneuraminic acid were found. Total carbonic anhydrase activity (CA) -- an indicator of neuroglial function was grossly reduced (40-50%). The ratio of CA to protein was low indicating a decreased synthesis of this enzyme in relation to the overall diminution of brain protein synthesis. To our knowledge, these findings are the first demonstration of an effect of thyroid ablation on the fetal primate brain.

TESTOSTERONE METABOLISM IN BRAIN TISSUE. O.C. Green, M.L. Berman and S.M. Perlman (Intr. by Wayne H. Borges). Northwestern Univ. Medical School, The Children's Memorial Hospital, Department of Pediatrics, Chicago, Ill.

Clinical studies in humans and other mammals suggest that testosterone affects cerebral function. In androgen-sensitive target tissues, testosterone (T) is converted to the active metabolite dihydrotestosterone (DHT) through the enzymatic action of 5 α-reductase. To test the hypothesis that this conversion of T to DHT may be of clinical significance in cerebral function, two approaches have been undertaken: clinical study of cognitive function in children with genetic absence of 5 α-reductase (feminizing testis syndrome) and a laboratory study of testosterone metabolism by rat brain tissues. A battery of tests to assess cognition, memory, divergent production, convergent production and evaluation was applied to 8 children with the feminizing testis syndrome, 8 boys and 9 girls with congenital virilizing adrenal hyperplasia, and an equal number of control children matched for sex, age and socio-economic index. Results indicated that children with the feminizing testis syndrome performed as normal females and could be distinguished from normal males on a specific task (Healy Pictorial Completion Test). Laboratory studies of rat brain homogenates confirmed the presence of 5 α-reductase. 4994 picomoles of DHT were formed from the metabolism of 8.47×10^{-8}M T per gram brain whole homogenate. Cell fraction studies indicated reductase activity was present in a distribution similar to sex tissues with the exception of the nuclear fraction. Male rat brains showed four times the reductase activity of female rat brains; there was twice as much microsomal protein per gram of whole brain in male rats.

These studies indicate (1) The brain is a target tissue for testosterone (2) testosterone is metabolized in the brain in a fashion similar to sexual target tissues, and (3) this metabolic conversion is of clinical significance.

THE EVALUATION OF ATYPICAL CONVULSIVE EPISODES IN INFANCY. Hilda Knobloch, Merrill E. Calvin and Frances Spencer; Albany Medical College, Albany, Suffolk State School, Melville, New York, Mt. Sinai Hospital, New York.

In order to determine the nature of atypical recurrent stereotyped alterations in behavioral function observed in infants and preschool children, a double-blind study using phenobarbital at 10 mg/Kg and a placebo was done. Previous follow-up of 200 infants into the school years indicates that the occurrence of seizures is an important factor in failure to maintain normal development, particularly in the presence of other signs of CNS impairment. Such studies also indicate that a significant number of infants with atypical manifestations, notably staring and crying spells, later developed grand mal.

In a series of only 19 cases sequential analysis and differential response to the first treatment regimen employed both demonstrated significant superiority of phenobarbital in controlling episodes and improving behavior.

Early treatment of seizures is believed to carry the best prognosis for sustained good control. The data in this small series indicate that therapeutic trials are warranted, with each infant in his own double-blind study, when unexplained recurrent episodic behavior occurs.

The following types of behavior are suspicious: staring, with or without immobilization, unprovoked and uncontrollable crying, intermittent blindness deafness or "autism," fragments of normal behavior in a seemingly mentally defective infant, discrepancies between adaptive and language development or between reported and observed behavior, unexplained daily variability in attention, peculiar organized behavior or even generalized disorganization.

The problem is complicated by the presence or absence of motor and mental defects, by degenerative diseases and even by extra-CNS pathology such as renal disease. Long-term controlled studies are difficult, but necessary, in order to determine the ultimate efficacy of early treatment in the prevention of later mental deficiency.

POSSIBLE MECHANISM FOR ENCEPHALOPATHY IN PYRUVIC DECARBOXYLASE DEFICIENCY. Derrick Lonsdale and J. Waide Price (Intr. by Robert Schwartz). Cleveland Clinic Dept. Ped. and Clin. Path.

The mechanism of encephalopathy in "effective" thiamine deficiency is still not completely understood. Defective transketolase, resulting in interruption of the hexose monophosphate shunt, or cerebral ATP deficiency caused by inefficiency of the Krebs cycle have both been suggested but have not so far been proven. A patient with intermittent cerebellar ataxia was studied during one of the ataxic episodes. Urine specimens revealed a direct relationship between increased concentrations of pyruvate, alanine and alpha keto glutarate, all of which were inversely proportional to concomitant concentrations of glutamate and aspartate. Cultured fibroblasts revealed deficient activity of pyruvic decarboxylase and thiamine pyrophosphate inhibitor was present in both urine and blood. Thiamine, 600 mg. per day has produced clinical improvement although optic atrophy has continued to progress. Levels of pyruvate and alanine decreased to near normal concentrations. In view of the primary defect in pyruvate metabolism in this child it is concluded that alanine and alpha keto glutarate are produced by a transamination reaction involving glutamate with consequent deflection from its role in the brain. A similar transamination between pyruvate and aspartate would produce oxaloacetate which is unstable for detection. These observations suggest a possible mechanism for the encephalopathy involving either nitrogen balance or deficiency of glutamate and/or aspartate in brain cells.

CHANGES IN URINARY METABOLITES IN AFFECTIVE DISORDERS IN CHILDREN
Donald H. McKnew, Jr., M.D. and Leon Cytryn, M.D. (Intr. by Robert H. Parrott, M.D.), Children's Hospital, Washington, D.C. and The Dept. of Child Health and Dev. (Psychiatry), George Washington Univ. School of Medicine, Washington, D. C.

In a preliminary study, 1 hypomanic and 8 depressed children ages 6 to 12 were studied during a 2 to 3-week hospitalization. Biochemical as well as behavioral data were collected. The urinary metabolites studied were: Norepinephrine (NE), Epinephrine (E), Vanillylmandelic acid (HVA), 3-methoxy 4-hydroxy-phenyl-ethylene glycol (MHPG), 17-hydroxycorticosteroids (17-OHCS), and 5-hydroxyindolacetic acid (5-HIAA). Significant deviations from normal controls were found in all the children. The metabolites most clearly affected include NE, VMA, and MHPG. The NE excretion was lower in 6 of our 8 depressed patients. The VMA was lower in 6 of our 8 depressed patients.

Our hypomanic boy and 2 children with reactive depression excreted more 17-OHCS than controls, while one chronically depressed child excreted less than controls. Two of our 4 chronically depressed children excreted less HVA than controls.

There were significant differences from normal controls of MHPG excretion in 4 of the 6 children in whom it was measured. Three of those children were chronically depressed and 1 was hypomanic.

Our conclusions were:

1. Changes in the excretion of urinary metabolites do occur in affectively disturbed children.
2. The metabolites most clearly affected include NE, VMA, and MHPG, although less frequently changes of the other metabolites studied, occured as well.
3. Changes are most clear-cut in children with chronic affective disorders in contrast to those with acute or masked affective states.

A Method of Clinical Staging of Reye's Syndrome. Lovejoy, F.H., Jr., Smith, A.L., Bresnan, M.J. Harvard Med. Sch., The Children's Hosp. Med. Ctr., Dept. of Ped., Boston. (Introduced by Dr. David H. Smith).

The current difficulty in the comparison of the severity of illness and efficacy of therapy in different experiences with patients with Reye's Syndrome suggests the importance of a system of clinical staging. The epidemic in 1971 of Reye's Syndrome stimulated a retrospective review of 40 children seen at this hospital with this diagnosis from January 1, 1968 to July 1, 1971. Our experience suggests that the clinical course passes through five stages, each of which correlates with a rostal-caudal progression of neurological symptoms. These include: Stage I - vomiting, lethargy, liver dysfunction, and a Type 1 EEG; Stage II - delirium, combativeness, hyperventilation, hyperactive reflexes, liver dysfunction, and a Type 2 EEG; Stage III - obtundation, coma, decortication, liver dysfunction, and a Type 2 EEG; Stage IV - deepening coma, decerebration, rostal-caudal progression of brain stem dysfunction, improvement of liver dysfunction, and a Type 3 or 4 EEG; Stage V - seizures, loss of reflexes, respiratory arrest, correction of liver dysfunction and an isoelectric EEG. The progression of physical and laboratory findings and modalities of therapy (decadron, mannitol, glycerol, exchange transfusion, gut sterilization) are correlated with the above stages. Illness confined to Stages I, II, and III is compatible with full recovery. Beyond Stage III, only death or a non-productive individual can be expected irrespective of the therapy used. In addition, a poor outcome is suggested by: a rapid passage through the first 3 clinical stages; the onset of seizure activity in Stage III; a presenting ammonia greater than 300 μg %; an elevated CSF pressure in Stage III; a prothrombin time in Stage III of 13 to 14 seconds longer than control; and a Type 3 EEG. Utilization of this system of staging should provide a basis for the definition of the patho-physiology of the condition and thereby the appropriate modalities of therapy. It should, in addition, permit a comparison of experiences with these patients at different centers.

UREMIC NEUROPATHY IN A CHILD, WITH MONITORING OF TRANSKETOLASE ACTIVITY INHIBITION, Melinda McVicar, Bernard Gauthier and Carl Goodman, Depts. of Pediatrics and Rehabilition Medicine, Downstate Medical Center, Brooklyn, New York (Intr. by Senih Fikrig).

Uremic polyneuropathy has not been reported in a child. A girl with chronic glomerulonephritis reached terminal uremia at the age of 11 years and developed peripheral neuropathy characterized by "burning foot" syndrome, sensory loss and severe weakness of the left leg, and bilaterally decreased nerve conduction velocities. Recovery was virtually complete after 8 months of intensive dialysis. Serial determinations of transketolase activity (TKA) inhibition by our patient's serum were performed. Transketolase is an enzyme which appears to have an important role in the maintenance of myelin sheaths and inhibitors of its activity have recently been detected in the serum of uremic patients. TKA inhibition by our patient's serum, initially high, returned to normal and clinical evidence of neuropathy disappeared at the same time (see Table).

TKA Inhibition (normal < 6.7%)	1/26/71 35.8%		3/5/71 34.8%		10/29/71 3.3%
Signs of Neuropathy	Right	Left	Right	Left	Right & Left
Hypesthesias	Absent	Severe	Absent	Absent	Absent
Light Touch	Normal	Absent	Normal	Decreased	Normal
Vibration	Normal	Normal	Normal	Normal	Normal
Ankle Jerk	Normal	Absent	Normal	Absent	Normal
Muscle Power (0-5)	5	3	5	4	5

These data and the postulated role of transketolase in the maintenance of myelin sheaths support the suggestion made by others that there is a relationship between TKA depression and uremic neuropathy.

ERYTHROCYTE PHOSPHOGLYCERATE KINASE (PGK) DEFICIENCY IN BROTHERS WITH ASSOCIATED NEUROLOGIC DISORDER. Dennis J. McCarthy, Alvin M. Mauer, Ronald G. Strauss, William N. Valentine, Donald Paglia, and Patricia Konrad. The Children's Hosp. Research Fndn., Cincinnati, and the Depts.of Med., Pathology and Ped., U. C. L. A. School of Med., Los Angeles.

In rare instances, an association of congenital hemolytic anemia secondary to erythrocyte enzyme deficiency and a neurologic disorder has been described. One such association, phosphoglycerate kinase (PGK) deficiency has been described previously in only one kindred in this country. It is thought to be a sex-linked recessive disorder. We have studied an additional kindred in whom two brothers are affected.

The two brothers, ages 17 and 19 years, have had a slowly progressive Parkinson-like neurologic disorder characterized by generalized resting tremor, hyperlardotic gait, dystonic posturing and persistent glabellar response. Also present were an expressive speech disorder and moderate mental retardation.

The patients had a hemolytic anemia of variable severity with hemoglobin values ranging from 6 to 14 gm% and reticulocyte counts of 1.6 to 34%. The red cells were normocytic and normochromic on blood smear. RBC half life by ^{51}Cr labeling was 8 days without evidence of splenic sequestration. Erythrocyte PGK activity was absent with increased amounts of the substrate intermediate, dihydroxyacetone, phosphate, and decreased amounts of ATP being found.

One brother and two sisters were normal and review of the family failed to reveal any additional instances of anemia or neurologic disorder.

ELEVATED LYSOSOMAL ENZYME ACTIVITIES IN CANAVAN'S DISEASE, Aubrey Milunsky, Julian N. Kanfer, Christine Spielvogel, Jacqueline M. Shahood, Harvard Med. Sch., Eunice K. Shriver Ctr., Children's Service, Mass. Gen. Hosp., Waltham and Boston, Mass. (Intr. by J.W. Littlefield).

Canavan's disease (spongy degeneration of the central nervous system) is an autosomal recessive fatal neuro-degenerative disorder with onset in early infancy. Widespread demyelination of the cerebral white matter and intense cortical vacuolation are the essential pathological features. A failure of myelin maturation has been proposed as the fundamental defect. An increase in cerebrosides in cerebral cortex with a reduction in all lipids in the white matter prompted this study of 10 lysosomal enzymes in cultured skin fibroblasts from 2 homozygotes, 3 heterozygotes, and 4 controls. All cultures and preparation of cell pellets were handled identically with particular attention to equal cell numbers, the same media, frequency of feeding and time and method of harvesting. The conditions used for the enzyme assays have previously been determined to be optimal for this laboratory. Cell pellets suspended in 0.9% NaCl were sonicated prior to assay in which 4-methylumbelliferyl glycosides or esters were used as substrates. Elevated activities were found for the enzymes shown in the table (mean values in mμ moles/mg protein).

	Pt.A.	Pt.B.	Heterozygotes	Controls (Range)
α-galactosidase	712	714	406	435 (347-544)
β-glucosidase	20	22	7.4	8.5 (2.8-16)
Xylosidase	2.3	2.5	1.2	1.5 (1.1-2.2)

α-mannosidase activity was reduced by 50% compared to controls and heterozygotes. α-fucosidase, β-galactosidase, acid phosphatase, β-glucosaminidase, arylsulfatase A and β-glucuronidase had comparable activities in all groups. Because of the wide range of activities noted in controls (and heterozygotes) the significance, if any, of some elevation in activity of 3 lysosomal enzymes in a non-storage disease is unknown.

BENIGN FAMILIAL MEGALENCEPHALY - Mark Platt and Andrea Nash, Dept. of Pediatrics (Neurology), Boston City Hosp. and Children's and Neurology Services, Massachusetts Gen. Hosp., Boston (Introduction by J.W. Littlefield)

Four unrelated megalencephalic children (head circumference well above the 97th percentile) with appropriate developmental milestones, unremarkable neurologic examinations, and normal intelligence were studied. Height and weight were within normal limits. All had one parent with similar megalencephaly, and some had other involved relatives as well. All of the megalencephalic relatives were of normal intelligence and neurologically intact, and were of no more than average height and weight. There appeared to be an autosomal dominant mode of inheritance in at least two of the families studied.

In these cases of benign familial megalencephaly, a family history and parental head measurements were useful in avoiding unnecessary, expensive or hazardous diagnostic procedures such as pneumoencephalography.

It has been pointed out in recent publications that megalencephaly implies disordered nervous system function. However, it is clear from our findings that increased head and brain size may be associated with either normal, superior, or inferior intelligence. No conclusion regarding intellectual potential should be drawn from head measurements alone.

EFFECTS OF PROLONGED MATERNAL HYPOXIA AND HYPEROXIA ON THE BRAIN DEVELOPMENT AND VASCULARITY OF NEWBORN RATS. Bijan Siassi, Feridoun Siassi and Carlos E. Blanco. (Intr. Paul F. Wehrle). Dept. of Pediatrics, Los Angeles County-USC Medical Center, and UCLA School of Public Health, Los Angeles, Calif.

In order to evaluate the mechanism of adaptation to prolonged intrauterine hypoxia-hyperoxia, 3 groups of 10 days pregnant Sprague-Dawley rats (gestation = 21 days) were assigned to control, hypoxia (10-11% O_2) and hyperoxia (50% O_2) environments until delivery and then removed to room air. Brain weight, body weight, hematocrit level and brain capillary density were measured. Using cortical landmarks, specific transverse section of cerebral cortex were employed for histological examination. Total number of cortical capillaries (vessels <μ) were counted under projection microscope (X285) in eight microscopic fields. At birth:

	Control (10)	Hypoxia (10)	Hyperoxia (10)
Body Wt. (g)	6.102 ± .376	5.750 ± .193*	5.394 ± .672*
Brain Wt. (g)	.239 ± .019	.257 ± .014*	.230 ± .021
Body Wt./Brain Wt.	.039 ± .003	.045 ± .002*	.043 ± .003*
Hct. (5)	42.70 ± 3.13	39.90 ± 4.14	41.50 ± 3.39
Vessel Count/(HPF)	10.04 ± .98	11.25 ± 1.26*	8.69 ± 1.61*

*p< .05; HPF = High power field (10) = No. of rats.

No significant difference in body weight, brain weight or cortical vascularity was present at one or two weeks of life indicating complete recovery. This study provides evidence for local adaptive mechanism in the developing rat brain in utero.

TROPOMYOSIN AND TROPONIN IN DUCHENNE AND MYOTONIC DYSTROPHY
F. Samaha, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, Department of Pediatrics and Neurology, Pittsburgh.

The proteins which render actomyosin calcium sensitive, tropomyosin (Tm) and troponin (Tn), were isolated and studied from seven normal, seven Duchenne dystrophic and two myotonic dystrophic patients. By sodium dodecyl sulfate acrylamide gel electrophoresis, the two Tm and four Tn bands from the dystrophic muscles had identical rf values to those obtained from normal muscle. The total amount of Tm and Tn per gram of dystrophic actomyosin was about one third that of normal. No abnormal protein bands were seen by electrophoresis of the dystrophic calcium regulatory proteins.

These studies show that there are no qualitative differences in molecular size between Tm and Tn proteins from normal and Duchenne and Myotonic dystrophic muscles. The quantitative decrease of Tm and Tn from dystrophic actomyosin probably represents a secondary alteration. Therefore, only the previously described abnormality of the sarcoplasmic reticulum remains as the likely primary abnormality in the Duchenne dystrophic contractile mechanism.

VARICELLA ENCEPHALITIS: DIAGNOSTIC AND PROGNOSTIC CLUES. Gerald A. Spunt, Avron H. Ross and Linda Rodriguez. Nassau County Medical Center, Department of Pediatrics, East Meadow, New York. (Intr. by P. J. Collipp).

22 cases of varicella encephalitis seen from 1965 thru 1970 were reviewed to find clues to early diagnosis, prognosis, optimal therapy. There were 11 cases of cerebellitis, 11 of cerebritis. Profile of cerebellitis: no mortality, onset 6.1 days after first rash, admission 1-3 days later; vomiting, ataxia, fever, lethargy; CSF with low normal protein, average 29 cells/mm^3; total WBC count 5 to 35,000/mm^3; usually complete recovery. Cerebritis resulted in 5 deaths (45%); onset 3.4 days after first rash. Comparison of fatal and surviving cases: The fatal were admitted earlier, within 2 days after onset; had frequent vomiting; trimethobenzamide used in 3, 1 of whom also received prochlorperazine; pulse pressures higher; dilated non-reactive or sluggishly reactive pupils; papilledema in only 1; stupor, disorientation, agitation, restlessness usual; positive Brudzinski's, Kernig's, Babinski's signs; nystagmus; higher hemoglobins; lower average blood glucose and HCO_3^-; hyperkalemia; lower ratio of blood/CSF glucose, no cells in the CSF (compared with average 58/mm^3 in survivors); CSF protein below normal range in all these as well as in survivors; no viral growth in CSF (or in survivors); death ½ to 26 hours after admission; no salvage with mannitol, corticosteroids, fluid restriction and hypothermia; post-mortem consistent with Reye's syndrome in 3 of 5; thymic hyperplasia in 3; interstitial pneumonitis in 3; cerebral edema in all; intracerebral hemorrhage in 3. Cytarabine therapy paralleled the reversal of signs and symptoms of severe encephalopathy in the one survivor whose course suggested a probable fatal outcome. Frequent vomiting is rare in uncomplicated varicella; vomiting and lethargy must be regarded as indicating encephalitis until proved otherwise; antiemetics are contra-indicated. Decreased CSF protein may be due to viral diversion of protein synthesis or to other alteration of formation, secretion, diffusion or dilution. Management must include drastic correction of electrolyte imbalance.

EFFECTS OF IMMEDIATE POSTNATAL FASTING UPON SUBSEQUENT BRAIN GROWTH OF RABBITS. Richard J. Schain, Kathy Watanabe and Shaul Harel. UCLA Sch. of Med., Dept. of Ped. & Neurol., Los Angeles.

The effects of a 48 hour postnatal fast upon subsequent brain development has been investigated in the rabbit. The rabbit is a "perinatal brain developer" in whom the peak of the brain growth spurt occurs during the immediate postnatal period. Newborn littermates were matched by birth weight and assigned to a fasting (F) or control (C) group. Both groups of animals were maintained in an incubator during the fasting period with the exception that the control animals were returned to the doe once daily for feeding. At the end of the three day period, both groups of animals were permanently returned to the doe. The control animals manifested normal growth patterns under these conditions. Control and fasted animals were sacrificed at 21, 38 and 60 days of life. The mean wet weights of the whole brains (gms.) were as follows: 21 days, F=5.1, C=5.3; 38 days, F=6.6, C=6.8; 60 days, F=7.8, C=8.2. Pair analysis revealed no significant difference at 21 or 38 days, but revealed a significant difference (p=0.025) at 60 days, suggesting a retardation of brain growth with advancing age. However, within the fasted group, the brain growth retardation varied according to the rapidity of body weight catchup to the growth curve of the control littermate. The body growth spurt of the rabbit begins at about 21 days of age. Those fasted animals whose body weight was 25% or more below the control littermate by the beginning of the growth spurt exhibited a mean 10% reduction of whole brain weight at 60 days of age. Regional brain areas were proportionately reduced in size. The fasted animals who rapidly caught up to controls revealed no difference in brain weights at the 60 day sacrifice time. We conclude that a postnatal fast adversely affects subsequent brain development only when body weight catchup does not promptly occur after the fasting period. This study suggests that an immediate postnatal fast plus a subsequent period of relative undernutrition are additive factors that operate together to retard brain growth in the rabbit.

OCCLUSION OF LARGE CEREBRAL ARTERIAL VESSELS (OLCAV) IN PATIENTS WITH SICKLE CELL ANEMIA. James Stockman, Michael Nigro, Mark Mishkin and Frank Oski. Univ. of Pennsylvania Sch. Med., Children's Hosp. of Philadelphia, Philadelphia, Pa.

The acute onset of central nervous system abnormalities, such as hemiparesis, in patients with sickle cell anemia is usually ascribed to the occlusion of small cerebral vessels. These interpretations have been based on clinical findings and meagre autopsy data and not from angiographic studies. In the past 2 years 6 patients with sickle cell anemia and neurologic deficits have been studied with cerebral angiography after reducing the level of sickle hemoglobin to less than 20% to avoid further occlusion by the injection of the hypertonic contrast material. In 2 patients no significant abnormalities were visualized and both patients made substantial neurologic recoveries. In the other 4 patients evidence of large vessel, rather than small vessel disease, was demonstrated and these patients have severe persistent neurologic impairment. Abnormalities included complete occlusion of left vertebral and bilateral occlusion of the internal carotid at the level of the supraclinoids in one patient; severe stenosis of one internal carotid artery at the level of the clinoid in 2 patients; and severe stenosis of the left anterior, middle cerebral and internal carotid arteries in one patient. The cerebral angiographic findings in these patients were indistinguishable from the "multiple progressive intracranial arterial occlusions" described by Tavares in patients without sickle cell anemia. Prospective studies will be required to determine if these abnormalities are of acute onset or are a consequence of a slow arterial occlusive process associated with sickle cell anemia. The possibility of OLCAV should be kept in mind in patients with sickle cell anemia and neurologic dysfunction because both therapy and prognosis are influenced by its presence.

HYPERKETONEMIA AND ANTICONVULSANT PROPERTIES OF THE KETOGENIC DIET IN YOUNG MICE. Edward R. Uhlemann and Allen H. Neims. The Johns Hopkins Univ. Sch. of Med., Dept. Ped. and Physiol. Chem., Baltimore.

Young (26-day), but not adult (50-day), mice that had consumed an 80% fat diet for 10 days exhibit statistically significant resistance to maximal electroshock and certain other induced seizures (J. Pharm. Exp. Ther., in press). In view of the cerebral utilization of ketones by suckling rat and the related ontogenetic pattern of pertinent enzymes (Page, et al., Biochem. J. 121, 49, 1971), studies were conducted to assess the relationship between hyperketonemia and the anticonvulsant character of the high fat diet. The degree of ketonemia achieved after 10 days of high fat sustenance was greater in young than adult animals (2.56 compared to 0.95 mM); mice on standard sustenance exhibited levels of 0.30 and 0.25 mM at the respective stages of life. In the 26-day old pups, resistance to induced seizures, as well as hyperketonemia, disappeared within 4-hours of replacement of high fat by standard sustenance. Nonetheless, other studies suggest that the relationship between hyperketonemia and anticonvulsant character, if causal, is complex and time-dependent. Hyperketonemia develops more rapidly than seizure resistance. Moreover, brief parenteral infusion of acetoacetate did not protect mouse pups, even when given following the brief exposure to standard sustenance after 10 days of high fat ingestion described above. We confirm, in mice, the ontogenetic organ pattern of D-3-hydroxybutyrate dehydrogenase in rats described by Page et al., which seems to favor cerebral ketone utilization in the young animal. No significant induction of the cerebral dehydrogenase coincident with high fat intake was detected. Certain future studies consider the possible effects of prolonged bulk utilization of anionic ketones as against neutral glucose by brain. Supported in part by grant NS-09232 from NIH and by the Epilepsy Foundation of America.

PULMONARY

SCANNING ELECTRON MICROSCOPY OF THE MAMMALIAN RESPIRATORY TRACT. Martha F. Greenwood and Phillip Holland, Univ.of Ky. Med. School, Dept. of Ped., Lexington, Ky.

Scanning electron microscopy (SEM) permits examination of the surface topography of the air conducting and air exchange segments of the respiratory system at the ultrastructural level. We have studied in detail the nasal cavity, trachea, main stem bronchus, distal bronchi and pulmonary alveoli of the mouse using SEM. Ciliated cells are the predominate cell type of the respiratory epithelium in the nasal cavity. These cells have 100-150 villous projections per cell which measure 5.5-6.5μ in length and are approximately 0.15μ in diameter. The epithelial surface of the non-ciliated supporting cells is covered by numerous microvilli. In the trachea and major bronchi the cilia are oriented in one direction and are approximately 4.5-5μ in length. Interspersed among the groups of ciliated cells are the supporting cells which are polyhedral in shape and variable in size. Their surface is characterized by microvilli which are approximately 0.1μ in length. Intercellular junctions are readily identified by the presence of a more compact arrangement of slightly longer microvilli. At the level of the distal bronchi the ciliated cells are diminished in number and the cilia are shorter. In this location the microvilli of the non-ciliated cells are not uniform in distribution, being sparse in some cells and numerous in others. In the periphery of the lung, the alveolar septae are seen as thin walled projections between the alveolar sacs. Looking into the alveolar sac, small openings are visible which represent alveolar pores. Capillaries with intraluminal erythrocytes are clearly outlined beneath the surface lining of the alveoli and alveolar septae. Alveolar macrophages are seen bulging into the alveolar lumen. This is the first characterization to our knowledge, of the total mammalian respiratory tract using the scanning electron microscope. The ability to study single cell surface topography and identify spatial orientation of varied respiratory cell types indicates the usefulness of this instrument in pulmonary disease investigation.

AN EVALUATION OF NIGHTLY MIST TENT THERAPY IN PATIENTS WITH CYSTIC FIBROSIS Nora Chang, Henry Levison, Douglas Crozier, Bernard Reilly, and Oswald Grosett, (Intr. by Andrew Sass-Kortsak) Dept. of Pediatrics, Univ. of Toronto, Research Inst., Hosp. for Sick Children, Toronto, Canada.

Nightly mist tent therapy has become standard treatment for patients with cystic fibrosis. Because there is little objective evidence to support this therapy, we undertook the following study. We examined 25 patients aged 6 to 32 years with cystic fibrosis whose pulmonary involvement varied from minimal to severe degree. The patients were studied for a four month period which comprised 2 months without mist tent therapy followed by a 2 month period during which the patients slept nightly in mist tents. Every 2 weeks the following studies were done: vital capacity (VC), timed vital capacity (FEV_1), maximal mid expiratory flow rate (MMEF), airway conductance (Gaw), the ratio of thoracic gas volume to total lung capacity (TGV/TLCp), diffusing capacity (D_{CO}), arterialized oxygen tension (PO_2), carbon dioxide tension (PCO_2) and the Shwachman clinical score. Results are

		VC*	FEV_1*	MMEF*	Gaw*	TGV/TLCp	DCO*	PO_2	PCO_2	Clinical Score
Out of	Mean	81.31	69.71	58.24	75.50	56.83	72.95	68.87	35.17	82.2
Mist	1SD	20.63	22.82	32.96	34.35	8.62	18.33	8.34	1.06	14.0
In	Mean	80.00	71.82	61.35	75.71	56.07	73.09	71.88	35.83	84.8
Mist	1SD	19.32	22.44	32.48	31.43	8.01	16.53	6.71	1.97	12.4

*Results are expressed as percent of predicted values

No measurement indicates statistically significant improvement with the mist tent therapy. Pseudomonus aeroginosa was isolated from the mist tent equipment of 2 patients during the time of therapy. The equipment of the remaining patients were free of pathogens. Thus we found no beneficial effect of mist tent therapy in Cystic fibrosis.

(Supported by a grant from the Canadian Cystic Fibrosis Foundation)

CERUMEN AND CERUMINOUS GLANDS IN CYSTIC FIBROSIS. Louis Kopito, Aaron Brand-Auraban, Gordon F. Vawter, and Harry Shwachman, Depts. of Ped. and Path., Harvard Medical School, The Children's Hospital Medical Center, Boston, Mass.

Cystic Fibrosis (CF) is a genetic disorder affecting many, and perhaps all exocrine glands, mucus producing and others. In some patients with CF the ceruminous apocrine glands located in the cartilaginous portion of the external ear canal have morphologically recognizable secretory abnormalities resembling those found in other glands. CF is one of the most common genetic disorders in caucasians but is rarely seen in mongolians.

Cerumen is a mixture of lipid-rich pigmented materials secreted by the ceruminous glands and the sebaceous glands. Normal fresh cerumen from caucasians contains about 50% water, 25% lipids, 12% proteins and 12% carbohydrates, electrolytes and contaminants. Cerumen appears in two phenotypic forms: the wet, and the dry believed to be controlled by a single pair of genes in which the wet allele is dominant over the dry. People of mongolian origin, including American Indians, characteristically have a high frequency of the dry allele whereas the wet allele predominates in caucasians. In the present study we compared cerum obtained from seven patients with CF and twelve controls and found statistically significant differences in the following:

Mean Values		Patients with CF	Controls
(1)	Quantity	8 mg	21 mg
(2)	Water Content	21%	54%
(3)	Zinc ug/g	118	1857
(4)	Magnesium ug/g	97	387
(5)	Calcium ug/g	254	1541

No significant differences were seen in the concentrations of Na, K, and Cu. Parts of the material in this presentation have been accepted for publication in Pediatrics.

DEVELOPMENT OF PULMONARY FUNCTION IN LATE GESTATION; MEASUREMENTS IN PREMATURE INFANTS. Gerald Lacourt and George Polgar, Université de Geneve, Dept. of Pediatrics (Switzerland) and Univ. of Pennsylvania, School of Med., Depts. of Pediatrics and Physiology, Philadelphia, Pa.

With recently modified methodology (J.Appl.Physiol. 32;No 4,1972) lung volume (FRC), airway conductance (G_{aw}) and lung compliance (C_l) was measured in 19 premature babies, including 2 sets of twins (gest. age: 25-35 weeks); and in 12 full term infants, including a set of twins and 1 small for date newborn.-FRC, ranging from 10 ml in the smallest (680 gm b.w.) to 123 ml in the largest (3350 gm b.w.) infant, was related linearly to gestational age, body length and weight. However, FRC increased at a greater rate, when related to weight, before 29 weeks gest., and when related to length, beyond 36 weeks. These discrepancies could be explained by varying growth rates of body length and weight, by discontinuous development of lung weight/volume ratio, and by an abrupt change in alveolar number per lung unit during gestation. Extrapolation of FRC revealed that zero lung volume would be present at 24 weeks gest., the accepted time for alveolization. - G_{aw} ranged from 0.014 to 0.071 L/sec/cmH_2O. Its linear relationship with lung volume in premature babies was similar to that in full term infants during the first weeks of life. The values in small for date and twin babies seemed more closely related to gest. age than to weight, i.e. lung growth surpassed growth of the whole body. The extrapolated conductance at zero volume was 0.01 L/sec/cmH_2O (airway resistance: 100 cmH_2O/L/sec). - C_l ranged from 1.2 to 8.6 ml/cmH_2O. Its relationship with body length, with gest. age and with lung volume was linear. The extrapolated intercept at zero C_l corresponded again to 24 weeks gest., or zero FRC. Specific compliance (C_l/FRC) was similar to that in infants, children and adults (0.056),for the group as a whole and also throughout the range of gestational age studied. - In 13 premature and 4 full term infants repeat measurements of pulmonary function were also made in order to compare postnatal development to gestational patterns of functional growth.

PHOSPHORYLCHOLINE-GLYCERIDE TRANSFERASE AND PHOSPHATIDYL METHYLTRANSFERASE OF HUMAN NEWBORN LUNG. Richard D. Zachman (Intr. by Stanley N. Graven), Univ. of Wis., Dept. of Peds., Madison, Wis.

The alveolar lining of normal lung contains lecithin, a surface active phospholipid. Lung extracts of human infants dying of respiratory distress syndrome have abnormal surface active properties and the phospholipid content of the lungs is significantly lower. Aspects of lecithin biosynthesis in human newborn lung tissue is being investigated indirectly by assaying the enzyme activities of various pathways. The activities and properties of phosphorylcholine-glyceride transferase and phosphatidyl methyltransferase, enzymes responsible for the final step in lecithin biosynthesis by the CDP-choline and trimethylation pathways, respectively, are reported here. A crude enzyme-phosphate buffer homogenate was prepared from human newborn lung samples removed at autopsy. Phosphorylcholine-glyceride transferase was assayed by incubating homogenate with $MgCl_2$, dipalmitin, and C^{14}-cytidine diphosphoryl choline, and the amount of C^{14}-lecithin synthesized per milligram protein per unit time was determined. Phosphatidyl methyltransferase was assayed by determining the amount of C^{14}-lecithin synthesized by the transfer of methyl-C^{14} from S-adenosylmethionine (methyl-C^{14}) to dipalmitoyl N, N-dimethyl phosphatidyl ethanolamine. The amount of product from each enzymatic reaction was dependent upon the amount of enzyme used, length of incubation, amount of respective radioactive precursor and was maximally active at 35-40°C. Phosphorylcholine-glyceride transferase required Mg^{++} or Mn^{++} for activity, and was inhibited by the non-ionic detergent used to solubilize the dipalmitin. Both enzymes were active in all human lung and liver samples assayed. Liver phosphatidyl methyltransferase was always more active than lung, while the ratio of lung/liver phosphorylcholine-glyceride transferase was variable.

BIOCHEMICAL ASPECTS OF PULMONARY OXYGEN TOXICITY.
Werner N. Keidel*, Louis Gluck and Marie V. Kulovich*, Univ. of Calif., San Diego Sch. of Med., Dept. of Ped., Div. of Perinatal Med., La Jolla.

Prolonged exposure to high O_2 tension causes profound morphologic and functional changes in the lung. This report describes progressive changes in surfactant phospholipids of 1 kg rabbits exposed to 90-100% O_2 for prolonged periods. The concentration of highly surface active (S.A.) lecithin in alveolar wash decreased with prolonged exposure. Changes in the fatty acid esters of the lecithin molecule also occurred. The two species of S.A. lecithin differing by the β carbon acyl ester are synthesized by separate pathways: (1) CDP-choline + D α, β diglyceride ⟶ dipalmitoyl lecithin (DPL); (2) ethanolamine phosphoglyceride + 3 CH_3 ⟶ palmitoyl myristoyl lecithin. Lecithin from both alveolar wash and lung homogenates had an initial increase in the % of 6 carbon myristate suggesting stimulation of the methylation pathway (2). With the onset of respiratory distress, acidosis and anatomic evidence of pulmonary edema, the % of β carbon myristate decreased. Loss of methylation activity with onset of acidosis correlates with previous work which demonstrated inhibition of methylation at low pH. DPL synthesis (1) as indicated by concentration of highly S.A. lecithin and acyl ester composition, decreased with prolonged exposure.

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EFFECT OF CONSTANT NEGATIVE PRESSURE ON LUNG MECHANICS IN IDIOPATHIC RESPIRATORY DISTRESS SYNDROME. Eduardo Bancalari, Otto Garcia and Mary J. Jesse. Univ. of Miami School of Med., Dept. of Ped., Miami, Florida
(Intro. by W. W. Cleveland)

Constant negative pressure (CNP) produces an increase in PaO_2 in most cases of Idiopathic Respiratory Distress Syndrome (IRDS). The mechanism by which this effect is obtained has not been elucidated. We studied eleven cases of IRDS treated with CNP in a range between 7 to 10cm H_2O. Mean PaO_2 prior to treatment was 52mm Hg while breathing 92% O_2. After 30 to 120 minutes of CNP, mean PaO_2 significantly increased to 146mm Hg on the same FiO_2. $PaCO_2$, HCO_3 and pH did not change significantly. In six newborns, tidal volume (TV) and esophageal pressure (EP) were determined simultaneously and lung compliance (CL) was calculated before and after 60 minutes of CNP. Functional residual capacity (FRC) was measured at the same time by the helium dilution technique. TV decreased from 17.83 ml to 13.17 ml while EP increased from 8.2 to 10.3cm H_2O after the CNP, resulting in a decrease of mean CL from 2.35 ml/cm H_2O to 1.4 ml/cm H_2O. Mean respiratory rate decreased from 87 to 79 per minute and minute ventilation from 1570 ml/min to 1069 ml/min. FRC increased from 17.9 ml/Kg of body weight to 24.1 ml/Kg. Specific compliance showed a decrease from 64 ml/cm H_2O to 31.6 ml/cm H_2O. In conclusion, CNP significantly increased PaO_2. This may be due to a decrease of intrapulmonary shunting secondary to the increase in FRC, resulting from expansion of previously collapsed alveoli. Lung Compliance and minute ventilation decreased. $PaCO_2$ did not change significantly suggesting that in spite of the reduction in minute ventilation no changes in alveolar ventilation occurred. This may be interpreted as a reduction in dead space ventilation, probably secondary to an augmented perfusion of ventilated areas.

TOXIC EFFECTS OF OXYGEN ON CULTURED HUMAN RESPIRATORY EPITHELIUM. Thomas F. Boat, Jerome I. Kleinerman, Avroy A. Fanaroff, and LeRoy W. Matthews, Case Western Reserve Univ. Sch. of Med., Depts. of Ped. and Pathology, Cleveland.

The effect of high oxygen (O_2) concentrations on epithelial cells lining human airways is unknown. Ciliated epithelium, maintained for 10 days in organ culture (Boat, Am.Rev. Resp. Dis., 1971) in the presence of 80,60, 40 and 20%±1% O_2 was compared by 1) daily microscopic detection of surface movement, 2) movement of carbon particles along the epithelial surface, 3) serial histological examinations, and 4) daily quantitation of macromolecules secreted into culture medium. Full length strips of trachea obtained within 100 minutes postmortem from 4 subjects who died in the early neonatal period, and fragments of surface epithelium from nasal polyps of 4 older subjects, were cultured in a high humidity environment. Tracheal and nasal epithelium exposed to 20% O_2 retained ability to transport carbon particles and secrete mucins for 10 days. Exposure of the same ciliated epithelium to 80% O_2 resulted in cessation of ciliary activity and particle transport after 3-4 days in culture. In 60% O_2 cessation of ciliary activity and particle transport did not occur for 6-7 days. In 40% O_2 some ciliary activity persisted, but focal areas of decreased motility and particle stasis were evident after 10 days. A variety of cellular changes were observed histologically in all explants. Initial observations suggest increased cell death, sloughing of surface cells and squamous metaplasia in the presence of 60-80% O_2. However, none of these changes were specific for high O_2. Release of total protein and lysozyme into medium was not significantly altered by high O_2. Incorporation of ^3H-glucosamine into secreted mucin by nasal epithelium decreased by 53-60% in the presence of 60% O_2, but only 37-42% in the presence of 40% O_2. Corresponding reductions in blood group titers were noted. These data suggest that O_2 concentrations of 40% and above decrease ciliary function and mucus secretion by cultured respiratory epithelium. Toxicity apparently is proportional to O_2 concentration and duration of exposure. O_2 therapy may similarly affect the mucociliary apparatus in vivo and impair this important defense mechanism of the lung.

PULMONARY FUNCTION DURING THE FIRST YEAR OF LIFE IN RECOVERING R.D.S.. M. Heather Bryan, Michael J. Hardie, Paul R. Swyer. Dept. of Pediatrics, Univ. of Toronto and The Research Inst., The Hosp. for Sick Children, Toronto, Canada.

The pulmonary function of 27 premature infants recovering from R.D.S. has been followed during the first year of life and compared to normal premature controls. Both ventilated and non-ventilated R.D.S. infants after the acute disease have a significantly lower F.R.C. (Helium dilution) than the normal $P < 0.02$. Following the first month most infants regain a normal F.R.C.. The exceptions are 4 babies who developed bronchopulmonary dysplasia (B.P.D.), in whom the F.R.C., 4.11 ± 0.77 ml./cm. length, became significantly larger than normal, 2.38 ± 0.37 ml./cm. length, after age 6 months. Dynamic compliance in recovering R.D.S. initially lower than normal, remains low in post ventilated infants up to 4 months of age (R.D.S. 0.106 ± 0.03; normal 0.136 ± 0.02 ml./cm. H_2O/cm. length). Dynamic compliance is markedly decreased in those who developed B.P.D. and it remains low at age 1 year (B.P.D. 0.110 ± 0.02; normal 0.224 ± 0.08 ml./cm. H_2O/cm. length). As there was marked frequency dependence of compliance, these low values probably indicate unequal time constants rather than true changes in elastic recoil. PaO_2 rapidly returns to normal in non-ventilated R.D.S., but the ventilated infants up to age 1 year are lower than normal ($P < 0.01$), particularly those with B.P.D.. $PaCO_2$ is elevated only in the latter. The slow return to normal of the dynamic compliance and arterial blood gases in ventilated R.D.S. indicates there is residual lung damage after the acute illness.

PULMONARY

Read by Title

VITAL CAPACITY IN RESPIRATORY DISTRESS. A.N. Krauss, D.B. Klain, J. Soodalter, P.A.M. Auld. Dept. of Pediatrics, Cornell University Medical College, New York City.

Atelectasis is the major lesion in hyaline membrane disease (HMD). Therefore an objective measure of lung volume should be of critical importance in evaluating the presence and treatment of HMD. Reductions of crying vital capacity (CVC) have been noted in HMD but never correlated with other parameters of pulmonary function. Thirty infants, 20 non-distressed premature infants, 6 with HMD, 4 with transient tachypnea of the newborn (TTN) underwent serial determinations of CVC, dynamic compliance, 1 second vital capacity (FEV_1), total pulmonary resistance, and functional residual capacity (FRC) by helium dilution. Birth weight ranged from 800 to 3940 grams. CVC correlated with length in centimeters (CVC=3.36L-104, r=.83, $p < .001$) and FRC (CVC=0.83FRC-4.86, r=.69, $p < .001$). Infants with HMD had reduced FRC and CVC. Infants with TTN had normal or reduced CVC but larger FRC than predicted. Only infants with TTN showed consistent reductions of FEV_1 below 80% of CVC. The CVC was measured in 70 additional infants, 16 of whom had HMD. No infant with CVC of over 0.6 cc/cm of body length required assisted ventilation. Eighty per cent of infants with severe atelectasis, as determined by a CVC of 0.4 cc/cm of body length or less, required assisted ventilation for acidosis, hypercapnia, or apnea. CVC is thus an accurate index of atelectasis and therefore 1) reflects the major lesion in HMD and 2) indicates the requirement for assisted ventilation. CVC is a rapid, reproducible means of estimating FRC at the bedside, and may also provide additional diagnostic and prognostic information in HMD and other syndromes of respiratory distress.

EFFECT OF PERITONEAL DIALYSIS ON ARTERIAL pO_2 DURING HYPOXIA. Platon J. Collipp, Michael A. Halle, Kenneth Kenigsberg, and Joan Bilder. Nassau County Medical Center, East Meadow, New York.

Because of several favorable responses to dialysis in children with respiratory distress syndrome of infancy and severe intractable asthma, we have investigated the changes in arterial pO_2 in hypoxic mongrel dogs and rabbits (New Zealand). Hypoxia was induced by underventilation in dogs anesthetized with barbiturate and curare maintained on a volume respirator. Oxygenated fluorocarbon emulsions, oxygenated blood, and 1.5% Dianeal^R were used as dialysis solutions. The increase in pO_2 in femoral artery blood twenty minutes after filling the abdomen with the solution were:

	pO_2	Range
oxygenated blood (8)	18	9 - 36
oxygenated fluorocarbon (10)	19	10 - 30
1.5% Dianeal (21 dogs)	19	11 - 30
1.5% Dianeal (12 rabbits)	17	5 - 40

Changes in position, external abdominal compression and changes in oxygen consumption did not account for the increase in pO_2. Coincident with the increase in arterial pO_2 the electrocardiogram improved, and blood flow through the carotid artery increased and femoral artery and vein decreased. The mechanism for the increase in pO_2 which occurs with dialysis is still not established, but the observation itself may have useful clinical application at present.

PHANTOM BREATHING IN MONITORED INFANTS. Neil K. Edwards, Harry C. Atherton, Paul H. Perlstein, and James M. Sutherland, Univ. of Cincinnati College of Medicine, Dept. of Pediatrics, Cincinnati, Ohio.

In this study it has been found that the reliability and safety of impedance apnea monitors is linked to voltage levels in the hospital power distribution system. When a hospital power distribution system does not supply adequate voltage levels apnea monitors may fail to function properly and falsely indicate that an apneic infant is breathing. Apnea monitors were randomly selected from a nursery in order to characterize the influence of power line voltage variations upon the proper functioning of the monitors. The power line voltages below which each of 5 tested monitors indicated false respiration were 103V, 105V, 97V, 108V and 100V. A 24-hour study of the line voltage in the nursery showed that the voltage was below 108 volts. Three of the five monitors tested would indicate respirations in an apneic infant under these line voltage conditions. The study was initiated because of the discovery of a dead infant who was attached to an apnea monitor that had failed to alarm and continued to indicate that the non-breathing infant was breathing 75 times/minute. This failure was caused by low power line voltage levels. The experience suggests the need for critical reappraisal of existing and proposed monitoring devices in the context of their "real-life" reliability. Studies such as this will hopefully create realistic standards and specifications guiding the application of this technology to patient care.

OXYGEN CHEMORECEPTORS IN LOW BIRTH WEIGHT INFANTS. A. N. Krauss, J. Brown, C. Tori, P. A. M. Auld. Dept. of Pediatrics, Cornell University, New York City.

Exposure to hypoxemia in early life has been shown to cause a lifelong diminished response to hypoxia. The age at which this occurs is not known. The present study was carried out to determine if premature infants had a blunted response to hypoxia, as suggested by the occurrence of apnea and periodic breathing, and if this could be accounted for by the normally occurring low Po_2 experienced by non-distressed premature infants. Fourteen premature infants (birth weight 880-2050 gms.) and 4 term infants under went serial study of chemosensitivity to oxygen. Minute volume (V_E) was measured in room air at thermoneutrality and compared with V_E in 10% O_2 and 100% O_2. V_E was measured only during the first 30 seconds of administration of the test gas to avoid secondary changes in Pco_2 and pH. All infants, including 4 weighing between 880 and 1460 grams at birth, showed increases in V_E in 10% oxygen and falls in V_E in 100% oxygen as early as the first day of life. Sixty percent of all tests resulted in a change in V_E of 25% or greater. Magnitude of response showed no systematic variation with age, weight, resting Po_2 in room air, or maturity. It is concluded that immaturity of oxygen chemoreceptors is not a cause of apnea, and that early hypoxemia does not result in blunting of the ventilatory drive in low birth weight infants born at sea level.

USE OF POSITIVE END-EXPIRATORY PRESSURE IN INFANTS WITH RESPIRATORY FAILURE. Thomas R. Harris, Dept. of Ped., Univ. of Arizona College of Medicine, Tucson, Ariz. (Intr. by Vincent Fulginiti).

Mechanical ventilation employing positive end-expiratory pressure (PEEP) with a volume respirator has found recent application in adult medicine in cases of respiratory failure (RF) involving inadequate oxygenation as well as insufficient ventilation. We have successfully used PEEP in newborns and young infants who could not be adequately oxygenated with intermittent positive pressure ventilation (IPPV) alone.

All infants in the series were placed on the respirator only after their arterial oxygen tension (PaO_2) dropped below 40 mm Hg while breathing 100% O_2. PEEP of between 8 and 12 cm H_2O was added only when the PaO_2 could not be raised above 60 mm Hg using IPPV with volume settings sufficient to maintain the $PaCO_2$ below 40 mm Hg.

The average fall in the alveolar to arterial oxygen gradient (P_IO_2-PaO_2), which quantitates the improvement in oxygen transport achieved with PEEP, was 180 or 30%. The time-course of this rise in PaO_2, and its fall after PEEP was discontinued, was studied in detail by frequent arterial blood gas sampling and by continuous PaO_2 monitoring with IBC in-vivo oxygen umbilical artery catheters. Greater than 50% of the total rise in PaO_2 is achieved within the first 30 minutes, and PaO_2 continues to rise after two hours. When PEEP is removed, the PaO_2 drops back to within 20 mm Hg of its original value with five minutes.

INCIDENCE AND CLINICAL CHARACTERISTICS OF CYSTIC FIBROSIS (CF) IN BLACK CHILDREN IN THE GREATER D.C. AREA. Lucas L. Kulczycki and Victoria Schauf, Children's Hospital of D.C., George Washington and Georgetown Universities, Washington D.C. (Intr. by Sanford Leikin)

CF has been reported in blacks so rarely that no incidence figures are known. As a consequence of surveillance of the black pediatric population of the D.C. area, 22 patients (11 boys and 11 girls) were identified since 1961 (6 retrospectively). From 1961-1970, a prospective study shows the incidence of CF in Washington D.C. to be 1 in 15,000 live black births. Reported incidence of CF among American white newborns ranges from 1 in 600 to 1 in 2400, or approximately ten times more.

Uncomplicated autosomal recessive inheritance best explains the equal number of males and females in the study, and the occurrence of CF in 22 out of the 66 children of the surveyed families. To determine whether this result is compatible with an autosomal recessive mode of heredity, we employed the percentage affected application of the binomial distribution, used earlier by Roberts. The apparent excess in the number of affected children in studied CF families is explained by the presence of unidentified heterozygous matings.

Clinically, most patients presented a combination of respiratory and intestinal problems, although a few had exclusively one or the other. Failure to thrive was noted at the time of presentation in 15 patients, respiratory complications in 14, steatorrhea in 10, rectal prolapse in 3, meconium ileus in 2. Clinical and pathological features of the disease are similar to those in whites.

The disease is still only rarely found in African blacks. This may reflect the lack of adequate studies, and/or genetic differences in African and American blacks because of inter-marriage with whites in the latter case. The initial failure to identify blacks with CF is not surprising in that CF was first studied in centers largely serving whites.

PULMONARY FUNCTION FOLLOWING CARDIO-PULMONARY BYPASS. William F. Howatt, Marvin M. Kirsh, E. Leeon Rhodes, P. Terrence O'Rourke and Michael Pryor. Univ. of Michigan Medical School, Univ. Hospital, Depts. of Pediatrics and Thoracic Surgery, Ann Arbor.

Changes in the lungs are thought to be one of the main causes of mortality and morbidity following cardio-pulmonary bypass during operative procedures. In order to examine changes caused by bypass alone, and to compare bubble and membrane oxygenators, pulmonary function testing was done on puppies before and immediately after total cardio-pulmonary bypass. Six control puppies had a thoracotomy only and were on a respirator for three hours. Seven puppies had cardio-pulmonary bypass using a bubble oxygenator for one hour. Seven puppies had bypass for one hour using the Pierce - General Electric membrane oxygenator and six were on this oxygenator for three hours.

In both groups which were on the membrane oxygenator there was a significant decrease in alveolar ventilation when compared with the control and bubble oxygenator groups. Right-to-left shunting increased in all groups on bypass with the largest increase in the three hour membrane group. Compliance decreased in all groups but the three hour control and three hour membrane groups showed the largest decreases. Carbon monoxide diffusion was decreased in all groups on the oxygenators but was least affected in the group on the membrane oxygenator for one hour.

It appears that a decrease in all aspects of pulmonary function occurred during the bypass procedure but that change in total compliance was mostly due to the thoracotomy. It is postulated that the difference in alveolar ventilation between the bubble and membrane oxygenators is due to abnormality of perfusion of the lungs. The membrane oxygenator, however, appears to cause less impairment of diffusion.

RELATIONSHIP BETWEEN AIRWAY CLOSURE AND ELASTIC RECOIL IN PATIENTS WITH CYSTIC FIBROSIS. Anthony Mansell*, Chagai Dubrawsky*, Arthur C. Bryan*, and Henry Levison, Dept. of Pediatrics and Anaesthesia, Univ. of Toronto, Research Inst., Hosp. for Sick Children, Toronto, Canada.

We have presented data showing that patients with cystic fibrosis had premature airway closure and suggested that this was due to loss of elastic recoil (Soc. Ped. Res. 1971). We have therefore measure quasi-static pressure volume curves in 12 patients with cystic fibrosis and compared these to the closing volume, measured by a modification of the single breath Fowler technique. We have also compared these measurements for normal children and adults. Our results show a highly significant correlation between static elastic recoil (at 60% TLC) and closing volume as a % vital capacity for both normals and patients with cystic fibrosis. Closing volume as % VC = 39.15 - 3.386 x $Pst_{(L)}$ cmH_2O at 60% TLC, r= - 0.91. It is clear that elastic recoil is a major determinant of airway closure in both normal individuals and patients with cystic fibrosis, and that loss of elastic recoil is responsible for the instability of small airways and thus early gas exchange failure in cystic fibrosis.

(Supported by The American and Canadian Cystic Fibrosis Foundations)

CEREBRAL HYPOXIA IN THE PATHOGENESIS OF HYALINE MEMBRANE DISEASE (HMD)

Gerald Moss, Arthur A. Stein, and Martin H. Greenberg (Intr. by Herbert S. Strauss)
Rensselaer Polytechnic Institute, Biomedical Engineering Laboratory, Troy, NY, and Albany Medical College, Departments of Pediatrics, Pathology, and Biochemistry, Albany

We demonstrated experimentally that the pulmonary pathophysiological features of HMD can follow a brief period of neonatal cerebral hypoxemia. We postulate that disturbance of cerebral oxidative metabolism (probably hypothalamic) leads to malfunction of the central autonomic control of the pulmonary vasculature, with increased venular resistance. This results in capillary hypertension and engorgement, interstitial and intra-alveolar edema and hemorrhage, "hyaline membranes", inactivation of surfactant and atalectasis.

We devised a benign cerebral perfusion technique, whereby the total cerebral blood flow could be delivered via a single cannulated common carotid artery. The experimental subjects were one day old calves (9) and piglets (3). The calves were anesthetized with sodium pentobarbital, but only local anesthetic was used for the piglets. Isolated cerebral perfusion was accomplished in each subject using mixed venous (atrial) blood as the perfusate (pO_2 approximately 25 mm Hg). Systemic blood pressure, pO_2, volume, flow, etc. initially remained in the normal ranges. Twelve control calves were perfused with arterial blood, pO_2 approximately 90 mm Hg.

All 3 piglets and 5 of the calves died during perfusion within 60 minutes. Indeed, 4 of the calves died within 20 minutes. The 4 calves surviving 1 hour of cerebral hypoxemic perfusion were sacrificed 2 hours later. All subjects demonstrated the gross and microscopic pathology of HMD ("hyaline membranes", edema, atalectasis, vascular engorgement, and hemorrhage). Pulmonary function was impaired prior to death. The control animals were long term survivors, with no functional or anatomical pulmonary changes.

THE USE OF AN EXTRACORPOREAL MEMBRANE OXYGENATOR IN PREMATURE LAMBS WITH HYALINE MEMBRANE DISEASE (HMD).

Jean-Pierre Relier, Hakan Sundell, Michel Dehan, Elsa Sell, Eugene Dolanski, Alex Tsiantos, Sten Swanstrom and Mildred Stahlman. Dept. of Ped., Vanderbilt Univ. Sch. of Med., Nashville, Tenn.

HMD is thought to be a self-limited process of 3 to 5 days duration, which, if death has not ensued, begins to improve. An extracorporeal membrane oxygenator might be useful in very severely ill infants to tide them over this critical time. A study has been designed utilizing a Sarns non-occlusive pump combined with a silicone rubber membrane developed by T. Kolobow, which has been demonstrated to have good diffusion properties for both O_2 and CO_2. Twin lambs with induced severe HMD have been delivered at 130 days gestation. One twin has been placed on the membrane oxygenator, the other used as a control and treated with buffers, O_2 and a Bird respirator. Venovenous pumping from SVC to umbilical vein or IVC has been used because of high output failure induced with arterio-venous pumping. Total ventilatory support has been possible with flows of 80 to 100 ml/kg/min. Large amounts of heparin have been necessary to keep the membrane from clotting, but because of bleeding problems in the lambs, regional heparinization has been attempted, monitored by clotting studies. All 8 control lambs have died first, with a mean survival time of 8 hours. Eight pumped lambs have also died, with a mean survival time of 30 hours. Major problems have been massive hemorrhage, severe hypotension, extravascular leakage of fluid and leaking artificial membranes. The longest pump survivor of 96 hours had subarachnoid hemorrhage and kernicterus at autopsy. Although the twin control which died at 05 hours showed severe HMD, the study lamb's lung showed only atelectasis with complete regeneration of Type II epithelium. It is thought that this may offer a support system for potentially fatal cases of reversible pulmonary disease in newborn infants.

PULMONARY CAPILLARY BLOOD FLOW IN PRETERM INFANTS WITH RESPIRATORY DISTRESS.

Richard L'E. Orme, Elizabeth A. Featherby, Henrique Rigatto and June P. Brady. Dept. of Pediatrics and Cardiovascular Research Institute, University of California, San Francisco, California.

We have adapted for sick preterm infants the technique for determining effective pulmonary capillary blood flow ($\dot{Q}pc$) described by Lee and Dubois. The infant rebreathes a mixture of 40% N_2O and up to 60% O_2 from a 100 ml bag for 40 seconds. The bag is enclosed in a 120 ml feeding bottle which is connected to a Krogh spirometer and the rate of uptake of N_2O is measured. Knowing mean alveolar N_2O concentration (measured at the nose), and the solubility of N_2O in blood, $\dot{Q}pc$ can be calculated. No blood samples are required. Studies can be performed on infants needing an F_IO_2 of 0.6 or less and are well tolerated. Blood gas determinations carried out before and after each study showed no significant change. F_IO_2, ECG, and ambient temperature are monitored continuously.

We studied 6 infants (B.W. 1060-2150 g) aged 17 hr to 44 days on 38 occasions. Five infants had IRDS, complicated in 2 cases by patent ductus arteriosus. The 6th infant had respiratory distress due to a pneumothorax. For the first 6 days of life mean $\dot{Q}pc$ was 108 ml/kg/min (SD±26). From the 7th to the 13th day it rose significantly to 185 ml/kg/min (SD±47), and from the 14th day onward to 203 ml/kg/min (SD±45) ($r=0.529$, $p<0.001$ for the power curve $y=110.6 \times^{0.171}$).

When ventilation/perfusion inequalities and shunting are present this method gives values for $\dot{Q}pc$ lower than the true pulmonary flow. Thus the rise of $\dot{Q}pc$ with age probably reflects improvements in overall pulmonary function as well as increased blood flow.

Measurement of $\dot{Q}pc$ by this method is a simple non-invasive procedure, suitable for use in an incubator. Our findings suggest that it may be a useful tool in the management of infants with respiratory distress.

TISSUE O_2 MONITORING OF INTERNAL ORGANS.

J. Strauss, R. Baker and A.V. Beran. (Intr. by W.W. Cleveland). Ped. Dept., U. of Miami Med. Sch., Miami, Fla. and Ped. Dept., Col. of Med. at Irvine, Irvine, Calif.

Oxygen sensitive bare wire electrodes eventually may be implanted in organs to monitor oxygenation during management of various types of shock. In the past we reported that: 1- in kidney, tissue oxygen (O_2a) during shock has earlier changes than central venous pressure; 2- in brain, O_2a changes are independent of arterial PO2 with hypoxic gas mixtures. This report comprises 10 rabbits studied before, during and after hemorrhagic shock of two hours duration. The following average results were obtained:

	ApH	PaO_2 mmHg	AO_2 Con. ml/ml	SKBF ml/min	SKO_2S ml/min	$SKVO_2$ ml/min	$C(O_2a)$ %	$P(O_2a)$ %
Control	7.37	86.9	.129	13.2	1.616	.333	100	100
Shock	7.16	105.5	.068	3.2	.217	.138	47	32
Re-inf.	7.26	88.4	.111	9.1	1.01	.349	124	132

Concomitantly with the acidemia there was a marked decrease in O_2 content (AO_2 Con.), blood flow (SKBF), O_2 supply (SKO_2S), O_2 consumption ($SKVO_2$), and O_2a (C=Cortex and P=Papilla) and an increase in PaO_2. It is concluded that during hemorrhagic shock renal O_2a closely followed the other renal or arterial blood measurements. This finding makes the O_2a wire electrode a potentially useful tool in the monitoring of patients during or after major trauma. Continuous and immediate supply of data directly pertaining to tissue oxygenation and even in the absence of blood changes makes this a desirable tool.

DEFICIENCY OF KALLIKREIN ACTIVITY IN THE PLASMA OF PATIENTS WITH CYSTIC FIBROSIS,

G. J. S. Rao*, Linda A. Posner*, and Henry L. Nadler. Department of Pediatrics, Northwestern University Medical School, Children's Memorial Hospital, Chicago, Illinois.

Saliva and serum of patients with cystic fibrosis (CF) contain "factors" which are unique to the disease (Mangos and McSherry, Pediatr. Res. 2:378, 1968; Spock et al. Pediatr. Res. 1:173, 1967; Bowman et al. Science 167:871, 1970). Rao and Nadler (J. Pediatr., in press) have recently reported that saliva of CF patients is deficient in trypsin-like activity and speculated that this deficiency explains the presence of the "Mangos factor" in saliva. Since trypsin-like activity resembles kallikreins in many of its properties, we have initiated studies of the kallikrein system in plasma of CF patients.

Citrated plasma samples from 15 normal adults (NA), 20 CF patients ages 3-15 years (CFP) and 20 age-matched controls (NC) were collected in siliconized tubes and treated with chloroform. The kallikrein in plasma was activated with ellagic acid and was assayed at 37° C using α-N-(p-toluenesulfonyl)-L-arginine methyl ester as substrate at pH 7.6 in the presence or absence of excess soybean trypsin inhibitor (STI). The results below are expressed as μmoles of substrate hydrolyzed/hr/ml plasma (Mean ± S.D.).

Kallikrein Activities	NA	NC	CFP
Total kallikrein activity	37.91 ± 15.09	37.09 ± 6.98	15.44 ± 6.37
STI inhibited fraction	25.74 ± 11.89	20.96 ± 5.73	8.62 ± 3.88
STI resistant fraction	12.17 ± 12.06	16.12 ± 4.96	6.77 ± 3.69

The differences in total kallikrein and STI inhibited fraction of controls and CFP were significant ($p<0.001$). The STI resistant fraction of NC was significantly different from CFP ($p<0.001$). In the few cases studied, heterozygotes had levels intermediate between controls and CFP. Kallikreins are known to be present in pancreas, saliva, sweat, urine, plasma and amniotic fluid. We have shown that CF patients are deficient in kallikrein activity in saliva and plasma. If generalized, this deficiency could represent a fundamental defect in cystic fibrosis.

THE PLASMA KALLIKREIN-KININ SYSTEM IN CYSTIC FIBROSIS.

Richard C. Talamo, Robert W. Colman, Aubrey Milunsky. Harvard Medical School, Children's Service and Department of Medicine, Massachusetts General Hospital, Boston.

Cystic fibrosis (CF) is a generalized disease of exocrine gland function. The kallikrein-kinin system is intimately associated with exocrine glands in a variety of ways, and may be involved in the control of their function. Several steps in the plasma kallikrein-kinin system have been examined in 6 patients with CF, using recently-developed biochemical and immunochemical methods.

The kinin-forming system was studied in 4 patients by measurement of arginine esterase activity before and during activation of citrated plasma by kaolin. Small amounts of free kallikrein (0.6-8.2 uM TAME hydrolyzed/ml/hr) were noted (nl 0-15); kallikreinogen, the precursor of kallikrein, ranged from 45.2 to 95.4 uM/ml/hr (nl 49-145).

Plasma bradykinin levels, determined by radioimmunoassay in all patients, ranged from 0.31 to 3.5 mug/ml (nl 0 to 3.0).

Total plasma bradykininase activity was studied by measuring the rate of destruction of intrinsically-labeled ^{14}C-2, 3-pro-bradykinin; peptide fragments were separated from intact bradykinin using ion-exchange columns. Bradykininase activity was equal in normal and CF plasmas. Potent bradykininase activity was found in lysates of both a normal and a CF fibroblast cell line from tissue culture, using similar methods.

No evidence has been found thus far of a severe abnormality of the plasma kallikrein-kinin system in CF.

FERTILITY IN MALES WITH CYSTIC FIBROSIS (CF). Lynn M. Taussig, Charles C. Lobeck, Paul A. di Sant'Agnese, Donald R. Ackerman, and John Kattwinkel, NIH, Bethesda, Md.; Univ. of Wisconsin, Madison; Univ. of California, Los Angeles.

Normal semen specimens were obtained from two unrelated CF male patients, both meeting all criteria for the diagnosis. One fathered children. Semen from Case #1 (age 26) revealed normal seminal volume, sperm count, sperm motility, morphology, pH, and citric acid and fructose concentrations. Case #2's (age 24½) semen also had a normal sperm count and seminal volume; he fathered two children. These findings are in contrast to the prevailing opinion that virtually all postpubescent males with CF are infertile.

The sterility found in most CF patients is due to aspermia and a low volume of ejaculate, secondary to abnormal, atretic or absent epididymides, vas deferens, and seminal vesicles (all mesonephric derivatives) (Denning et al., Pediatrics, 1968, and Kaplan et al. New Eng. J. Med., 1968). In aspermic CF patients semen is primarily derived from prostatic secretions as shown by its acidic pH, high citric acid and acid phosphatase content and conversely by the low or absent fructose (Rule et al., Fertil & Steril., 1970). The normal urinary tracts in CF patients indicate that when infertility occurs mesonephric development proceeds normally until the 10th to 12th week of gestation. Maldevelopment may occur at variable times thereafter in fetal life or even after birth and the variety and type of findings on pathologic examination suggest it may be secondary to obstruction of structures by abnormal secretions.

In summary, fertility occurs in a small but significant percentage of male patients with CF and it is mandatory, therefore, to evaluate the semen from all postpubescent males with CF prior to counseling.

MIST TENT EFFECTS ON VENTILATORY MECHANICS AND OTHER FACTORS IN CYSTIC FIBROSIS

William W. Waring and Frank L. Seleny, Tulane University School of Medicine, Dept. of Pediatrics, New Orleans and Northwestern University Medical School, Dept. of Anesthesia. Chicago (Intr. by Harry B. Shirkey)

The efficacy of nocturnal mist tent therapy was evaluated in 5 girls (4 with cystic fibrosis and 1 normal control). All subjects volunteered for a 5-week period of hospitalization in which the primary variable was aerosol exposure: Weeks I and V (child's own equipment, usually jet-type nebulizer-JTN) Weeks II and IV (ultrasonic nebulizer set to deliver 4 ml/min-USN), and Week III (no aerosol). Total water concentration in each tent was monitored nightly and varied between 18 and 33 mg/l in JTN tents and between 60 and 73 mg/l in USN tents.

Most standard tests of ventilatory mechanics, including analysis of forced expiratory and inspiratory flow-volume loops, were performed twice daily on each subject for the entire 5-week period. More than 3000 of these tests were thus generated for analysis. The means of 9 tests for each child for the 4 weeks during which she was receiving aerosol therapy (I, II, IV, V) were compared to those of Week III, when she was not receiving aerosol therapy in the CF patients 100 weekly means of pulmonary function were worse than the means for Week III (35 signif. at $P<.01$), whereas only 44 weekly test means were better (2 signif. at $P<.01$).

Many additional pulmonary function and clinical tests, including sputum volume with postural drainage, were systematically done, none of which altered the conclusion that in this study nocturnal mist tent therapy did not significantly improve pulmonary ventilation.

SOCIETY FOR PEDIATRIC RESEARCH

Plenary Session

THE GROWTH AND DEVELOPMENT OF NEWBORNS WITH KNOWN HEXACHLOROPHENE (HCP) LEVELS. M. Douglas Cunningham* and Nicholas G. Tsoulos*, Univ. of Calif., San Diego Sch. of Med., Dept. Of Ped., Div. of Perinatal Med., La Jolla, & Dept. of Ped., Naval Hosp., San Diego. (Intr. by Louis Gluck)

Recent experimental data with hexachlorophene (HCP) showing spongy degeneration of white matter in rats and monkeys and HCP blood levels in infants one third those of experimental animals led to precautions against HCP for total body bathing of infants (FDA Drug Bull.; Dec., 1971). However, no known CNS lesions in infants have been attributed to HCP used in nurseries for routine bathing. Serum HCP levels were measured in 80 infants, 10 of whom had prolonged intensive care with daily routine bathing 13 to 82 times with 3% HCP (pHisoHex®). Bloods were drawn from antecubital veins after careful skin preparation with acetone. Specimens were obtained at discharge and infants followed through sixth month for subsequent growth and development. HCP levels were assayed by gas/liquid chromatography and ranged from 0.11 to 3.44 mcg/ml. There was no correlation between serum levels of HCP, numbers of baths, body surface area, or age. Six high risk infants with prolonged bathing were at or above the third percentile for height, weight and head circumference at six months. Neurological examinations at discharge were normal in five. One infant had severe birth asphyxia with developmental and motor retardation also seen at six months. The remaining five at six months had normal Denver Developmental Screening Tests for post-conceptual age. On neurological examinations one infant had increased muscle tone, one had left esophoria, and one had increased muscle tone and increasing head circumference (97th percentile). High levels of HCP may be seen in infants with prolonged total body bathing and continued neurological and surveillance is necessary.

CELLULAR GROWTH CHANGES IN NEWBORN RATS EXPOSED TO PHOTOTHERAPY. Paul Y.K. Wu, Takashi Yoshida, Joan E. Hodgman, Bijan Siassi. (Intr. by Paul F. Wehrle). Dept. of Pediatrics, LAC-USC Medical Center and Univ. of Oklahoma Sch. of Med.

The effect of phototherapy on acute and long term growth of newborns has been questioned. Smaller gains in total body weight have been observed in newborn infants during phototherapy compared to controls. To assess the effects of phototherapy on growth at the organ and cellular level a controlled study was performed in newborn rats. Each of 6 litters of Sprague Dawley newborn rats was randomly divided into 3 groups at 24 hrs. of age, totalling 18 in each group. Each group was housed in transparent plastic cages with 2 mother rats. Group I was used as controls and did not receive phototherapy. Group II received intermittent phototherapy, 12 hrs. on and 12 hrs. off, for 96 hrs. Group III received continuous phototherapy for 96 hrs. Lights were mounted to permit exposure on all sides with intensity at animal level of 400 candlewatts. At 120 hrs. animals were sacrificed.

Mean body weight in Group II (9.19 ± 1.23 G) was significantly lower ($p<0.01$) than Group I (11.87 ± 1.21 G). Mean body weight in Group III (7.98 ± 1.23 G) was significantly lower ($p<0.01$) than Group II. Mean organ weights followed the same pattern with two exceptions. In Group II, the mean brain weight was similar to Group I while the mean weight of the liver was not different from Group III. DNA and protein content, protein/DNA ratio cell number and cell size were also significantly reduced ($p<0.01$) in Group II compared to Group I, and Group III compared to Group II with the same two exceptions as organ weights. Percentage of water and RNA content of the different organs were comparable in the three groups. Within the limitations of our experimental design, newborn rats exposed to light demonstrated reduction in cell number and cell size; differences in protein content suggest qualitative differences in the cells in the 3 groups. Further study is needed to assess the long term implications of these observed differences and to relate these findings to the human infant.

THE UTILIZATION OF MICROWAVE RADIATION IN DEVELOPMENTAL BIOLOGY RESEARCH. Robert L. Brent and Jack Wallace. Jefferson Med. Col., Depts. Ped. & Radiol. Phila.

Our laboratory has been interested in developing newer methods of interrupting pregnancy. As part of this program, commercially available microwave ovens have been converted to microwave generators so that the radiation can be directed with specially designed antennae and remotely controlled. The first series of experiments utilized pregnant rats on the 9th day of pregnancy. The animals were anesthetized and both uterine horns were mobilized. Microwave radiation (2450 megacycles) was directed toward one uterine horn, while the other uterine horn and the mother were shielded. The radiation flux was controlled in order to raise the temperature of the irradiated uterus to from 40°C to 49°C and for periods of time ranging from 1 min. to 30 min. Over 400 pregnant rats were utilized in order to determine the exposure time temperature combinations that result in a 100% interruption of pregnancy. Many combinations have been found to consistently result in resorption of the embryo: 48°C for 1 min.; 46°C for 5 min.; 45°C for 10 min., 43°C for 15 min. and 41°C for 30 min. Safety and feasibility studies reveal that animals exposed to 45°C for 10 min. are able to become pregnant in subsequent matings in the irradiated horn and that histological examination of the irradiated uterus reveals no obvious pathology. The ability to selectively raise the temperature of the mammalian embryo provides experimental opportunities beyond the possibility of developing a method of interrupting pregnancy that does not surgically violate the body. The techniques described here provide the opportunity to study drug metabolism and physiological responses at elevated temperatures. Preliminary studies indicate that the biological effectiveness of abortigenic and chemotherapeutic drugs are markedly increased by elevating the embryonic temperature. Thus, microwave radiation in combination with drugs may provide an even simpler method of interrupting pregnancy and in combination with drugs and/or radiation, a more effective treatment for malignancy. (NIH 70-2306; Travelling Fel.Roy.Soc.Med.)

INTRAUTERINE DIAGNOSIS OF SICKLE CELL ANEMIA AND THALASSEMIA. Yuet W. Kan, Andrée M. Dozy, Blanche P. Alter, Fredric D. Frigoletto and David G. Nathan. Children's Hosp. Med. Ctr., Boston Hosp. for Women, and Harvard Med. Sch., Boston, Mass. 02115.

Hemoglobin chain synthesis has been measured in human fetuses of 3 month gestation. The results show that such fetuses synthesize the β^A chain (Science 174,698,1971). To develop a potential method for intrauterine diagnosis of homozygous sickle cell disease and Cooley's Anemia, the following studies were performed. Cord blood of 8-10 cm fetuses produced at hysterotomy was incubated with ^{14}C-leucine and the globin chains isolated by urea-CMC chromatography. Radioactive γ β^A and α chains were demonstrated and the β^A conclusively identified by fingerprinting. β^S chains added to the hemolysate were widely separated from β^A and γ. Therefore absence of β^A and replacement with β^S (or β^C) would identify a fetus with SS or CC disease. In fact one mother had Hb C trait. Her fetus did not produce Hb C. A system was then designed to exclude maternal radioactivity from the hemoglobin mixture. Due to the active synthesis in fetal cells as little as 10% fetal blood in a total volume of 100 µl demonstrated fetal chain synthesis without a contribution by maternal cells. In addition, maternal chain synthesis can be measured independently and subtracted from the results of the mixture. Finally 20% fetal RBC were obtained accidentally at amniocentesis for Rh incompatibility. Incubation of these cells revealed the typical fetal synthesis of α, β^A and γ chains. We conclude that it is technically possible to establish the intrauterine diagnosis of SS disease by measurement of globin chain synthesis in mixed placental blood. The criteria for the diagnosis of Cooley's Anemia and the safety of aspiration of 100 µl of blood from a 1st trimester placenta must now be established.

RA27/3 RUBELLA VIRUS STRAIN: THE FINAL SOLUTION TO THE RUBELLA VACCINE PROBLEM? by Stanley A. Plotkin, John D. Farquhar, and Pearay L. Ogra. Wistar Inst., Dept. of Pediatrics, Univ. of Pa., Phila.; and Dept. of Pediatrics, State Univ. of N.Y. at Buffalo.

The policy of mass vaccination against rubella advocated in the United States is based on the assumption that herd immunity can be induced by HPV-77 or Cendehill vaccine strains. However, no evidence has been adduced for such immunity and studies of vaccinees have shown absence of nasal antibodies and high reinfection rates on challenge with wild virus. In this paper the evidence concerning RA27/3 vaccine strain, not yet licensed in the U.S., is reviewed. In comparative studies humoral immune responses to RA27/3 have exceeded those following inoculation of the other strains. For example, the mean HAI titers and neutralizing antibody titers postvaccination with RA27/3 have exceeded Cendehill vaccine by threefold in trials done throughout the world. Precipitating antibody responses to vaccination with RA27/3 differed from the pattern following Cendehill or HPV-77, but resembled that following natural infection. Titration of nasal antibodies to rubella virus revealed the following descending order of response: natural infection, RA27/3 intranasally (IN), RA27/3 subcutaneously (SC), and other strains subcutaneously. The presence or absence of nasal antibodies may be responsible for the observation in six separate studies of low reinfection rates on intranasal challenge with rubella virus of RA27/3 vaccinees (SC or IN). RA27/3 by either route was well tolerated by adult seronegative women. When given to Cendehill vaccinees, RA27/3 (IN) caused frequent increases in serum antibody, suggesting a specific utility of this strain for booster vaccination. Thus in a number of respects RA27/3 strain possesses the immunologic properties of natural virus.

BILE SALT METABOLISM IN NEWBORN INFANTS. J. B. Watkins, P. D. Klein, D. Ingall and R. Lester. (Intr. by R. Klein) Depts. of Med. and Ped., Boston Univ. Sch. of Med., Boston, and Argonne Nat. Lab., Argonne, Illinois.

Fat absorption is essential for neonatal nutrition. Bile salt plays a key role in micellization of fat, but nothing is known about the synthesis of bile salt in newborns. We, therefore, determined the cholate pool size and synthesis rate in full-term normal infants, 3-8 days of age. Cholate(CA) labeled by enolization exchange with the nonradioactive stable isotope deuterium, was administered by mouth. Bile salts were extracted from consecutive 24 hour fecal collections and from bile obtained by duodenal drainage. The isotopic abundance of deuterium, expressed as "atoms percent excess" (approximate equivalent of "specific activity" for radioisotopes), was obtained by GLC-mass spectroscopy-alternating voltage accelerator techniques.

Results: Secondary bile salts were absent from bile and feces. Consistent, regular curves of isotope dilution were obtained, indicating that excreted bile salt was replaced with newly synthesized(unlabeled)material. CA pool size was 12.8 $\pm$ 0.2 mg/Kg(mean $\pm$ SE) and the synthetic rate was 4.2 $\pm$ 0.4 mg/Kg/day. Chenodeoxycholate(CDCA) pool size, estimated from the CA/CDCA ratio in biliary drainage, was 4.1 mg/Kg and synthesis of CDCA, estimated from the CA/CDCA ratio in feces, was 0.85 mg/Kg/day.

Conclusions: 1) The newborn infant synthesizes bile salt in response to losses incurred by fecal excretion; 2) The newborn bile salt pool size and synthetic rate, while comparable to the adult on a weight basis, is markedly contracted on the basis of surface area and estimated liver weight. The absence of secondary bile salts, the contracted pool size, and synthesis rate suggest that bile salt metabolism in infants resembles that observed in germ-free or partially colonized animals. Moreover, the steatorrhea observed in newborn infants on formula diets suggests that the low synthetic rate and contracted pool may represent a "decompensated" state with inadequate bile salt available for complete lipolysis.

IMPAIRMENT OF PYRUVATE METABOLISM IN PHENYLKETONURIA. M.R. Sutnick, W.D. Grover, and M.S. Patel, (Intr. by V.H. Auerbach). Depts. of Ped. and Biochem., Temple Univ. Sch. Med. and St. Christ. Hosp. Child., Philadelphia, Pa.

In patients with untreated phenylketonuria (PKU), phenylalanine, phenylpyruvate, and other metabolites are found in abnormally high concentrations in blood and urine. Recently we reported that phenylpyruvate inhibited pyruvate metabolism via pyruvate carboxylase in rat brain mitochondria and in human brain homogenates. In clinical studies, we have found pyruvate and lactate, as well as phenylalanine and phenylpyruvate, to be elevated in plasma from untreated PKU patients. Levels of all four metabolites returned to normal after dietary treatment was instituted. Phenylalanine loading of both PKU and non-PKU children caused a marked increase in plasma pyruvate, lactate, phenylpyruvate and phenylalanine. After three hours, phenylpyruvate levels diminished, with a concomitant decrease in pyruvate and lactate. Blood glucose decreased during the time that phenylpyruvate was elevated returning towards normal as phenylpyruvate declined. Because of these observations and of the role of the liver in the maintenance of glucose, pyruvate, and lactate levels, we investigated the effect of phenylpyruvate on pyruvate utilization by human and rat liver preparations. The fixation of $H^{14}CO_3^-$ in the presence of pyruvate by human liver homogenates and rat liver homogenates and mitochondrial preparations was decreased in the presence of phenylpyruvate. The extent depended on the relative concentrations of pyruvate and phenylpyruvate; inhibitions of 50 to 80% were observed with equal concentrations of substrate and inhibitor. Furthermore, pyruvate carboxylase activity in human and rat liver preparations was also inhibited by phenylpyruvate. Phenylalanine had no effect on either system. Since pyruvate carboxylase is the first committed enzyme in the synthesis of glucose from pyruvate or lactate, its inhibition by phenylpyruvate may impair hepatic gluconeogenesis from three-carbon precursors. These observations suggest that abnormal pyruvate metabolism is an aspect of PKU. (Supported by USPHS Grants NS-10125, HD-05874, RR-75, RR-5624 and CB-416).

HYPOGLYCEMIA DUE TO FRUCTOSE-1,6-DIPHOSPHATASE DEFICIENCY AND THE TREATMENT OF TWO PATIENTS WITH FOLATE. Harry L. Greene, Fred B. Stifel and Robert H. Herman. (intr. by H. Peter Chase) U.S. Army Medical Research and Nutrition Laboratory, Denver, Colorado 80240.

Fructose-1,6-diphosphatase (FDPase) is a gluconeogenic enzyme which catalyzes the conversion of fructose-1,6-diphosphate into fructose-6-phosphate. Human jejunal FDPase activity increases with folate (15 mg). Thus, we studied the effect of folate in two patients with hypoglycemia and hepatic FDPase deficiency. Patient #1 (18 mo. old female) had persistant hypoglycemia for 9 months. Diazoxide, Hydrodiuril, Prednisone and subtotal pancreatectomy had not been effective in controlling her hypoglycemia. Patient #2 (26 mo. old female) had findings consistant with the diagnosis of ketotic hypoglycemia. Both patients became hypoglycemic (< 20 mg/100 ml) within 40 min. after an oral glycerol or fructose load (1 gm/kg). Jejunal and hepatic FDPase activity was deficient and fructose-1-phosphate aldolase, fructose-1,6-diphosphate aldolase and pyruvate kinase were normal. Treatment with oral folic acid caused 60% increase in hepatic FDPase activity in both patients. Patient #1 showed a significant increase in preprandial blood glucose concentrations and all other medications were discontinued. Although her blood glucose still remains abnormally low, severe hypoglycemia is rare. Patient #2 no longer developed hypoglycemia with the ketogenic diet even after ketosis was present for 36 hours. Both patients showed an improved ability to convert glycerol, fructose and alanine to glucose.

DEVELOPMENT OF B-LYMPHOCYTES IN THE HUMAN FETUS. A.R. Lawton, K.S. Self, S.A. Royal, and M.D. Cooper. Depts. of Pediatrics and Microbiology, University of Alabama in Birmingham, Birmingham, Alabama 35233

B-lymphocytes may be easily identified in blood and peripheral lymphoid tissues by the presence of membrane bound immunoglobulin (Ig) on the cell surface. These cells bind antigens and are the precursors of antibody-secreting plasma cells. The development of B-lymphocytes has been studied in eight human fetuses, aged 9.5 to 23 weeks. Suspensions of viable cells from liver, spleen, bone marrow, thymus, and peripheral blood were stained with fluorescine-labeled antibodies specific for μ, γ, and α chains to detect membrane-bound Ig. Cells from fetuses aged 11, 14.5, 15.5 and 23 weeks were stained following fixation to detect cytoplasmic Ig. A single IgM positive B-lymphocyte was found in liver at 9.5 weeks. Rare cells with μ or γ surface determinants were present at 11 weeks. Cells staining for α chain were consistently found at 11.5-12 weeks. By 14.5 weeks the percent of blood lymphocytes staining for each class was within the range found in 10 neonates and 29 normal children and adults. In agreement with other studies, cells containing cytoplasmic Ig were absent at 11 and 14 weeks; rare spleen cells were stained with antibodies to light chains at 15.5 weeks. An occasional IgM positive cell, and very rare IgG and IgA producers, were found at 23 weeks.

B-lymphocyte development occurs rapidly between 9 and 15 weeks gestation. The considerable lag between attainment of normal numbers of B-lymphocytes and onset of antibody synthesis may be explained by the antigen-sheltered fetal environment. The results help to define 2 stages of plasma cell development: antigen-independent differentiation of stem cells to B-lymphocyte clones genetically programmed to synthesize antibody of a given class and specificity, and a selective antigen-induced clonal proliferation and terminal differentiation to antibody-secreting plasma cells.

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