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ABSTRACTS

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1 *Hypersarcosinemia.* W. HAGGE, J. BRODEHL and K. GELLISSEN, Universitäts-Kinderklinik, Bonn, Germany.

It has been 2 years since GERRITSEN and WAISMAN first described hypersarcosinemia (Fed. Proc. *24:* 470 [1965]). These authors presumed a defect to metabolize sarcosine in the human organism which is caused by a deficiency of sarcosine dehydrogenase. We would like to present an additional case of hypersarcosinemia.

The patient, a boy, is the third child of an Indonesian couple. The parents are first grade cousins. Two siblings died early in infancy. On the third day of life, the patient developed slight jaundice, which lasted a few days. He also started to vomit and gavage feeding was necessary throughout the neonatal period.

At the age of 3 months he presented a marked hepatomegaly (4 cm) and spleenomegaly (6.5 cm). Otherwise the physical examination, routine blood tests and an EEG were within normal limits. A liver biopsy showed fatty metamorphosis. Column chromatography of the serum showed a large peak, which was identified as sarcosine (2.8; 5.6; 3.2 mg %). In addition the chromatography of the urine revealed a considerable excretion of sarcosine (77 mg/24 h). All other amino acids were within normal limits. Sarcosine and dimethylglycine loading tests were performed in the patient and the parents. After sarcosine load the propositus showed a rise in the serum sarcosine from 3.3 to 9.6 mg % within 3 hours. The father showed a maximum peak of 7.1 mg % after 1.5 hours and in the mother the sarcosine serum concentrations did not differ from curves of normal controls after sarcosine load. But both the father (165 mg/8 h) and the mother (103 mg/8 h) showed a marked sarcosinuria as compared with normal controls (18 mg/8 h) after a sarcosine loading test. We suggest that the parents react as true heterozygotes and that hypersarcosinemia is a recessive trait.

At the age of 8 months the patient presented a history of recurrent upper respiratory infections. The hepatospleenomegaly was unchanged, and there was no sign of mental retardation.

2 *Partial Galactose-1-Phosphate Uridyltransferase Deficiency due to Variant Enzyme.* RICHARD GITZELMANN, Laboratory for Metabolic Research, Pediatric Department, University of Zurich, Kinderspital, Zurich, Switzerland.

Galactosemia is characterized by a deficiency of galactose-1-phosphate uridyltransferase and inherited in an autosomal recessive way. Transferase activity of red blood cells of healthy heterozygotes (genotype Gt^+/gt) is approximately one half of normal persons (Gt^+/Gt^+). Recently, a second genetic trait affecting transferase activity was recognized by BEUTLER and named Duarte variant. Homozygotes for this trait (Gt^D/Gt^D) are healthy and have 50 % red cell transferase activity; heterozygotes (Gt^+/Gt^D) have 75 %. The traits for galactosemia and for the Duarte variant appear to be allelic. Carriers of both traits have approximately 25 % transferase activity.

Two cases with partial galactose-1-phosphate uridyltransferase deficiency are reported from Switzerland. Both individuals had approximately 25 % red cell transferase activity and were found to be carriers of both genetic traits (gt/Gt^D).

Case 1. A newborn infant was discovered by screening for hypergalactosemia using the metabolite inhibition assay of Guthrie. The infant was breastfed and thrived well. Elevated red cell galactose-1-phosphate returned to normal when the infant was given a galactose-restricted diet. *Case 2.* The mother of two galactosemic boys was identified as doubly heterozygous when parents of known galactosemics were examined for the occurence of the Duarte trait (reported gene frequency for a population in the western part of the USA, about 5 %; BEUTLER).

Transferase purified from red blood cells of both individuals had higher electrophoretic mobility than transferase from normal controls and thus resembled the Duarte variant enzyme.

Ref.: GITZELMANN, R.; POLEY, J.R. and PRADER, A.: Helv. paed. Acta (in press).

3 *An Inborn Error of Metabolism with the Clinical Picture of 'Neonatal Hepatitis'.* OYSTEIN AAGENAES, Children's Department, Rikshospitalet, Oslo, Norway.

Sixteen cases of 'neonatal hepatitis' are reported. All subjects were related and consanguinity was present in five of seven matings. The parents all came from the southwestern part of Norway. The children were jaundiced at birth or during the first days of life, and from this time on, acholic feces and dark urine were observed. The jaundice lasted from one to six years, and during this period the patients complained of severe itching. The other symptoms (bleeding tendency, rickets, anemia and growth retardation) were thought to be secondary to the presence of malabsorption since pronounced steatorrhea was observed.

Seven children died in infancy, at least five of these from hemorrhages. The introduction of vitamin K has changed the prognosis. No deaths from hemorrhages have been reported since vitamin K has been used regularly.

Laboratory examinations showed hyperbilirubinemia (conjugated bilirubin), increased transaminases

and alkaline phosphatase, hyperlipemia and increase in pre-β and β-lipoproteins, as well as slight decrease in albumin and increase in α_2-globulin.

Following the cholestatic period, growth of the children improves and as adults, height is normal. From prepuberty, all adult patients have had a severe tendency to edema in the legs. The cause of this is unknown. One or more periods of cholestasis have occurred in all adult patients. Liver histology shows 'giant cell hepatitis'; in the adult patients no progressive fibrosis is found.

An examination of the serum bilirubin patterns in the parents has shown an increase in conjugated bilirubin, compared with a control material. The pattern of inheritance appears to be that of an autosomal recessive characteristic.

'Hereditary, recurrent, intrahepatic cholestasis from birth' is proposed as the name for this new inborn error of metabolism.

4 *Relation of Severe Jaundice from G-6-PD Deficiency to the General Pattern of Neonatal Hyperbilirubinemia in the Population.* TIMOS VALAES and ARIS KARAKLIS, Queen Anna-Maria Institute of Child Health, Athens, Greece.

The incidence of G-6-PD (glucose-6-phosphate dehydrogenase) deficiency and severe neonatal jaundice was studied in the population of male newborns of the islands of Lesbos and Rhodes and in the Alexandra Maternity Hospital, representative of the general population of the southern part of Greece. The frequency of G-6-PD deficiency was 2.92 % in the population of Alexandra, 4.93 % in Lesbos and 12.5 % in Rhodes. The corresponding incidence of severe neonatal jaundice (S.B. over 16 mg/100 ml) was 1.14 %, 12.52 % and 3.42 %. Neonatal jaundice was not only much more frequent in Lesbos, but also much more severe in both the G-6-PD deficient and the normal newborns. The difference was mainly due to newborns who developed severe jaundice in the absence of incompatibility or prematurity.

In all surveys the incidence and severity of neonatal jaundice was significantly higher in the group with G-6-PD deficiency.

The results of the present surveys, as well as that from the literature, strongly indicate that the frequency of severe jaundice among the G-6-PD deficient newborns runs in parallel with the frequency of unexplained hyperbilirubinemia in the population. This suggests that icterogenic factors are operating in some places on the entire population and these factors, in combination with G-6-PD deficiency, produce even higher hyperbilirubinaemia.

Based on hematological and other data collected from the above surveys, we shall discuss the nature and mechanism of neonatal jaundice in G-6-PD deficient infants and those with unexplained jaundice.

5 *Blood pH in Acute Methemoglobinemia.* F. VARGA, Dept. of Pediatrics, University of Pecs, Hungary.

The behavior of arterial blood pH and its parameters has been studied in 14 young infants with acute methemoglobinemia. The disease had been caused by the high NO_3 content in the well water. All the infants were in the first trimenon. Only 30 % of the infants had diarrhea. In all of the infants pronounced metabolic acidosis was found, the lowest pH value being 6.98. This shows that in addition to anemic hypoxia, acidosis also played an important role in the clinical picture. The intravenous administration of methylene blue and vitamin C promptly abolished the anemic hypoxia and the characteristic gray color of the skin. However, with the intravenous administration of bicarbonate, the acidosis only became normal after 1–2 days. The blood lactic acid level was high, but the course of the load curve was normal. The value of lactic acid took longer to normalize than the blood pH. The exact mechanism of metabolic acidosis is not known at present.

6 *Fetal Hemoglobin in Twins.* G. WEIPPL, Universitäts-Kinderklinik, Vienna, Austria.

The average hemoglobin percentage in 120 newborn twins is 71.3 ($\pm$8.8). This is the normal average of cord blood. Average fetal hemoglobin percentage of monozygotic and dizygotic twins does not differ from this average, being 70.9 ($\pm$7.4) and 71.8 ($\pm$10.2), respectively. The average of the difference between the individual twins is 2.4 % in the monozygotic types and 6.8 % in the dizygotic types. The differnce of these two values is statistically significant (mean value difference D- and t-test), and the cause of this finding may be due to genetic factors.

Between dizygotic twins and randomly paired subjects (children from different families) there is no significant difference. Between twins with different birth weight (more than 500 g) there is the same difference as in other twin pairs, but it is highly different from the value of random pairs with the same differences in birth weight.

These findings support the concept that the percentage is dependent upon developmental and also genetic factors.

7 *2,3-Diphosphoglycerate Metabolism and Cation Permeability in Erythrocytes of Newborn Infants.* WERNER SCHROTER, Department of Pediatrics, University of Hamburg, Germany.

Washed red cells of newborn infants and adults were incubated in a buffered isotonic medium without substrate. During incubation the intracellular concentrations of 2,3-diphosphoglycerate (2,3-DPG), potassium and sodium, and the rate of hemolysis were measured. In both cell types there was only a low rate of hemolysis within 7 hours. The changes in the concentrations of cations were small, but 2,3-DPG decreased in erythrocytes of newborn infants to 10 % and in erythrocytes of adults to 50 % of the original level. Addition of either of the two sulfhydryl reagents, iodoacetic acid or ferricyanide, both of which attack the membrane (iodoacetic acid also inhibits glycolysis) did not affect the investigated parameters. The simultaneous addition of the two substances, however, caused marked alterations; within 5 hours the erythrocytes of adults lost 80 % of their potassium, sodium increased up to 600 % of the original level, and marked hemolysis occured. The influence on the decrease of 2,3-DPG was only minimal. In erythrocytes of newborn infants, both the potassium efflux and the sodium influx were lower than in erythrocytes of adults. Despite this, hemolysis occurred to a greater extent than in erythrocytes of adults, though the level of 2,3-DPG was not affected.

The experiments allow speculation that in the absence of the two sulfhydryl reagents, the efflux of potassium and the influx of sodium in newborn infants are independent of the concentration of 2,3-DPG. The effects of iodoacetic acid plus ferricyanide show that in erythrocytes of newborn infants, the membrane

of the remaining nonhemolyzed cells is less affected by these agents than the membrane of red cells of adults. On the other hand, with regard to the simultaneously occurring marked hemolysis, it is suggested that there might be two sorts of red cells in newborn infants, one of which is more sensitive to iodoacetic acid plus ferricyanide. (Supported by the Deutsche Forschungsgemeinschaft, Bad Godesberg)

8 *Suspension of Free Brown Fat Cells as a Tool for the Study of the Mechanism of Thermogenesis.* EVA RYLANDER, INGERT WILSON and OLOV LINDBERG. Wenner-Gren Institute and Kronprinsessan Lovisas Barnsjukhus, Stockholm, Sweden.

The function of brown adipose tissue (BF) as a heat-producing organ has only recently been realized. From the physiological point of view, this tissue differs from white adipose tissue in its capacity to oxidize internally liberated free fatty acids (FFA) and its lack of any major capability to release liberated FFA. The cells are extremely rich in mitochondria which upon stimulation with noradrenalin (NA) oxidize FFA almost exclusively. A lipase stimulated by NA supplies the mitochondria with FFA by catalyzing the hydrolysis of cellular triglycerides (Handbook of Physiology, section 5 [ed. RENOLD, A. E. and CAHILL, G. F.], Washington, American Physiological Society, Washington 1965).

By a modification of the Rodbell technique, single cell suspensions of BF have been prepared. This offers a new approach to the problems of induction and mechanism of thermogenesis. The cells might be suitable both to spectrophotometric and combined biochemical and ultrastructural studies. The cells are highly permeable and accessible to external influence.

In an earlier attempt to visualize the biochemical mechanism of nonshivering heat production, we have adapted the 'reesterification theory' to only involve the substrate level phosphorylation coupled to the oxidative decarboxylation of α-ketoglutaric acid. The theory was mainly based on our inability to demonstrate a significant electron-transport coupled phosphorylation in isolated mitochondria from brown fat (LINDBERG, O.; DE PIERRE, J.; RYLANDER, E. and AFZELIUS, B.A.: J. Cell Biol. [in press, 1967]). In the work to be discussed we have demonstrated that intact cells from BF are well suited for studies of ATP generation by means of 2-deoxyglucose and hexokinase as trapping agents according to MORTON and LARDY (MORTON, B. E. and LARDY, H.A.: Biochemistry *6:* 43 [1967]). The results confirm our proposed theory.

Further biochemical and ultrastructural studies in connection with the effect of NA on these cells will be presented.

9 *Cardiovascular Adjustments to Acute Hypo- and Hypervolumina During Exchange Transfusion in Newborn Infants.* O. CELANDER, L. S. PROD'HOM, N. FRENCK and J.E. SIGDELL, Clinique Infantile Universitaire, Hôpital Cantonal, Lausanne, Switzerland, and Div. of Applied Electronics, Chalmers University of Technology, Gothenburg, Sweden.

1. A new principle for volume recording in connection with plethysmography on newborn infants is described, by which displacements of water in the plethysmograph is picked up by a capacitive transducer. This has a variable sensitivity; if necessary, down to one microliter. It is supplied with a 'servo-control', which makes this system of recording possible to use on infants put in incubators under the sterile conditions of an exchange transfusion.

2. Changes of circulating blood volume have been induced in connection to exchange transfusions in full-term and premature infants. The fluctuations of the circulating blood volume have been up to ± 12.5 % of estimated initial blood volume.

3. During the course of the exchange transfusion the following parameters of circulation have been repeatedly measured: rate of arterial inflow to the foot and calf; the systolic arterial systemic blood pressure; the amplitude of the pulsatile volume changes in the extremity to the arterial pulse wave; and the frequency of the heart.

4. The results obtained uniformly follow the same pattern. Hypovolumia is counteracted and compensated for in its effects on cardiac performance and hemodynamic stability by a) A marked reduction of arterial inflow to the extremity by active vasoconstriction, most probably over sympathetic constrictor fibers. b) A reduction of the capacitance of the vascular bed in the extremity, which will enhance the venous return. c) A moderate to marked increase in heart rate, which will counteract a fall in cardiac output from reduced stroke volume at a decrease of diastolic filling.

5. The net result on hemodynamic stability is a small to moderate fall in systolic blood pressure in the systemic circulation, and most probably a lesser fall in mean arterial blood pressure. In general, hemodynamic stability is well maintained.

6. These findings strongly support the view that vasomotor reflexes from volume receptors or baroreceptors are quite active in the newborn infant. Most probably, they are tonically active already at basal conditions, from which plus or minus alterations on the heart and systemic circulation may be elicited by hypo- or hypervolumia.

10 *Demonstration of the Accumulation of Metabolites in Hypoxic Conditions of Premature Infants to Indicate the Gravity of the Disease. Therapeutical Trials with Peritoneal Dialysis.* D. BODA, L. MURANYI, M. BELAY, P. EBREY and E. ECK, University Clinic of Pediatrics, Szeged, Hungary.

The leading idea in our present investigations was that in hypoxic conditions over a certain phase the events would be determined by the metabolites produced in the course of the disturbance of oxidation and accumulating in large amounts in the body fluids. As another homeostatic factor, the metabolite accumulation would inhibit the vital processes taking place in the cell.

To demonstrate the accumulation of metabolites, the best suited for this purpose has proved to be the determination of Chemical Oxygen Demand (COD) that may be defined by the chemical destruction of the deproteinized blood serum. By another method used for this purpose we determined the activity of deproteinized serum with chemical oxidants on room temperature.

Both tests can be carried out, with parallels, in the Sanz microliter system, in 50 μ of serum. We compared the results with the data of clinical symptoms, of serum creatinin and of acid-base values obtained by Astrup method.

In cases of symptom-free, more or less seriously hypoxic but ultimately cured premature infants, in comparison with the cases having fetal outcome, the laboratory investigations showed that a correlation existed

between the metabolite accumulation demonstrated by the tests and the severity of the hypoxic complication. This in addition to pathological relations, points out that the laboratory tests mentioned may also be used for an objective evaluation of the severity of the affection.

In the course of further investigations we then argued that the fundamental hypothesis mentioned in the introduction may be considered proved true in case under experimental conditions the tolerance to hypoxia can be enhanced with dialysis. The experiments were carried out in newborn rabbits and adult mice.

We found that as a result of dialysis, the animals lived much longer than the controls, or did not perish at all due to the otherwise lethal hypoxic condition. This applies equally to the newborn animals and the adult ones.

In the light of the most convincing results of animal experiments, we have treated also a few premature infants by peritoneal dialysis.

11 *Effects of Hypoxia on Different Vascular Sections of the Isolated Kitten's Lung.* I. KJELLMER, Childrens' Hospital, Gothenburg, Sweden.

The isolated lung preparation from newborn kittens, perfused from an adult donor cat, was used as a model for studying the vasoconstriction elicited by hypoxia. The purpose of the investigation was to establish whether environmental changes, supposed to occur in the infant with idiopathic respiratory distress syndrome, could potentiate or counteract the hypoxic vasoconstriction.

To make a detailed study of the pulmonary vascular reactions both changes of vascular resistance and of the weight of the lungs were followed—the latter parameter revealing variations of lung blood volume as well as any edema formation.

Hypoxia provokes a vasoconstriction in this preparation that increases flow resistance and lowers regional blood volume moderately. Acidosis is in itself a vasoconstrictor, resulting in an increased flow resistance and a varying effect on lung blood volume. A severe degree of acidosis tends to induce edema formation. As has been demonstrated by others, acidosis strongly potentiates the hypoxic vasoconstriction. Hyperkalemia raises the vascular resistance and potentiates the hypoxic constriction also when the increase of the potassium concentration is too moderate to cause a constriction of its own.

Also, when pH and potassium concentration were compensated for, it appeared that the condition of the donor animal influenced the reactivity of the vessels in the isolated lung preparation. Thus both the hypoxic vasoconstriction and the vascular tone were augmented as the donor animal deteriorated. Therefore, the effects of catecholamines and corticoids were investigated. It appears that both epinephrine and norepinephrine in some preparations are potent constrictors both with regard to resistance and capacity functions. Unlike the situation in the systemic circulation, the constrictor response of the catecholamines is not abolished by hypoxia or acidosis; instead, a potentiation might be present. The possible role of corticoids as regulators of pulmonary vascular reactivity will be investigated.

12 *Acid-Base Pathways in Clinical Pediatrics.* KNUD ENGEL, Department of Pediatrics, College of Physicians and Surgeons, Columbia University, New York, N.Y., USA.

Acid-base measurements and interpretations of such measurements play an important role in the management of a variety of pediatric disorders. In an attempt to gain more information from acid-base data, our group has been investigating the quantitative displacement of the acid-base status of whole blood in a large number of patients with 'simple' (i.e., with a single etiologic disturbance) metabolic or respiratory disturbances. The criteria for the selection of such patients have been very strict so that patients with mixed disturbances and patients in a nonsteady state have been excluded. The results obtained, together with data from the literature (ALBERT, M.S.; DELL, R.B. and WINTERS, R.W.: Quantitative displacements of acid-base equilibrium in metabolic acidosis. Ann. intern. Med. *66:* 312 [1967]; ENGLE, K.; DELL, R.B.; RAHILL, W.J. and WINTERS, R.W.: Quantitative displacements of acid-base equilibrium in respiratory acidosis. Submitted for publication; KILDEBERG, P.: Respiratory compensation in metabolic alkalosis. Acta med. scand. *174:* 515 [1963]; A computer model for the *in vivo* CO_2 titration curve. Amer. Ped. Res., Atlantic City, N.J., p. 53 [1966]), have been statistically examined and regression equations expressing the expected degree of compensation to the primary acid-base disorder have been calculated. These regression lines, together with the 95 % confidence limits, can be graphed.

It is our belief that such studies may have clinical usefulness in assessing the degree of compensation. For example, 95 % of patients with metabolic acidosis and with a given low value for Base Excess should have values which fall in the shaded zone for this disorder, if they are making the appropriate degree of respiratory compensation. A patient falling outside the zone is a suspect for the presence of some factor interferring with maximal respiratory compensation.

13 *Dissecting Microscope Appearances of Small Bowel Mucosa in Childhood.* J.A. WALKER-SMITH, Kinderspital, Zurich, Switzerland.

The dissecting microscope appearances of thirty-six consecutive duodenal or jejunal biopsies from Australian children with the malabsorption syndrome or chronic diarrhea are described.

Three patterns were observed. Firstly, thirteen biopsies from coeliac children were characterized by a flat mucosa without villi. Five were completely flat, but the remaining eight had a pitted surface, divided by grooves, into irregular areas. Secondly, seven biopsies from six children with the malabsorption syndrome were characterized by thickened, blunt ridges. Lastly, sixteen biopsies from thirteen children, four with chronic diarrhea and the remainder with malabsorption, were characterized by broadly based leaf-like villi with occasional finger-like forms. These were histologically normal, except for two, with inflammation of the lamina propria.

The mucosa in the first two groups is abnormal. Although leaf-like villi are probably found normally in the duodenum of children, the dissecting microscope appearance of normal small bowel mucosa in childhood is uncertain. Thus, the significance, if any, of leaf-like villi in the jejunum is unknown. Using the technique of LOEHRY and CREAMER (LOEHRY, C.A. and CREAMER, B.: Postmortem study of small-intestinal mucosa. Brit. med. J. *1:* 827–829 [1966]) to examine the villous 'cores' of postmortem bowel may help elucidate this problem. The mucosa of a neonate examined in this way clearly showed long finger-like villi.

14 *Chronic Urinary Tract Infection and Levels of Immunoglobulins. A study of 278 Cases.* K. KOUVALAINEN, PIRKKO IMMONEN and K.V. PARKKULAINEN, Children's Hospital, University of Helsinki, Finland.

Gram-negative rods, above all *E. coli*, are known to be the most common cause of urinary tract infections. Antibodies to this group of bacteria reside mainly in the gamma-M fraction of immunoglobulins. Chronic urinary infection might thus, in single cases, reflect an impaired capacity to form gamma-M antibodies. On the other hand, prolonged antigenic stimulus from gram-negative rods is supposed to elevate gamma-M in patients with normal immunological capacity. In this study the levels of immunoglobulins of 278 children with chronic urinary infections were studied immunoelectrophoretically and by means of a quantitative agar plate diffusion method. The ages of the patients varied from 1 to 17 years. In the majority of cases anomalies of the urinary tract were regarded as primary causes of the infection. Most of the patients were receiving a long-term chemotherapy. Gamma-G was definitely elevated only in four cases and slightly below the normal level in two. Abnormally low gamma-A was observed in three patients. A low gamma-M was a common finding. In patients at 1–3 years of age, gamma-M was nearly unexceptionally below the normal mean value. Elevation of gamma-M was observed only on few occasions. No cases with a total lack of any of the immunoglobulins were seen. The high frequency of low gamma-M might indicate that the long-term therapy with sulfonamides, nitrofurantoin and antibiotics keeps the patient 'germ-free', thus resulting in decreased antigenic stimulation necessary for antibody formation. Whether this plays a role in the recurrence of the infection cannot be said with certainty.

15 *A Possible Metabolic Basis for Experimental Nephrosis.* J. METCOFF, Michael Reese Hospital, Chicago, Ill., USA.

16 *Comparison Between Functional and Morphological Studies of Nephrotic Syndrome in Childhood.* A. ROSENKRANZ, Kinderklinik der Stadt Wien Glanzing, Vienna, Austria.

A series of 18 children with clinical and biochemical signs of nephrotic syndrome was studied.

The usual biochemical examinations were performed in combination with examinations of the kidney function. Furthermore, a human albumin test was used. A 20 % solution of human albumin was injected intravenously, and the excretion of protein in the urine before and during the infusion was determined. The aim was to determine whether it is possible to judge the damage of the glomerular membrane by means of this test.

In all cases, morphological studies were made by renal biopsy. The results of the functional and morphological examinations were compared. It was found that there is no significant correlation between biochemical and functional results and the morphological findings. All tests can be normal, in spite of pathological changes of the morphological structure in the kidney biopsy.

It could be concluded that there is no correlation between functional and morphological findings in the nephrotic syndrome in childhood. It is believed that the response to glucocorticoid treatment is one of the best criteria as to the prognosis of this disease. The quicker and more intensive the normalizing effect of the hormone treatment, the better the long term prognosis seems to be.

17 *Type I Glycogenosis with Normal in Vitro Activity of Hepatic Glucose-6-Phosphatase.* J. BADOUAL and H. LESTRADET, Centre d'Etudes sur la Diabète et la Nutrition chez l'Enfant et Hôpital Herold, Paris, France.

A two-year-old boy had all the signs of the Type I glycogenosis, except for enzymatic deficiency as measured *in vitro*. The patient, the product of a nonconsaguine marriage, had vomiting from the first week of life and convulsions from the fourth month. Glycogenosis was diagnosed because of gross hepatomegaly and frequent attacks of severe hypoglycemia with sweating, loss of consciousness, and, occasionally, convulsions. These attacks occurred after fasting for three hours.

Ketonuria and mild acidosis were frequently observed. Parenteral injection of glucagon or epinephrine, galactose orally and intravenously and fructose orally did not cause any rise in the blood glucose level, but the blood lactic acid was increased. Oral and intravenous glucose tolerance tests were normal. The fall in the blood glucose level after fasting was not affected by tolbutamide or l-leucine. Fasting immunoreactive insulin was normal and a normal rise was seen after ingestion of glucose. Immunoreactive glucagon was normal. Human growth hormone level was high. Cholesterol, total serum lipids, NEFA, uric acid, cortisol, serum transaminases and aldolases levels in blood, as well as the urinary excretion of vanilmandelic acid, were high. The urinary excretion of amino acids was normal, and no renal anomaly was observed. Platelet function was normal.

Histochemical study of the liver showed increased glycogen content. Repeated studies (by Dr. H.G. HERS) of the enzymes involved in hepatic glycogenolysis, particularly glucose-6-phosphatase, revealed no abnormalities.

The further course of the disease was characterized by recurrent attacks of hypoglycemia and progressive deterioration of the psychomotor function, as well as increasing abnormality of the EEG. The growth was normal. High blood pressure and frequent respiratory infections were noticed.

The only effective treatment was feeding every three hours with glucose, maltose or starch, and a supplement of sodium bicarbonate. In case of anorexia or vomiting, hypoglycemia could only be avoided by intravenous administration of glucose. Prednisone caused a slight clinical improvement, but had to be discontinued because of untowards effects (enlargement of the liver, moon face and osteoporosis). Ephedrine, diazoxide, and zinc-glucagon had no effect and did not change the outcome of the function tests, except slight improvement of the oral tolerance tests.

To explain these symptoms which involve a functional block of the glucose-6-phosphatase, three hypotheses are put forward: 1. Isolation by *in vitro* assay of an enzymatic activity unlike the physiologic glucose-6-phosphatase; 2. presence *in vivo* of an inhibitor eliminated at the time of *in vitro* assay; 3. disturbance of one or several activation factors of glucose-6-phosphatase activity.

18 *Ethanol in Glycogen Storage Disease.* KLAUS ZUPPINGER and ETTORE ROSSI, Universitäts-Kinderklinik, Berne, Switzerland.

The effects of ethanol administration were studied in three subjects with glycogen storage disease: type I (lack of glucose-6-phosphatase activity); type III (lack of amylo-1.6-glucosidase activity); and one without demonstrable enzyme defect. The results were compared to the effects in two normal subjects.

Quantitative evaluation of ethanol oxidation during a rapid ethanol loading test showed that in type I disease, ethanol is oxidized approximately four times faster than in normals. In type I disease, prolonged infusion of a dose of ethanol, which was four times larger than a normal would be able to oxidize, maintained the increased rate of oxidation. In the subjects with type III disease and the unclassifiable type, ethanol oxidation did not differ from normal. The reason for this increased ethanol oxidation in type I, which is unique and seems to be specific for the type, is yet unknown.

During ethanol administration, the blood sugar remained essentially unchanged in the type I patients and in the unclassifiable type, but profound hypoglycemia appeared in type III. Free fatty acid levels were decreased in type I and the unclassifiable type but showed a large increase in type III. Lactic and pyruvic acid levels decreased moderately from elevated levels in type I, and increased in type III and the unclassifiable type. During intravenous ethanol administration, however, the elevated levels of lactic and pyruvic acid were almost normalized and remained low. Capillary blood pH was not improved in type I disease and remained unchanged in the unclassifiable type, but showed a severe metabolic acidosis in type III. This could be avoided when ethanol was given during a glucose infusion.

19 *Glycogenose généralisée simulant une dystrophie musculaire progressive chez un adolescent de 17 ans.* Etude clinique, enzymatique et en microscopie électronique de foie et du muscle. V. COURTECUISSE, Hôpital Parrot, Bicetre, France.

Cette observation concerne un garçon actuellement âgé de 17 ans qui présente une grande insuffisance musculaire globale avec amyotrophie extrême et insuffisance respiratoire grave ayant nécessité a deux reprises la mise en respiration assistée.

Les premiers symptomes sont apparus à l'âge de 4 ans sous forme d'une fatigabilité anormale. C'est seulement à l'âge de 14 ans qu'il nous est adressé avec le diagnostic de «myopathie». L'insuffisance musculaire est alors nette ainsi que l'amyotrophie prédominant aux racines des membres et au psoas. A ce stade, il n'y a pas encore d'atteinte respiratoire, ni cardiaque. L'électromyogramme montre une altération de type myogène. Le taux des enzymes sériques est élevé.

La biopsie musculaire (microscopie optique) montre de volumineuses vacuoles au sein de certaines fibres musculaires. Ces vacuoles contiennent parfois de masses basophiles denses. Sur cet aspect, le diagnostic de glycogénose est suspecté.

L'étude de la régulation glycémique ne montre aucune anomalie.

La lacticidémie monte normalement après effort sous garrot.

L'étude enzymatique (Professeur HERS) montre l'absence d'activité maltasique acide dans le muscle et une activité maltasique d'un type anormal dans le foie.

En microscopie électronique, on constate que la charge glycogénique est très variable d'un hépatocyte à l'autre. Certains sont manifestement surchargés en glycogène cytoplasmique. Mais on observe, fréquemment, des amas de glycogène à l'intérieur de sacs entièrement fermés par une membrane. Certains de ces sacs atteignent 2 à 3 microns de diamètre. Ces aspects correspondent à ceux qui ont été décrits dans le foie de la maladie de POMPE du nourrisson.

L'étude du muscle en microscopie électronique montre une très grande inégalité d'atteinte. En certains points, il existe une surcharge glycogénique diffuse avec importantes lésions des myofibrilles, dans d'autres zones, on observe comme au niveau du foie, des aspects de surcharge glycogénique «en sacs» de type dit «lysosomial».

Sur le plan clinique, la maladie a actuellement tendance à s'aggraver et l'apparition de signes cardiaques (tachycardie, souffle systolique) et de signes respiratoires, font redouter une évolution fatale à brève échéance.

20 *Pyrimidine Biosynthesis in Mammals During Development.* N. KRETCHMER, R. HURWITZ and A. GALOFRE, Stanford University School of Medicine, Palo Alto, Cal., USA.

For some years we have been investigating the *de novo* synthesis of pyrimidines as an approach to a comprehension of cell proliferation and differentiation. Pyrimidines are essential for formation of nucleic acids and are synthesized in the mammal from primitive compounds such as ammonia and carbon dioxide. Our studies indicate that the activity of aspartate transcarbamylase, the enzyme responsible for the first obligatory step, is much more active in liver and heart from the fetal rat than from the adult animal. We have studied the pathway by analysis of intermediate steps *in vitro* and have determined that the pathway of *de novo* synthesis of pyrimidines is physiologically active in fetal heart but not in maternal heart. In our experiments, fetal and adult liver do not utilize uracil. The formation of carbamyl aspartate from NH_3, CO_2 and ATP was observed with preparations of liver from rats 2 days of age, but less intensively with maternal liver. Fetal heart did not convert these simple compounds to carbamyl aspartate.

Recently, the chick embryo was utilized to facilitate studies of more immature tissues than could be obtained from fetal rat. The results of these preliminary investigations indicate that maximal activity of aspartate transcarbamylase of liver and heart is attained within 6–10 days of embryonic life. Since the heart is very large in the embryo, it is possible to make analyses as early as four days of embryonic life and the activity of the enzyme may be less than that attained at maximum (7 days). The data indicate that aspartate transcarbamylase is synthesized early in embryonic life, reaches a maximum, and then soon after hatching descends to an almost negligible value. Our future activities will be concerned with the major questions of whether the enzymes involved in *de novo* synthesis of pyrimidines are controlled by one regulatory gene, and whether as this gene becomes quiescent the entire pathway disappears at a rate equivalent to that of the degradation of each of the enzymes. The coordinate questions that we would like to answer and for which we have only preliminary data are: the intracellular localization of the pathway for pyrimidines biosynthesis and the time of appearance of salvage pathways.

21 *Observations of Radioactive Strontium and Probable Ca/Sr renal Preference.* G.C. ARNEIL, University of Glasgow, Scotland.

The advent of radioactive ^{89}Sr and ^{90}Sr focussed attention on biological implications of preferential calcium/strontium handling. Results obtained from 1400 children who died in Scotland and were investigated by us are available and show interesting age variability. Some observations on serum/urine levels of strontium/calcium are available through the use of activation analysis. Results indicate preferential calcium relative to strontium absorption by the renal tubules. A tentative difference of 3.4 % is suggested.

22 *Effects of Acidosis on Parathyroid Activity.* P. Cuisinier-Gleizes, H. Mathieu and P. Royer, Hôpital Bretonneau, Paris, France.

NH_4 Cl load in parathyroidectomized rats results in parathormone-like effects: increase of calcemia and phosphaturia, decrease of phosphatemia and tubular reabsorption of phosphates (TRP). In the normal rat it results in hyperphosphaturia and decrease of TRP but does not change either calcemia or phosphatemia. In both normal and acidotic-parathyroidectomized rats, calciuria increases rapidly. In acidotic parathyroidectomized rats, the exogenous parathormone maintains a hypercalcemic activity.

These findings suggest 1. a direct action of NH_4 Cl load upon tubular transfer of phosphates and calcium, and 2. a reduction in endogenous parathyroid hormone production in parathyroid-intact rats as a compensatory effect of acidosis on calcemia and phosphatemia.

23 *Is There a Hypervasopressin in Adrenogenital Syndrome?* M. Boulange, P. Vert, J. Cuillier and M. Pierson, Children's Departments A and B, and Hydromineral Metabolism Unit, Department of Physiology, University of Nancy, France.

Salt-losing in the adrenogenital syndromes has been carefully studied, but troubles of water metabolism have not attracted much attention, although they are well known in Addison's disease.

We sought existence of opsiuria in a 9-year-old girl with adrenogenital syndrome whose treatment had been stopped for 6 years.

The diagnosis was established during the first month of life, because of intersexual aspects of the genitalia, salt-losing syndrome, excretion of pregnanetriol; all patterns of C-21 hydroxylase deficiency. Free water clearance in the basal state was very negative (–1.386 ml/min/1.73 m^2) and was scarcely sensitive to the effect of a 20 ml/kg/water overload (–0.142 ml/min/1.73 m^2).

This trouble was successfully treated with DOCA (+0.458 ml/min) or cortisol (+0.455 ml/min/1.73), and was not made worse by 5 units of ADH (–0.155 ml/min/l). These findings suggested an excessive ADH activity. We investigated 5 girls and 2 boys presenting adrenogenital syndrome with a 21-hydroxylase deficit. Treatment was discontinued for one week to permit:

1. Free water clearance measurements with normal water intake, with a water load, with overhydration and with DOCA or cortisol.
2. Urinary ADH bioassay with Berde-Cerletti technics using ethanolized rats.

Results

In 6 of 7 patients studied, there was evidence of an important opsiuria, possibly corrected by DOCA or cortisol.

In 5 patients, urinary ADH levels were 31.7 m U/12 h/1.73 m^2 (Ts = 16.9) which was significantly higher than in normal subjects investigated at the same time (X = 13.5 m U/12 h/1.73 m^2; Ts = 10.7)

Discussion

After treatment, six patients seemed to present a permanent antidiuretic influence, with inability or strong difficulty to excrete 'free' water.

The antidiuresis is in relation with a hypervasopressinism.

The ratio osmolality/ADH output in the urine shows that the hypervasopressinism is partially inefficient.

We found no noticeable differences between the salt losers and the non-salt losers. This fact is an argument for unicity of 21-hydroxylation deficiency mechanism.

Our experimental results do not permit us to choose among the different hypotheses concerning this hypervasopressinism.

24 *Duchenne Dystrophy and the Transmission of Mental Defect.* Frederick Richardson and Scott Faulkner, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Md., USA.

One hundred years ago, Duchenne in his continuing observations on 'paralysie musculaire pseudohypertrophique' (Duchenne [1868]) abandoned reluctantly his original belief that every patient with pseudohypertrophic muscular dystrophy was also mentally retarded to some degree (Duchenne [1860]).

Since that time, there has been controversy, even contention, as to the relationship, if any, between Duchenne dystrophy and mental deficiency (Gowers, [1879], Erb [1891], Adie and Greenfield [1923], Walton and Nattrass [1954], Truit [1954], Worden and Vignos [1962], Dubowitz [1965]).

One year ago, a preliminary survey of families with one or more children with Duchenne dystrophy suggested that several possible modes of transmission existed (Richardson [1966]) and, although sporadic cases might be of average intelligence, the occurrence above and beyond random risk of mental retardation in male siblings with the disease, and the significant degree of mental retardation when this occurred, suggested that the retardation associated with the 'phénomènes morbides cérébraux' (Duchenne [1868]) was organic in origin.

As mental retardation may be due to many causes and occurs so frequently without associated specific features, the identification of modes of inheritance of a recessive trait in individual families is difficult. However, mild clinical manifestations in Duchenne dystrophy carriers and abnormality of the enzyme creatine phosphokinase have made this easier (Emery [1963]).

From our small series, the following modes of inheritance are suggested:

1. Duchenne dystrophy—sporadic without mental defect
2. Duchenne dystrophy—sporadic with variable degree of mental defect
3. Duchenne dystrophy in siblings with marked mental defect
4. Familial Duchenne dystrophy with marked mental defect appearing in different generations

Of particular interest is a family in the fourth generation where traits for Duchenne dystrophy and mental

retardation are segregated together and transmitted through the female carriers alone.

Recently, work by ROSMAN and KAKULAS (1966) suggests that significant cytoarchitectural abnormalities are present in the brains of retarded Duchenne dystrophy patients which are not present in intelligent Duchenne dystrophy controls, although accurate measurements of mental function were lacking. The precise relationship of such neuropathological findings to the transmission of mental defect in these families remains to be elucidated and raises further interesting questions.

25 *Etude clinique biochimique et ultrastructurelle de la maladie de Fabry chez l'enfant.* H. LOEB, Clinique de Médecine Infantile, Hôpital Saint-Pierre, Université Libre de Bruxelles, Belgium.

L'observation clinique concerne un garçon marocain de 12 ans présentant un amaigrissement important, des douleurs au niveau des poignets, des malléoles et de l'abdomen ainsi que de la fièvre avec céphalées, anorexie et vomissements.

L'examen clinique révèle, en outre, des lésions érythémateuses et élengiectasiques disposées en masque lupique.

Les tests inflammatoires sont fortement perturbés et le phénomène de Hargraves est positif. Il existe une hématurie microscopique.

Le diagnostic de collagénose de type lupus érythémateux diffus est posé, mais l'examen microscopique d'une biopsie rénale montre une accumulation de vacuoles d'allure lipidique.

L'hypothèse d'une dyslipidose de type Fabry est alors envisagée et divers examens sont entrepris en vue de confirmer ce diagnostic.

L'examen ophtalmologique décèle une lactescence diffuse des deux cornées, intéressant les couches profondes de l'épithélium cornéen. La spécificité des lésions oculaires nous permet, par silleurs, de relever l'atteinte de la mère, d'un frère et d'une sœur de notre malade; ces trois sujets sont asymptomatiques.

L'étude biochimique d'un fragment de foie montre la présence d'un glycolipide de type céramide-trihexoside. La chromatographie en couche mince scinde le glycolipide en deux taches, la séparation pouvant être due à des différences dans la composition des acides gras ou des glucides. L'identification des glucides par chromatographie en couche mince et sur papier révèle deux taches bien séparées, l'une, correspondant au glucose et l'autre, nettement plus importante, correspondant au galactose.

L'étude ultrastructurelle de fragments de rein, de foie et de rate prélevés chez le malade, ainsi que des fragments hépatiques prélevés chez le frère et la sœur présentant de lésions oculaires montrent la présence d'inclusions anormales au sein du cytoplasme des différents types cellulaires considérés. C'est au niveau des cellules épithéliales des glomérules que ce processus est le plus important, mais il est également manifeste au niveau des hépatocytes et des éléments constitutifs du système réticulo-endothélial.

Ces enclaves anormales sont poléiomorphes et limitées le plus souvent par une membrane unitaire. Leur contenu est hétérogène: Des amas osmiophiles, présentant l'ultrastructure typique des lipides complexes (en lamelles alternativement sombres et claires), baignent dans une matrice non imprégnable par les techniques habituelles, la nature lysosomiale de ces corps est probable. L'hypothèse d'un processus d'accumulation complexe, touchant à la fois certaines substances lipidiques et mucopolysaccharidiques peut être considérée.

26 *A New Glycolipid Storage Disease.* P. DURAND, M. PHILIPPART, C. BORRONE, and G. DELLA CELLA, Third Department of Pediatrics, G. Caslini Institute, Genova, Italy, and Antwerpen, Belgium.

A four-year study of two brothers delineated a new glycolipidosis. The patients (ages 3 years 9 months and 5 years), sons of healthy first cousins and with five normal brothers, presented a clinical picture of severe progressive cerebral degeneration, with increasing mental deterioration progressing to dementia and gradual loss of muscle strength; intense spasticity of the muscles; tremor and finally decerebrate rigidity. Enlargement of the heart, extrasystoles and electrocardiographic changes were also observed. Repeated respiratory disturbances and infections had been noted. The skin was thick and abundant sweating was present. Enlarged salivary glands were observed in only one case. The bodies of L_2 and L_3 were hypoplastic and beaked.

Laboratory studies showed cytoplasmic vacuoles in many lymphocytes. Chloride and sodium content of sweat was increased 3–9 times normal. A progressive inability of the gallbladder to concentrate dyes was demonstrated. Skin biopsy showed a diffuse connective tissue abnormality and anomalous accumulation of deposits of homogeneous, eosinophil, picrophil material between dermis and epidermis. Liver biopsy repeatedly showed hepatic cells containing abundant stored substance, producing the clear, swollen appearance of balloon or pseudogargoyle cells, only faintly PAS positive. Electron-microscopic examination of the liver showed many cytoplasmic, intravacuolar and mitochondria lipid inclusions (lamellar bodies).

The younger child died at the age of 3 years 9 months, and the other one at 5 years. Autopsy showed moderate hypertrophy of the cerebral hemispheres, cerebellum and optic thalamuses; the pallidum was of a yellow color; liver and heart with cloudy swelling; gallbladder was strawberry-like. At the brain level was noted above all a demyelination with a cellular tesaurosis; infiltration of the cardiac fibers, lungs, pancreas and spleen were evident.

Clinical analyses showed an accumulation in the liver of two unusual glycolipids, one of which was a ceramide tetrahexoside.

27 *Somatosensory Evoked EEG Responses in Newborn Infants.* A. HRBEK, Department of Developmental Neurology, State University Hospital, Groningen, The Netherlands.

Somatosensory cortical evoked responses accompanying monosynaptic reflexes were studied in newborn infants and also for comparison in several adults.

For analysis a computer of average transients (CAT 400 B) and Dawson's superimposition technique were used.

The stretching of a muscle which elicits the monosynaptic reflexes thus evokes at the same time distinct cortical responses. They are always present irrespective of what muscle or joint is stimulated.

The evoked responses are best expressed in the corresponding projection area; the contra-lateral central region. They consist of several waves and can be divided into an early and a late component. Both components show some differences in localization and behave differently during regular and irregular sleep.

In comparison with visual evoked potentials, there is no essential difference between the shapes of the responses in newborn infants and adults. Somatosensory responses differ only in latency and duration; therefore, the type of these responses is more mature.

The stimulus used, percussion of a muscle or a tendon, is a complex one. Several sensory modalities may be involved, but the described responses are most probably proprioceptive in origin.

Various applications of the evoked EEG responses in pediatrics and some methodical difficulties are discussed.

28 *Preliminary Evaluation of an In Vivo Model for Determining the State of Protein Metabolism.* CHARLES U. LOWE, W.B. WEIL, Jr. and ARTHUR L. KOCH, University of Florida, Gainesville, Fla., USA.

Nitrogen balance techniques have been developed as indirect ways of measuring rates of protein synthesis, though this method is open to a number of serious theoretic and practical criticisms. To avoid this, an indirect scheme has been examined; a mathematical model developed; and preliminary study in rats undertaken to evaluate the model.

The model assumes that although growth is characterized by constant change in body composition, at any moment in time an individual is in a relatively steady state. Under these circumstances, the rate of change in protein content is small and therefore the rate of synthesis may be considered constant. The metabolism of an amino acid during a steady state will be a function of net protein synthesis and the utilization of an essential or nonessential amino characteristic of the specific amino acid and a function of the steady state.

Data from study of two groups of rats, one fed a high protein (60 %) diet, the other a low protein (15 %) diet from the 21st to the 50th day of age, will be presented. They received uniformly labeled carbon 14 glycine and subsequently uniformly labeled carbon 14 tyrosine by intraperitoneal injection. Urine was collected for the first 24 hours after each injection and the excretion of isotopically labeled products measured. The relation between the excretion of the original isotope and its principle derivative provides indirect measurement of protein synthesis when subjected to mathematical analysis. The preliminary study suggests usefulness of this model for assessing protein anabolism.

29 *Studies on Familial Protein Intolerance.* M. KEKOMAKI, J.K. VISAKORPI, J. PERHEENTUPA, P. KUITUNEN and K. LAUNIALA, Children's Hospital, University of Helsinki, Finland.

Familial protein intolerance with deficient transport of basic amino acids is probably a recessively transmitted inborn disorder of amino acid metabolism, described in 10 Finnish children belonging to seven families. Clinically, it is characterized by a strong aversion to protein-rich nutrients, episodes of diarrhea and vomiting in infancy, hepatosplenomegaly, slight granulocytopenia and grave retardation of growth. Two typical findings for the biochemical derangement in this disease are: 1. impaired synthesis of urea from amino nitrogen, evidenced by hyperammonemia, high plasma amino nitrogen concentration and deficient rise in plasma urea level following an intravenous amino acid load; and 2. a deficient tubular reabsorption of basic amino acids especially of lysine. It has so far been impossible to explain the interrelation between these two defects. In contrast to the findings in other inborn defects of urea synthesis, the activities of the enzymes concerned in urea production in the liver, measured in conditions of substrate excess, do not differ significantly from those found in healthy children. Studies on the jejunal absorption of basic amino acids have revealed a subnormal mucosal concentrating capacity for arginine in familial protein intolerance, and the plasma arginine level is lower than normal. A lack of arginine in the organism cannot, however, be the sole explanation for the deficient urea synthesis, since supplementary arginine, although capable of abolishing the hyperammonemia, does neither produce a rise in plasma urea nor a fall in plasma amino nitrogen to the levels found in controls following an amino nitrogen load. Furthermore, as the patients have at least normal levels of plasma ornithine and citrulline, closer studies on liver urea synthesis have been initiated.

30 *Septic Granulomatosis.* W.H. HITZIG, H. PLUSS and R. RENNER, Department of Pediatrics, University of Zurich, Switzerland.

Recurrent infections in children are a major pediatric problem. Since the description of 'congenital agammaglobulinemia' (1952), several distinct deficiencies of defense mechanisms could be elucidated; of greatest importance are specific immune deficiencies involving either humoral or cellular mechanisms or both.

Since 1957, a group of boys was investigated in which all immunological reactions were found to be normal. They presented severe bouts of pyodermia, lymphadenopathy, hepatosplenomegaly and septicemia, which eventually led to death in the first years of life. The invading organisms are mostly saprophytes. The predominant tissue reaction is a granulomatous infiltration. The disease seems to be inherited by a sex-linked mode.

Studies of leukocyte activities by HOLMES *et al.* (1966) BAEHNER *et al.* (1967) opened the way for an understanding of the pathogenesis. Marked anomalies of the phagocytic mechanisms were demonstrated. The granulocytes of the patients are unable to digest particulate material although they ingest it rapidly; ingested bacteria are still viable within the white cell (HOLMES). Digestive activity is accompanied by increased glucose oxidation via the pentose shunt in normal granulocytes which is lacking in the patients. This can be demonstrated using a relatively simple color reaction (BAEHNER). The mothers were found to have intermediate values.

Summaries of 4 typical case histories will be presented. Two elder brothers of one of these patients had died in earlier years under similar circumstances; in one of them fairly detailed data are available. Of two other affected families we obtained detailed data. Extensive cytochemical investigations were carried out in 3 patients. In one living boy the phagocytic activity of the granulocytes was repeatedly found to be deficient, using the above-mentioned tests.

The study of this disease improves our understanding of normal defense mechanisms.

31 *Pharmacokinetic Studies with a Long-Acting Sulphonamide in Different Age Group Subjects (A Modern Approach to Drug Dosage Problems in Developmental Pharmacology).* F. SERENI, L. PERLETTI and E. MARUBINI, University Clinic of Pediatrics, 'G. e D. De Marchi', Milano, Italy.

Pediatric Research (in press).

32 *Serial Arterial pO_2, pCO_2 and Acid-Base Changes in Idiopathic Respiratory Distress Syndrome.* R. COOKE, B. FRIIS-HANSEN and M. LUNDING, Neonatal Unit and Department of Anesthesiology, Rigshospitalet, Copenhagen, Denmark.

In patients with idiopathic respiratory distress syndrome (IRDS) the fall in arterial oxygen tension while breathing 100% oxygen is an early index of the progression of the disease before hypercapnia and acidosis ensue.

By contrast, in atelectasis, the pCO_2 tends to remain at low levels, even at very low levels of pCO_2.

Serial measurements of the arterial oxygen tension is the best guide for the commencement of artificial ventilation which can reverse the biochemical changes and should be started before irreversible changes have taken place.

33 *Studying the Morquio's Syndrome.* P. DURAND, C. BORRONE and G. DELLA CELLA, Third Department of Pediatrics, G. Gaslini Institute, Genova, Italy.

There are no satisfactory criteria for the diagnosis of Morquio's syndrome; there appears to be some confusion whether this diagnosis is based only on clinical symptoms and not on biological criteria.

The heterogenicity existing in this group of Morquio's syndrome could be further elucidated by investigations at the cellular level; the definition of 'Morquio's syndrome' is to be reserved only for those patients with a demonstrable accumulation of mucopolysaccharides in viscera and with hypermucopolysaccharidurie and not for other cases of bone dysplasias with platyspondylia, unassociated with mucopolysaccharide metabolism troubles.

Our studies suggest that there are two forms of Morquio's syndrome, with hyperkeratosulphaturia and with hyperchondroitinsulphaturia B.

Recently we have studied a case of Morquio's syndrome, a patient, 5 years old, the first child of healthy first cousins (a sibling, a 4-year-old girl was healthy); he was a dwarf with a short trunk, characteristic deformities of the hip, pigeon breast and platyspondylia with tongue-like vertebrae, in which many of the symptoms of Hurler's syndrome were present as retardation of motor and mental development, corneal opacities, deafness, moderate hepatosplenomegaly and metachromatic granules in the leucocytes.

We have repeatedly searched in the urine the presence of mucopolysaccharides and we have found a hypermucopolysaccharidurie with increased amount of chondroitin sulphate B (by chemical, electrophoretic and infrared spectroscopic investigations).

Epidermal cells and dermal fibrocytes from biopsy specimens showed clear cytoplasm and small nuclei. These cells contained abundant stored substance producing the clear, swollen appearance, that histochemically, because of alcianophilia at pH 2.5, hyaluronidase resistant, and because of the negative reaction with alcian yellow stains and metachromasia at pH 4.5 would consist of chondroitin sulphate B.

Our patient, therefore, showed an increased intracellular content of chondroitin sulphate B, a mucopolysaccharide which is normally found in the skin.

Separation of Morquio's syndrome into at least two groups is mandatory for clinical understanding and biochemical counselling.

34 *Gastric Secretion in Early Childhood.* P.A. KRASILNIKOFF, P. RODBRO, and P.M. CHRISTIANSEN, Department of Pediatrics and Medical Department F, Glostrup Hospital, and Surgical Department A, Bispebjerg Hospital, Copenhagen, Denmark.

The gastric secretion of acid and intrinsic factor was studied after stimulation with 40 microgram histamine diphosphate per kg body weight in 18 children (aged between 9 and 30 months), without gastro-intestinal disorders.

As in adults the secretory patterns after stimulation showed for acid, a sustained response; for intrinsic factor, a wash-out response. The maximal concentrations of both components were about half of those found in healthy adults.

The stimulated hourly output of acid varied between 0.27 and 3.73 mEq, and was related to age, body weight and body surface area. The stimulated hourly output of intrinsic factor varied between 1050 and 3965 units and was also related to age, body weight and body surface area.

Acid and intrinsic factor are both products of the parietal cell. The present results indicate a dissociation in the parietal cell function in the first years of life, as the secretion of intrinsic factor is more mature than the secretion of acid.

35 *Autoimmunity in Ulcerative Colitis.* R. LAGERCRANTZ, S. HAMMARSTROM, and P. PERLMANN, Karolinska Sjukhuset, Stockholm, Sweden.

In sera from patients with ulcerative colitis an increased incidence of elevated autoantibody titers against colon antigen(s) has been demonstrated. These titer values are not elevated in patients with bacillary or amoebic dysentery, Salmonellosis or ulcerous cancer coli. The autoantibody titers in ulcerative colitis do not correlate with clinical factors such as extent of colon lesions, duration or severity of disease or presence of extracolonic symptoms. Pancoloproctectomy does not seem to influence the titer levels. Lymphocytes from patients with ulcerative colitis have cytotoxic effects on fetal human colonic mucosa cells grown *in vitro;* sera have not. The colon antigen is a mucopolysaccharide related to but immunologically distinct from blood group substances A and H. The autoantibodies are preferably found in 19S—immunoglobulin and to lesser extent in 7S.

The colon antigen from man, rabbits and rats cross-react. Immunization of rats and rabbits with homologous and heterologous colon antigen in Freund's complete adjuvans provoked autoantibodies against colon. The colon antigen cross-react with a bacterial antigen from *E. coli* 0.14. The incidence of elevated autoantibody titers against colon is higher among relatives of patients with ulcerative colitis than in the general population.

Autoimmunity in ulcerative colitis might possibly be provoked by immunization (infection) with a bacterial strain cross-reacting with colon antigen(s) which in predisposed individuals breaks the natural tolerance. This might possibly be of importance in the pathogenesis of the disease.

36 *Urinary Excretion of Tryptophan and Tyrosine Metabolites by Premature Infants.* D. NICOLOPOULOS, N. MATSANIOTIS and A. AGATHOPOULOS, Pediatric Clinic of Athens University, Agahia Sophia Children's Hospital, Athens, Greece.

It is well known from the work of LEVINE, GORDON *et al.* that tyrosine and phenylalanine metabolism is

impaired in the premature infant. Preoccupation with maintenance of biochemical homeostasis in the treatment of prematures and renewed interest in tryptophan, tyrosine and phenylalanine metabolism by the newborn prompted us to this study of urinary excretion of tryptophan and tyrosine metabolites by 11 full-term and 12 premature infants on their 1st day of life and 9 full-term and 11 prematures on their 15th day of life. Metabolites from all three main catabolic pathways of tryptophan were detected in both groups of infants. The main differences between full-term and prematures were a) 5-indole-propionic acid was found only in the urine of full-term infants on the first day of life; b) 3-indoleacetic acid was not found on the 15th day of life in the urine of full-term infants; and c) on the first day of life the urine of 10–20 % of prematures contained 5-OH-tryptophan, indoxyl-acetyl-glutamine and 5-OH-anthralinic acid. On the 15th day of life the number of metabolic products was decreased, probably because tryptophan was now incorporated in proteins.

Twenty phenolic acids were observed in both groups of infants, but their excretion varied a great deal. Homogentisic acid was excreted in the urine of half of the full-term infants on the 15th day of life, but not on the 1st day of life. The appearance of this acid in the urine of some full-term infants on the 15th day of life is suggestive of the maturation of the enzymes functioning in the main metabolic pathway of tyrosine via homogentisic acid.

The 24-hour urinary metacatecholamines and vanilmandelic acid (VMA) were also determined in the same premature and full-term infants. Variations of excretion of VMA generally followed those of metacatecholamines, but the excretion of VMA by the prematures on the 15th day of life was 4–5 fold that of the 1st day. In contrast, a moderately decreased VMA excretion was noted in the urine of full-term infants.

We are inclined to believe that the observed differences in metacholamine and VMA excretion are due to the delayed maturation of 3-O-methyltransferase and monoaminoxidase, the enzymes responsible for the metabolism of catecholamines to VMA. But the marked increase in VMA excretion on the 15th day by the prematures has to be attributed to an 'overmaturation' of the last enzyme or to other factors.

37 *Acid-Base and Electrolyte Changes During Exchange Transfusion in the Newborn.* Francesca Severi, C. Belloni and G. Rondini, Pediatric Clinic of the University of Pavia, Italy.

Twenty-six newborn infants (eighteen full-term infants and eight prematures) requiring exchange transfusion have been included in this investigation. Citrated blood was used. 1 ml of calcium gluconate was added to every 100 ml of blood in 9 full-term infants and in all the prematures; 3 ml of calcium gluconate were added in 9 full-term infants. The exchange transfusion lasted in every case about 2 hours.

The blood samples for plasma Na, K, Ca, bilirubin and total protein levels were taken from the umbilical vein before the transfusion, during its course and 1, 2, 3 and 24 hours after the end of the transfusion. At the same time, but also once daily up to the 5th day, pH, pCO_2, base excess and standard bicarbonate were measured with the micromethod of Astrup in the arterialized capillary blood.

The mean values show that in full-term newborns the exchange transfusion caused a continuous rise of the pH which became more evident after the first half an hour; the highest value was reached 2–3 hours after the end of the transfusion. The pH gradually decreased during the following 5 days. The base excess and the standard bicarbonate values, after a slight initial reduction, rose during the transfusion and afterwards, up to the 2nd-24th hour and gradually decreased in the following days. Only slight differences have been observed between the group treated with 1 ml of calcium gluconate to every 100 ml of blood and that treated with 3 ml.

In premature infants, a slight initial fall of the pH values was observed; afterwards the rise of the pH and the tendency to metabolic alcalosis was slower and less evident than in full-term newborns. Neither in full-term newborns nor in prematures was observed serious metabolic acidosis caused by exchange transfusion.

K and total protein plasma levels showed a slight reduction in almost every case during exchange transfusion; bilirubin decreased constantly; Ca plasma levels increased almost in all cases. Na plasma levels showed only slight variations.

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