859 PREDNISOLONE PHARMACOKINETICS IN CHILDREN: Orville C. Green, Frank S. Kawahara, Robert J. Winter, Peter R. Lewy and Lauren M. Pachman, Northwestern University Medical School, Department of Pediatrics, The Children's Memorial Hospital, Chicago, Illinois.

Clinical observations suggest that some children with chronic diseases respond variably to corticosteroid treatment. 33 children have been studied for bio-availability and metabolism of orally administered prednisone. Physiological doses have been investigated in 5 children with congenital virilizing adrenal hyperplasia; pharmacological doses in 8 patients with dermatomyositis (DMS), 7 with systemic lupus erythematosus (SLE), 9 with childhood nephrosis (N), 2 with regional enteritis, 1 asthmatic and 1 renal transplant patient. Plasma prednisolone values have been determined by a specific radioimmunoassay developed in our lab. Bio-availability was calculated from peak plasma prednisolone levels attained; plasma $t_{\frac{1}{2}}$-life values from % disappearance from peak values over hourly time intervals. Results indicate: (1) a regression line may be calculated for dose vs peak levels but there is wide variation among patients in bio-availability; (2) $t_{\frac{1}{2}}$-life in children differs from adults (mean 125 minutes vs adult 205 minutes); (3) some children with N and DMS have impaired bio-availability but normal $t_{\frac{1}{2}}$-life values; (4) a few children with severe disease (SLE, DMS) have markedly prolonged $t_{\frac{1}{2}}$-life values. These studies support observations of clinical variability of drug effects when prednisone is utilized in pharmacolgical doses. Knowledge of bio-availability and metabolism may allow more precise and rational therapeutic programs.

860 HYPERURICEMIA IN GLYCOGEN STORAGE DISEASE TYPE I (GSD-I). Harry L. Greene, Fred Wilson, Pat Hefren, Annie Terry, Alf Slonim and Ian Burr, Dept. Pediatrics and Dept. of Medicine, Vanderbilt University Hospital, Nashville, TN

The etiology of hyperuricemia in patients with GSD-I is multifactorial, and in part due to an increase in urate production. The increased urate production caused by fructose infusion in normal liver has been shown to result from the rapid formation of fructose-1-P which depletes ATP and traps intracellular phosphate (Pi) (Woods H.J., Biochem. J. 119:501, 1970). By analogy, increased urate production in GSD-I patients could be due to ATP depletion and trapping of Pi during the frequent periods of hypoglycemia and glucagon release. The latter would cause rapid hydrolysis of glycogen to fructose-1,6 diP rather than to glucose. If the analogy is true, hepatic ATP depletion and increased levels of phosphorylated glycolytic substrates should occur following glucagon (G) infusion in patients with GSD-I. Six patients with GSD-I had percutaneous liver biopsies performed before and 5 minutes after intravenous glucagon (20µg/kg over 1 min). Glycogen content decreased from 7.64±0.6 to 5.71±0.4% ($p < .02$) and ATP levels decreased from 2.2±0.1 to 0.79±0.9 µm/gm liver ($p < 0.01$). Two patients with GSD due to defects other than GSD-I showed only slight decreases in hepatic ATP and glycogen, similar to the changes noted in 12 rats. One patient with GSD-I requiring open biopsy of hepatic nodules had hepatic measurement of ATP, glycogen, glu-6-P, F-6-P, F-1, 6-diP and lactate done before and 5, 10, 20 minutes following glucagon. Findings were analogous to those seen after fructose infusion and supports the thesis described above.

861 INSULIN DELAYS THE MORPHOLOGIC MATURATION OF FETAL RAT LUNG IN VITRO. Ian Gross and G.J.Walker Smith. (Spon. by J.B. Warshaw) Yale Univ. School of Medicine, Depts. of Pediatrics and Pathology, New Haven, Conn.

Infants of diabetic mothers, who have increased circulating levels of insulin, are prone to an increased incidence of RDS. In order to evaluate the relationship between hyperinsulinism and lung maturation we have examined the influence of insulin on the morphologic development of fetal rat lung in organ culture. Explants of 19 day gestation fetal lung were cultured in F12 medium, to which 1.0 u/ml insulin had been added, for 24 hours. Explants grown in F12 medium alone served as controls. After 24 hours the control cultures demonstrated evidence of continued maturation as evidenced by: larger alveolar spaces, less interstitial mesenchyme, decreased glycogen content, and increased numbers of lamellar bodies. Explants cultured in medium containing insulin had the following features: very tall alveolar lining cells which were filled with glycogen and extended into the alveolar spaces, frequently obliterating them, more interstitial tissue and markedly fewer lamellar bodies than in the control cultures. The control cultures had 8.3±2.1 lamellar bodies per 10 alveolar lining cells, whereas the insulin treated cultures had 1.1±0.4 lamellar bodies per 10 lining cells.

These observations indicate that insulin delays the appearance of lamellar bodies and increases the glycogen content of the alveolar lining cells in this culture system. Insulin may act by stimulating glycogen synthesis from glucose thereby diverting substrate away from phospholipid synthesis. Supported by USPHS grant no. HL 19752.

862 USE OF 2-DEOXYGLUCOSE AS AN ALTERNATIVE TO FASTING FOR DIAGNOSIS OF HYPOGLYCEMIA. Inger L. Hansen, Marilyn M. Levy, Douglas S. Kerr (Spons. by Marshall H. Klaus). Case Western Reserve Medical School, University Hospitals of Cleveland, Department of Pediatrics, Cleveland, Ohio.

Fasting has been the most useful general test for diagnosis of hypoglycemia in children but may require 36 to 48 hours. 2-Deoxyglucose (2DG) is a competitive inhibitor of glucose transport which rapidly and selectively stimulates the hypothalamic counter-regulatory response to hypoglycemia. 2DG was evaluated as an alternative to fasting by administering both fasting and 2DG tests to 7 children found to be normal and to 14 found to have fasting hypoglycemia (ages 2 to 11). 2DG (50 mg/kg) was given IV over 30 minutes and samples collected for 3 hours. In the normal children glucose increased 30 mg% (14 to 54). In the hypoglycemic children glucose did not increase (-30 to +3 mg%) ($p<.001$). Insulin remained at low fasting levels except in one child with an insulinoma. Normal children excreted urinary epinephrine at a maximum of 310 ng/mg creatinine (250 to 430) 2 to 3 hours after 2DG. This was greater than the maximum after fasting, 130 ng/mg creatinine (20 to 310). In 11 of the hypoglycemic children the maximum epinephrine excretion after 2DG was well below the normal range (20 to 200 ng/mg creatinine) and no other cause of hypoglycemia was found. The 2DG test is therefore superior to fasting in identifying epinephrine deficiency. It is concluded that the glucose response to 2DG is as reliable as fasting in distinguishing normal from hypoglycemic children and has the advantage of being more rapid without producing symptoms.

863 THE USE OF 1,25-DIHYDROXYCHOLECALCIFEROL (1,25-$(OH)_2$ D) IN THE TREATMENT OF RICKETS WITH NEONATAL LIVER DISEASE. J.E. Heubi, R.C. Tsang, J.J. Steichen, G.M. Chan, I-W. Chan, and H.F. DeLuca, Dept. Pediatrics, U. of Cincinnati, Dept. of Biochemistry, U. of Wisconsin.

Rickets associated with liver disease is believed to be caused by malabsorption of vitamin D and Ca and decreased hepatic 25-hydroxylation of vitamin D. 1,25-$(OH)_2$D, normally synthesized in the kidney from 25-hydroxyvitamin D (25-OHD), theoretically should bypass the blocks in vitamin D metabolism. Two patients had radiographic and biochemical evidence of rickets with severe neonatal hepatitis and extrahepatic biliary atresia. Both received phenobarbital to enhance bile flow. 1,25-$(OH)_2$D was initially given orally (0.10 µg/kg/day) without improvement. Thereafter, i.m. divided doses (0.20 µg/kg/day) were given with complete biochemical, bone mineral (photon absorptiometric analysis) and radiographic evidence of healing.

Patient	Ca mg/dl	P mg/dl	Bone Mineral Content gm/cm	PTH µl-Eq/ml (N<180)	25-OHD ng/ml (N 13-81)
T.S. 35 mos.old baseline	8.3	4.0	.0926	55	<5
2 mos. oral 1,25-$(OH)_2$D	7.1	4.2	.0944	50	<5
4 mos. i.m. 1,25-$(OH)_2$D	10.4	5.9	.3381	<40	9
J.S. 23 mos.old baseline	9.5	2.1	.1142	82	<5
10 wks.i.m. 1,25-$(OH)_2$D	10.4	5.3	.2201	52	8.9

I.M. 1,25-$(OH)_2$D which theoretically overcomes blocks in vitamin D metabolism, can be effectively used in infantile biliary rickets. Healing occurs in spite of continuously low 25-OHD. The need for higher doses of 1,25-$(OH)_2$D, four times the "physiologic dose", may reflect enhanced catabolism or end organ resistance.

864 MATERNAL AND CORD SERUM CONCENTRATIONS OF 24,25-DIHYDROXYVITAMIN D (24,25-$(OH)_2$D) Laura S. Hillman and John G. Haddad (Intr. by R. E. Hillman) Wash. Univ. School Med., St. Louis Children's Hosp., Dept. of Ped. and Jewish Hospital of St. Louis, Dept. of Med., St. Louis, Mo. 63110

Increased Parathyroid hormone serum concentrations, [PTH] enhance 1,25-$(OH)_2$D and decrease 24,25-$(OH)_2$D synthesis from 25-hydroxy vitamin D (25-OHD). At term, pregnant women have elevated [PTH] and infants have low [PTH]. 16 pairs of maternal (M) and umbilical cord (C) venous sera were analyzed for 24,25-$(OH)_2$D, 25-OHD, calcium, magnesium and PTH. Both M 24,25-$(OH)_2$D (2.6±0.5 ng/ml) and C 24,25-$(OH)_2$D (3.0±1.2 ng/ml) were lower than 29 adult normals (5.0±0.6 ng/ml). Normal adult 24,25-$(OH)_2$D is correlated with 25-OHD ($R=.40$ $P<.03$) with a 24,25/25 of .21±.02. C 24,25-$(OH)_2$D was also correlated with C 25-OHD ($R=.49$ $P<.05$) with a 24,25/25 of .21±.10 whereas M 24,25-$(OH)_2$D was not correlated with M 25-OHD ($R=.10$, N.S.) with a 24,25/25 ratio of .13±.05. Whereas M and C 25-OHD are correlated ($R=.71$), M and C 24,25$(OH)_2$D were not correlated ($R=.26$), with the majority of C 24,25$(OH)_2$D higher than M 24,25$(OH)_2$D. C-M differences were 1.79±1.04 mg% calcium and .17±.15 meq/L magnesium. C-M calcium and C-M magnesium was positively correlated ($R=.87$) as were M calcium and magnesium ($R=.81$) and C calcium and magnesium ($R=.69$). No significant correlations were found between C, M, or C-M calcium and magnesium and M or C 24,25-$(OH)_2$D and 25-OHD. The decreased M 24,25-$(OH)_2$D is consistent with the recognized increased M [PTH]. Since C [PTH] is low, the relatively low C 24,25-$(OH)_2$D suggests little fetal synthesis of this sterol.