**847** THYROID DYSFUNCTION IN DOWN SYNDROME. Siegfried M. Pueschel. Brown University, Program in Medicine, Rhode Island Hospital, Department of Pediatrics, Providence, Rhode Island.

We investigated the thyroid function of 151 children with Down syndrome. Compared with a control group of 89 siblings nearest in age to their brother or sister with Down syndrome the mean TSH value was significantly higher in children with Down syndrome than in the non-Down syndrome children (8.49 μU/ml vs. 3.55 μU/ml). However, the mean $T_4$ levels in both groups were nearly the same (8.36 μg/dl and 8.60 μg/dl). In the Down syndrome group there was a trend for TSH values to increase and for $T_4$ values to decrease with advancing age. Of the 151 patients with Down syndrome, 10 had both significantly elevated TSH levels ($>$ 9.5 μU/ml) and significantly decreased $T_4$ levels ($<$ 5.5 μg/dl) 21 had abnormally high TSH values ($>$9.5 μU/ml), 7 had markedly increased $T_4$ levels ($>$ 12.0 μg/dl), and 3 had significantly decreased $T_4$ levels ($<$ 5.5 μg/dl). The intellectual functioning of children with both abnormal TSH and $T_4$ levels was significantly lower (mean IQ 41.7) than that of Down syndrome children with only increased TSH values (mean IQ 53.8) and that of Down syndrome children with normal thyroid function (mean IQ 55.3).

This study provides evidence that there is an increased prevalence of thyroid dysfunction in children with Down syndrome. Therefore, children with Down syndrome should have thyroid function studies performed at regular intervals and prompt treatment should be instituted if thyroid dysfunction has been identified.

**848** GALLOWAY SYNDROME IN A BLACK INFANT. Qutub H. Qazi, Tariq Sheikh, Eva Beller, Joanna Sher, Downstate Medical Center, State Univ. of New York, Dept. of Pediatrics, Brooklyn, New York

We report a black infant with Galloway syndrome (congenital microcephaly, hiatus hernia and nephrosis), a rare autosomal recessive disorder. Previously reported four cases of the syndrome belonged to two families of European ancestry.

The proposita was the first born of a young, healthy, nonconsanguineous couple, who denied exposure to teratogens prior to and through pregnancy. During the seventh month fetal size was judged to be small, and fetal movements were considered of low intensity. Three ultrasound examinations demonstrated microcephaly. The infant, born at term, weighed 2.6 Kg and had occipitofrontal circumference (OFC) 28.5cm. Other pertinent findings included very small anterior fontanelle, sloping forehead, prominent root of the nose, hyperteloric eyes, micrognathia, narrow high arched palate, small umbilical hernia, long tapering fingers, and generalized hypotonia. A giemsa-banded karyotype was normal.

Infant's postnatal growth was poor and psychomotor development remained at a standstill. She frequently vomited her feeds. At the age of seven months grand mal seizures appeared, and at 10 months she was admitted to a hospital for diagnosis and management of nephrosis. At this time her weight and length were below the 5th percentile, and OFC was 35.5cm. Barium study did not show hiatus hernia. A renal biopsy specimen showed segmental glomerulosclerosis.

● **849** THE INSULIN GENE POLYMORPHISM IN TYPE I DIABETES (IDDM) FAMILIES. LJ Raffel, GA Hitman, GI Bell, JH Karam, PH Yen, DJ Galton, GF Bottazzo, JI Rotter. Harbor-UCLA, Med. Genetics, Torrance, CA; Chiron Corp. and UCSF; St. Bartholomew's and Middlesex Hosps., London.

Population studies have suggested an increased frequency of small DNA insertions (class 1 alleles) 5' to the insulin gene in IDDM. The present study was undertaken to examine this relationship within families. 27 families with at least one IDDM offspring were studied. Analysis of the insulin gene polymorphism was performed by digestion of DNA with Bgl I, Sst I, Rsa I, or Pvu II and hybridization with either a 32-P-labelled insulin gene probe or polymorphic region-specific probe. An increased frequency of matings between two individuals homozygous for small inserts (genotype 1/1) was found among the parents of diabetics ($p<.04$), as well as an increased frequency of the 1/1 individuals within the entire sample, and increased total frequency of 1 alleles ($p<.055$). This increased frequency was present in nondiabetic siblings as well ($p<.05$). These results show that ascertainment through an offspring with IDDM selects for families with high frequencies of homozygosity for small inserts and thus suggest that the insulin gene polymorphism is providing part of the genetic predisposition to IDDM. When the major portion of genetic predisposition is provided by other genes (HLA accounts for 60-70% in IDDM), identification of additional susceptibility genes becomes difficult. Even when formal linkage analysis is uninformative, our studies indicate that analysis for aggregation of specific alleles within families is a useful approach to this problem.

**850** GENETIC LOCALIZATION OF THE DOWN SYNDROME REGION IN THE MOUSE. Roger Reeves, Catherine Fedako, Bruce O'Hara, and John Gearhart (Spon. by John W. Littlefield. Johns Hopkins University School of Medicine, Developmental Genetics Laboratory, Department of Pediatrics, Baltimore.

Down Syndrome in humans is caused by trisomy for the distal portion of chromosome 21 (HSA 21). HSA 21 contains several genes which map to mouse chromosome 16 (MMU 16), establishing the presence of homologous linkage groups on the two chromosomes. The length and character of this conserved region and its position on MMU 16 are unknown. To define the DS region more precisely, we have undertaken genetic mapping studies in the mouse. Our results indicate that a segment of HSA 21 which includes the DS region is conserved on MMU 16.

To map the homologous regions of HSA 21 and MMU 16, molecular probes specific to HSA 21 were hybridized to mouse DNA. Probes for superoxide dismutase-1 (SOD), which is proximal to the DS region, and pH33, a DNA fragment distal to the DS region on the q arm of HSA 21, hybridized strongly to mouse DNA. These probes also hybridized to somatic cell hybrids containing MMU 16 as the only mouse chromosome, indicating conserved linkage on MMU 16 and HSA 21. These probes were then used to detect restriction fragment length polymorphisms (RFLPs) by hybridizing them to a panel of DNAs from eight different inbred mouse strains which had been digested with restriction endonucleases. The CBA strain demonstrated RFLPs different from BALB/c with the SOD and pH33 probes. The genetic distance between these sequences was determined by backcrossing the progeny of an F1 cross between these strains and calculating cross-over frequency.

● **851** RIBOFLAVIN-RESPONSIVE (RR) MULTIPLE ACYL-COA DEHYDROGENATION DISORDERS (MAD). Vickie R. Roettger and William J. Rhead (Spon. by Jean Robillard), Department of Pediatrics, University of Iowa, College of Medicine, Iowa City, Iowa.

RR inborn errors of fatty acid metabolism have been recently identified (Ped. Res. 16,801 (1982); J. Peds. 103,394 (1983). Fibroblasts from the first patient described with a clinically RR mild MAD variant oxidized [1-$^{14}$C]octanoate (OCT) at 35% of control after culture for 2 weeks in R-free MEM but at 75% of control after culture in 2 mg/L R. This patient's cells oxidized [1-$^{14}$C]butyrate (BUT) at 19% of control after culture in R-free MEM and at 72% of control after culture in 2 mg/L R. Assay of acyl-CoA dehydrogenases and electron-transferring flavoprotein in this patient's R-supplemented and -depleted cells and mitochondria have not yet distinguished between FAD-synthesis/transport or FAD-apoenzyme binding defects. Mitochondrial $^{14}$C-FAD content was normal after culture of this patient's cells in 8nM $^{14}$C-R for 24 hours, similar to Dr. E. Christensen's results in cell homogenates (personal communication). Further studies on this RR-MAD patient are in progress. In other experiments, cells from 2 patients with severe MAD variants (Clin. Chim. Acta 66,227 (1976); Helv. Ped. Acta 38,9 (1983)) were also RR in vitro, oxidizing BUT and OCT at 4% and 23% of control, respectively, after culture in R-free MEM and at 16% and 38% of control after culture in 2mg/L R. Since all MAD lines studied here are RR in vitro, careful trials of R supplementation in vivo are justified in suspected MAD patients.

**852** PRENATAL VITAMIN $B_{12}$ THERAPY OF A FETUS WITH METHYLCOBALAMIN DEFICIENCY. David S. Rosenblatt, Bernard A. Cooper, Sheila M. Schmutz, Witold A. Zalesky, and Robin E. Casey. Dept. of Pediatrics, Physiology, Biology and Medicine, McGill University, Montreal; Dept. of Pediatrics, University of Saskatchewan, Saskatoon.

We have recently described a child who presented early in life with homocystinuria and megaloblastic anemia. Fibroblasts from this patient had low levels of methylcobalamin ($CH_3$-$B_{12}$) and a decreased incorporation of ($^{14}$C) methyltetrahydrofolate ($CH_3$-THF) into methionine which was unresponsive to the addition of vitamin $B_{12}$ to the tissue culture medium. In contrast to the cultured cells, in the patient the megaloblastic anemia and homocystinuria resolved on treatment with OH-$B_{12}$. Fibroblasts from the parents of this patient had normal levels of $CH_3$-$B_{12}$ but intermediate levels of $CH_3$-THF incorporation and a variable response to vitamin $B_{12}$ in the culture medium. When the proband's mother became pregnant, prenatal diagnosis was attempted. The incorporation of total vitamin $B_{12}$ derivatives which was $CH_3$-$B_{12}$ in the fetal amniocytes was only 7.4%, as compared to 26.1% and 48.7% in control amniocytes, and 37.1% and 32% in fibroblasts from the obligate heterozygotes. Values for $CH_3$-THF incorporation were variable. Because the proband responded well to vitamin $B_{12}$ therapy, it was decided to treat the mother prenatally. She received IM hydroxycobalamin (OH-Cbl) 1 mg twice weekly beginning at 25 weeks gestation. Diagnostic studies on fibroblasts obtained at birth confirmed that the baby has $CH_3$-$B_{12}$ deficiency. The baby has been maintained on 1 mg IM OH-Cbl twice weekly and is clinically well.