(S) studied under conditions of: sodium restriction and excess; ACTH stimulation; Metyrapone inhibition and Decadron suppression in 2 normotensive siblings and father reveal that only the patient demonstrates deficiency in cortisol secretion but the hypertensive mother has an abnormal aldosterone regulation. On the basis of steroidal data obtained, a partial 17-hydroxylase defect in the adrenal and not the gonad appears to explain the syndrome best. This form of hypertension is noteworthy because it is alleviated by medical treatment and may be misdiagnosed as primary hyperaldosteronism.

Baseline values	Normal for size	Patient	Twin sister	Brother
Urine aldosterone	up to 14 μg/d	17–26	12	9.5
Plasma aldosterone	3–15 mμg %	24	–	–
Plasma ACTH	0.3–0.7 mu %	1.5	0.3	0.4

(SPR)

19 *Familial Growth Hormone (GH) Deficiency.* BAGHER M. SHEIKHOLISLAM* and ROBERT S. STEMPFEL, Jr., Duke University Medical Center, Durham, N. C.

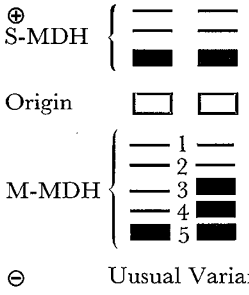
Isolated GH deficiency has been observed in a number of instances, but its occurrence as a recessively inherited defect has been previously documented only in adult members of two families. The present study concerns a family of 9 in which the father and 4 siblings had growth retardation, truncal obesity, facial infantilism and impaired glucose tolerance. Plasma GH responsiveness to insulin-induced hypoglycemia and to bacterial pyrogen administration was absent in those whose growth was retarded, but indirect studies of thyrotropin and adrenocorticotropin demonstrated the presence of these pituitary factors in all members of the family. Human GH administration to the 18-year-old, dwarfed, sexually infantile, female sibling resulted in objective changes in sexual maturation, alterations in fat distribution and greatly accelerated growth. The similarly treated 9-year-old male sibling experienced marked increase in the rate of statural growth, but remained sexually infantile. No discernable change in urinary corticoid responsiveness to adrenocorticotropin and no measurable change in gonadotropin excretion occurred during the therapeutic period. Studies of glucose tolerance and plasma insulin responsiveness in 4 of the dwarfs revealed an increase in peripheral resistance to insulin during GH administration. It is concluded that this form of familial dwarfism is related to GH deficiency and that the defect is monotropic. The patients described clearly illustrate the natural course of the condition, wherein delayed adolescence is the rule rather than the exception. Observations presented support the possibility that GH alters responsiveness of endocrine end-organ tissues. Serious doubts are raised regarding the validity of diagnoses which exclude hypopituitarism in patients with retarded growth on the basis of eventual sexual maturation. (APS)

20 *Growth Hormone (GH) Responsiveness to Stimulation by Insulin Hypoglycemia, 2. Arginine, 3. Piromen in normal and Growth Deficient Children.* M.H. MAC GILLIVRAY*, T. ACETO, Jr.* and L.A. FROHMAN*, Departments of Pediatrics and Medicine, State University of New York at Buffalo, Buffalo, N.Y. (introduced by M.I. Rubin).

Plasma GH levels in 11 normal children, in 5 children with hypothalamic-pituitary disorders, in 8 children with idiopathic GH deficiency and in 4 children with a constitutional growth delay were examined in the fasting state and following stimulation with insulin hypoglycemia, arginine, and bacterial pyrogen (Piromen). Normal children exhibited a marked fluctuation in fasting GH levels (radioimmunoassay). An elevated prestimulatory GH value was associated with a diminished response. Of the 3 stimuli, insulin hypoglycemia resulted in the highest GH levels. In normal children, GH responses to Insulin Hypoglycemia ($\bar{x}$ 20.4±6.4) Arginine ($\bar{x}$ 15.2±4.3) and Piromen ($\bar{x}$ 9.9±2.8) were not significantly different because of the marked variability observed within each group. In children with a constitutional growth delay, both fasting and poststimulatory GH values were indistinguishable from normal. In idiopathic GH deficiency, GH values prior to stimulation ($\bar{x}$ 2.4±0.4) and after the three stimuli ($\bar{x}$ 3.6±1.0) were significantly lower than those values observed in the normal or constitutional delay groups. The data suggest 1. Insulin Hypoglycemia, Arginine and Piromen are suitable stimuli with which to evaluate GH responsiveness; 2. failure to respond to stimuli in normal children is associated with elevated resting levels of GH; 3. children with idiopathic GH deficiency have significantly lower pre and post stimulatory GH values than do the normal but do respond better to stimulation than children with pituitary-hypothalamic disorders; 4. constitutional delay in growth is not associated with abnormal GH responsiveness; 5. normal GH secretion can be diagnosed if a resting GH level 6 mμg/ml. (APS)

21 *A Genetic Variant of Human Mitochondrial Malate Dehydrogenase.* JEAN A. CORTNER* and RONALD G. DAVIDSON*, Roswell Park Mem. Inst. and State Univ. of N.Y., Buffalo, N.Y. (introduced by Mitchell I. Rubin).

The enzyme malate dehydrogenase (MDH) is known to exist in two distinct forms in most mammalian tissues. One is present in the cytoplasm as a soluble enzyme (S-MDH), and the other is bound to the mitochondria (M-MDH). Among the distinct physical and chemical properties of these two enzymes are the different patterns seen after starch gel electrophoresis and specific enzymatic staining (see diagram: usual). Recent studies have suggested that the usual minor mitochondrial bands (1–4) are conformational modifications of a single protein, band 5. We have previously reported a rare genetic variant of soluble MDH found in the red cells of one apparently normal Negro female out of 3000 individuals examined. This report concerns a new inherited electrophoretic variant of M-MDH found in either leukocyte or placental extract of 3 of 350 unselected normal individuals. The electrophoretic pattern of this variant is shown in the diagram. The two additional major bands of MDH activity have identical electrophoretic mobility with minor bands 4 and 3 of the normal mitochondrial pattern. Family studies of two of the probands show that affected individuals are heterozygous for a relatively common autosomal mutant gene. All of the individuals found to have the mitochondrial variant have normal S-MDH patterns, adding further evidence that the two intracellular forms of MDH are under the control of different genes. (SPR)



22 *Developmental Noise and Congenital Malformation.* MORTON S. ADAMS* and JERRY D. NISWANDER*, Nat. Inst. of Health, Bethesda, Md. (introduced by Robert W. Miller).

The causes of non-directional asymmetry of paired organs has been referred to as developmental 'noise' (WADDINGTON, C. H.: *The Strategy of the genes* [Allen and Unwin 1957]). Thus the level of asymmetry is inversely correlated to the degree of developmental stability.

We report here a greater asymmetry in the atd angle of the palmer dermatoglyphics and the maximum buccal-lingual diameter of the lower first molars of children affected with familial cleft lip±cleft palate. This increased asymmetry was not present in the normal sibs or parents of the affected children. Neither was it present in propositi and families of sporadic cleft lip±cleft palate or isolated cleft palate. Sufficient data are not available to determine the asymmetry of familial cleft palate without cleft lip. A total of 88 families with at least one member affected with an oral cleft and 82 families with no cleft history were examined.

The action of polygenes with a quasi-continuous distribution may be consistent with this new observation. Consideration of such mechanisms may offer some explanation for the diversity of results from investigations seeking to identify characteristic dermatoglyphic and dental anomalies in patients with congenital malformations. (SPR)

23 *Studies of the Biochemical Basis of Kinky Hair Disease.* JOSEPH H. FRENCH* and EARL S. SHERARD*, Montefiore Hospital and Medical Ctr. and Albert Einstein Col. of Med., New York, N.Y. (introduced by Laurence Finberg).

Kinky Hair Disease, first described by MENKES in 1962 as an X-linked recessive neurodegenerative disorder, may represent an abnormality of lipid metabolism. Studies have been carried out on a 16-month-old male patient showing the clinical features of: 1. scant, pale, lacklustre, kinky hair which microscopically revealed twisting about their axes (pili torti), a rather even almost sine wave variability in the diameter of the hair shaft (monilethrix) and many broken hair shafts (trichorrhexis nodosa); 2. slow growth and weight gain from birth; 3. micrognathia and high arched palate; 4. a clear history of marked decline in mental development; 5. onset of severe focal and generalized major and minor motor seizures; 6. spasticity with quadriparesis, clenched fists, opisthotonos and scissoring.

Biochemical studies show: 1. a depressed tocopherol content of the serum; 2. a normal amino acid composition of the hair, serum and urine; 3. an abnormal pattern of autofluorescence of the hair. Other patients at autopsy have shown this same abnormal fluorescence of their Purkinje cell axons. Together with previously described alterations in the lipid composition of the brain (O'BRIEN, 1966), these findings support the hypothesis of an alteration in lipoperoxidation of lipid molecules. (SPR)

24 *Cerebro-Hepato-Renal Syndrome. A Newly Recognized Familial Disorder.* EBERHARD PASSARGE*, Dept. of Pediat., Col. of Med., Univ. of Cincinnati, Cincinnati, O. (introduced by Josef Warkany).

A familial disorder, consisting of congenital abnormalities of the central nervous system, the liver, and kidneys has been observed. The predominant features of the disorder are severe, generalized hypotonia; a characteristic, narrow face with hypertelorism, epicanthic folds, prominent forehead, and open metopic suture; hepatomegly with development of jaundice and hypoprothrombinemia; and cortical renal cysts. Less constant findings include moderately low birth weight, brain maldevelopment, minor skeletal defects, cardiac maldevelopment, and possibly eye and genital anomalies. These children died in infancy.

Five sisters with this disorder have been studied and are compared with two similar pairs of sibs reported by BOWEN, LEE, ZELLWEGER and LINDENBERG (Bull. Johns Hopk. Hosp. *114:* 402 [1964]) and SMITH, OPITZ and INHORN (J. Pediat. *67:* 617 [1965]). The clinical and pathological findings in these 9 patients suggest that this disorder constitutes a clinical entity, for which, in view of the unknown pathogenesis, the descriptive term cerebro-hepato-renal syndrome is proposed. No detectable chromosomal or metabolic abnormality, or an exogenous causative factor has been detected.

The 5 affected individuals, of normal, nonconsanguineous parents of Alsacian extraction, had a mean birth weight of 2493 g at 37–40 weeks gestation and died at 4, 2, 14, 1/7 and 20 weeks respectively. They had 8 normal sibs (5 males, 3 females).

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25 *Ahaptoglobinemia in Puerto Rican Newborns.* JOSÉ MIGUEL GARCÍA-CASTRO* and HOWARD M. CANN, Stanford Univ. Sch. of Med., Palo Alto, Cal.

Although the frequency of ahaptoglobinemia in the newborn has been determined in Caucasians, little is known about the frequency of this condition in other populations. We are studying ahaptoglobinemia in cord blood specimens from 314 infants born in Puerto Rico, a sample from a heterogeneous population: Caucasian, Negro and mulatto. The frequency of ahaptoglobinemia, as defined by lack of a haptoglobin pattern on starch gel electrophoresis, was found to be 0.777 in 94 samples of the Puerto Rican newborn group studied to date. When this result was compared to the frequencies found in an American-USA (0.873), two southern Italian (0.809 and 0.800) and two Scandinavian (0.767 and 0.900) newborn populations, significant heterogeneity was found in the data ($X^2_{(5)} = 16.612$). Data from the American (USA) and one of the Scandinavian populations account for the heterogeneity; our data do not differ from those of the remaining three Caucasian populations. Ahaptoglobinemia in the Puerto Rican sample was analyzed by studying the effects of several variables. The frequency of ahaptoglobinemia was not affected by sex of the child, birth weight and race of the mother. Parity did not