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NEONATAL SCREENING FOR AMINOACIDURIA IN THE PROVINCE OF QUEBEC, 1971-1977.

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Between August 1971 and 1973, 113,680 5-day-old newborns were screened for aminoaciduria by one-dimensional TLC using dry urine samples. Only 5 abnormal patterns were observed: Histidinuria (emia)(2), tyrosinuria (emia)(2), cystinuria (5) and dicarboxylic aminoaciduria (1). The frequency was 2.64 per 100,000 for "overflow" and 6.16 per 100,000 for "renal" aminoacidurias. From September 1973 to June 1977, 276,000 14-day-old newborns were studied. 5 additional pathological patterns were found: Argininosuccinic aciduria (emia)(3), phenylketonuria (9), dibasic aminoaciduria (1), generalized (3) and neutral (Hartnup) aminoaciduria (5). The frequency of all 10 abnormal patterns increased to 15.92 per 100,000 for "overflow" and 26.76 per 100,000 for "renal" aminoacidurias. Non-pathological aminoacidurias were found in 10.49 per 100,000 newborns. Our results agree with others regarding the frequency of pathological aminoacidurias except for tyrosinuria (emia) and dicarboxylic aminoaciduria, both found with a higher frequency in the Quebec population. We conclude that neonatal screening for aminoacidurias at 14 days of age offers a valuable back-up system for blood screening programs and permits the detection of new inborn errors of metabolism in a given population.

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DIETARY THERAPY OF ORNITHINE TRANSCARBAMYLASE (OTC) DEFICIENCY

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Keto acid dietary therapy of complete OTC deficiency in one male resulted in survival to 5 months of age (Pediatr. Res. 11: 511, 1977). We are treating similarly a male who presented with hyperammonemic coma at 3 days of age. The family history was positive and liver OTC activity was <0.1% of normal. Acute therapy relied on peritoneal dialysis. A major change in the dietary therapy has been severe protein restriction with the milk protein/kg/d progressively decreased from 1.09 gm at 3 weeks of age to 0.16 gm by 6 months. The intake of free amino acids has been adjusted frequently to 0.62 gm/kg/d of amino acids and 1.12 gm/kg/d of keto acids. Although the milk protein plus amino acid intake is now only 0.78 gm/kg/d, the minimum nitrogen intake for growth in patients with urea cycle defects is unknown. At 6 months of age the patient's weight was in the 50%ile and length slightly above the 3%ile. Developmental quotient was 50, which could be attributable to severe neonatal difficulties. Hematocrit was 40.4%, Hgb 11.5 gm/dl, total protein 6.2 gm/dl, and albumin 3.7 gm/dl. Serum glutamine has been a more sensitive index for dietary management than has blood ammonia which has remained normal since the neonatal period. Slight increases in glutamine have responded to increase in keto acid intake.

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CHEMILUMINESCENCE: A RAPID, SENSITIVE METHOD FOR DETECTION OF PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE (CGD) AND IDENTIFICATION OF CARRIERS.

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Neutrophil chemiluminescence was measured in 14 CGD patients and 17 CGD carriers during phagocytosis of opsonized zymosan. The mean and range of peak chemiluminescence of phagocytizing neutrophils was 10 x 10^3 CPM (0-20) for CGD patients, 126 x 10^3 CPM (83-227) for carriers and 252 x 10^3 CPM (207-288) for normal adult controls ($p < .001$). Bactericidal capacity of neutrophils paralleled the chemiluminescence response when a 1 to 1 bacteria: neutrophil ratio was used. Neutrophils of CGD patients killed 43% (0-55) of S. aureus, CGD carriers killed 72% (51-97), and normal controls killed 98% (93-100).

A broad range of phenotypic expression may be expected in heterozygotic carriers of sex-linked recessive disorders since there is random inactivation of the X-chromosome. Except for one carrier mother whose chemiluminescence response was repeatedly within the normal range, though always decreased compared to the control of the day (80-88%), there was no overlap in chemiluminescence values between CGD carriers and controls. This carrier had normal neutrophil bactericidal capacity, oxygen consumption, oxidation of (1-14C)glucose and reduction of nitroblue tetrazolium. Thus, chemiluminescence during phagocytosis is not only a simple, rapid method for diagnosing CGD patients and detecting CGD carriers but also appears to be a sensitive and valuable method for the identification of near-normal CGD carriers.

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FAMILIAL ATHYREOTIC HYPOTHYROIDISM IN TWO SIBLINGS.

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Familial athyreosis is a cause of hypothyroidism seen much less frequently than sporadic athyreosis or cryptothyroidism. The present report concerns a brother and sister, now age 22 and 14 years respectively, who appear to have little or no functioning thyroid tissue. In both patients diagnosis was made and treatment begun in early infancy. There are 3 other normal siblings, and there is no family history of thyroid disease. The boy was first seen at age 13 years, exhibiting short stature, retarded bone age, mental retardation and other signs of hypothyroidism. Thyroid scan with 100 μCi of ^{131}I revealed no detectable uptake. Under treatment with 60 mg desiccated thyroid/day TSH was 4.7 μU/ml, T4 4.7 μg/dl and T3 162 ng/dl (N 110-230). In the girl treatment had been stopped 4 years before we first saw her at age 9 years. She was below the 3rd percentile in height, was mentally retarded and exhibited the Kocher-Debré-Sémélaigne pseudohypertrophy of muscles. Bone age was 4½ years. T4 by CPB was 1.3 μg/dl (N=3-7) and TSH 54 μU/ml (N<10). Thyroid scans using 5 μCi of ^{131}I and later with 2.5 mCi of Tc-99m failed to demonstrate any evidence for functional thyroid tissue. Parietal cell autoantibody titer in serum was not elevated. It has been suggested that Tc-99m provides a more critical evaluation of athyreosis than does ^{131}I. Unlike the syndrome of familial athyreosis with thyrotropin deficiency (Miyai et al., NEJM 285:1043, 1971), in the present syndrome thyrotropin feedback appears to be normal.

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HETEROGENEITY OF CARDIAC FINDINGS IN NOONAN'S SYNDROME: NINE CASES WITH A FAMILIAL EXAMPLE.

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Since Noonan's syndrome was described (J. Ped. 63:468, 1963), more than 200 cases have been reported. Although pulmonic stenosis is generally thought of as the classical cardiac finding, many such patients have cardiac anomalies other than pulmonic stenosis. Of the 9 cases seen by us, 5 are males and 4 are females. Hypertelorism and low-set ears were present in all, as was short stature with one exception. Three cases were mentally retarded. All males presented cryptorchidism. Pulmonic stenosis was found or suspected in 5 patients; transposition of great vessels in one. In a mother and daughter with the Noonan phenotype the mother had an atrial septal defect, but cardiological evaluation was refused in the daughter. A boy showed pseudocoarctation of the aorta, bicuspid aortic valve and cardiomyopathy. Another boy showed unusual bleeding at surgery, neonatal macrosomia and adolescent gynecomastia. An autosomal dominant mode of inheritance has been postulated. However, several examples of male to male transmission as well as phenotypic overlap with 45,X Turner's syndrome suggest the possibility of inheritance via the homologous regions of the X and Y chromosomes (partial sex-linkage).

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PRENATAL DIAGNOSIS OF HYPOPHOSPHATASIA.

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Three approaches to the prenatal diagnosis of the severe, early onset form of hypophosphatasia, a rare inborn error of metabolism, were investigated in 2 pregnancies of a family with a previous history of the disease. Two of these approaches, ultrasonography and the determination of the bone and liver isozyme activity of alkaline phosphatase (ALP) in cultured amniotic fluid cells have proven useful diagnostically. The third approach, assay of the bone and liver isozyme activity or total activity in supernatant amniotic fluid was not found to be informative.

In 1 pregnancy, the failure of ultrasonography at 16, 18, and 19 weeks gestation to reveal a well defined fetal skull, when the level of alpha-fetoprotein in the amniotic fluid was normal, suggested hypophosphatasia. This diagnosis was supported by the finding that cultured amniotic fluid cells from this fetus had an ALP specific activity which was 4% of the mean of 68 control cultures and much less than the lowest control value.

A subsequent normal sibling who has heterozygous serum levels of ALP had normal ultrasound findings and normal cultured amniotic fluid cell enzyme activities. The study has emphasized the differences in tissue specific ALP isozyme composition of amniotic fluid supernatant and cultured cells. These differences are crucial in the diagnosis of this defect of bone and liver ALP.