

CYTOGENETIC STUDIES IN PREGNANCY WASTAGE. R. Schmidt, H. Dar and H. M. Nitowsky, Depts. Ped. and Gen., Albert Einstein Coll. of Med., Bronx, N. Y.

In a consecutive series of 1,040 families seen in our Genetic Counseling Program, 58 families were referred because of pregnancy loss or wastage (2 or more spontaneous abortions or stillbirths). In 41 families cytogenetic studies were done on both parents and in four instances only the mother was studied. One mother was found to be a mosaic Turner's syndrome (46XX/45X); two mothers and one father were balanced translocation carriers (46XX, t (13q-; 3q+); 46XX t (17p-; 3q+); 46XY, t (4q-; 13+)). Of the 78 parents in whom cytogenetic studies were carried out, five families had children with trisomy 21 in addition to two miscarriages or one miscarriage and a stillbirth. Six families had children with anomalies of the nervous system (anencephalus, hydrocephalus or meningomyelocele). In one mother pregnancy wastage was associated with maternal hyperthyroidism. In two other families fetal wastage, which occurred late during pregnancy, could be attributed to blood group incompatibilities. Thus, in 40 families no obvious cause could be found for fetal loss. The overall percentage of obvious chromosomal abnormalities in our series is approximately 10%, and exceeds previously reported frequencies of significant cytologic aberrations in couples who present with fetal wastage.

MONOZYGOTIC (MZ) TWINS DISCORDANT FOR SEX. R. Schmidt, H. M. Nitowsky and E. H. Sobel. Depts. Ped and Gen., Albert Einstein Coll. Med., Bronx, N. Y.

A pair of adolescent twins, discordant for sex, was identified as MZ on the basis of concordance for 22 blood groups and other biochemical markers. The proband has short stature, webbed neck, malformed left kidney, high plasma gonadotropins and other features of Turner's syndrome. Cytogenetic studies revealed a 46XY chromosome complement in peripheral blood, 46XY/45X in skin fibroblasts and 45X in fibroblasts cultured from streak gonads. Her MZ normal appearing male twin has a 46XY karyotype. The dermatoglyphics are similar in both twins but the total ridge count is higher in the girl. A review of the literature reveals 3 other reports of MZ twins discordant for sex. In one pair there was a phenotypically normal male with a 46XY karyotype, and the female twin had a 45X karyotype and findings of Turner's syndrome. In the second pair the male, although phenotypically normal, showed a 45X karyotype while the female twin showed 45X/46XY mosaicism with features consistent with mixed gonadal dysgenesis. Both members of the third twin pair showed findings characteristic of mixed gonadal dysgenesis. The male twin had a 45X/46XY chromosome complement and the female, with findings more suggestive of Turner's syndrome, had a 45X chromosome pattern. The concurrence of gonadal dysgenesis and MZ twinning may shed light on embryonic gonadal development and pathogenesis of the various types of gonadal dysgenesis.

COMBINED IMMUNODEFICIENCY DISEASE CAUSED BY AGENOSINE DEAMINASE DEFICIENCY: DETECTION OF THE CARRIER STATE AND IDENTIFICATION OF A SILENT ALLELE (ADA). C. Ronald Scott, Shi-lian Chen and Eloise R. Giblett. Univ. Wash., Dept. Pediat., and King County Central Blood Bank, Seattle.

Adenosine deaminase (ADA) deficiency is now recognized as a cause of one type of severe combined immunodeficiency (CID). Of major interest is the genetic transmission and the identification of heterozygotes for ADA deficiency. A large family in which an infant had died with CID and ADA deficiency was studied by determining the enzyme activity and isoenzyme pattern of ADA in red cells.

By electrophoresis three red cell phenotypes, ADA 1, ADA 2 and ADA 2-1 could be recognized in the family. In one mating a father had ADA 2-1, the mother had ADA 1, and one of their three children had ADA 2. The mother and child had ADA activity below the normal range. This anomalous inheritance could only be explained by the existence of a "silent" allele (ADA⁰) at the structural locus for red cell ADA. Each parent of the affected child had ADA values 2.3 and 3.8 SD below the mean of 67 normal persons (36.1 U/gm Hb; 22.5-58.1 (± 2SD)). Nine additional family members in 3 generations could be recognized as having ADA values similar to the parents' values. The mean activity of the combined heterozygotes was (19.2 U/gm Hb; 14.0-24.4 (± 2SD)). One sibling of the proband could not be accurately classified as normal or heterozygous. Our data suggests that ADA deficiency is autosomally transmitted and heterozygotes for ADA⁰ can be correctly detected with a probability of 90 percent.

ELEVATED IgA LEVELS ACCOMPANIED BY CHROMOSOME ABERRATIONS. David J. Segal, Henry F. Pabst and Ernest E. McCoy. Univ. of Alberta, Dept. of Pediatrics, Edmonton, Alberta, Canada.

Persistently increased IgA is a rare clinical observation, occurring in liver cirrhosis (all immunoglobulins increased) and myeloma (IgA is monoclonal). We have observed 4 patients with IgA greater than 300 IU/ml (normal range 25-200 IU/ml) with no evidence of liver dysfunction or myeloma; IgG and IgM values were normal, as were *in vitro* responses to PHA and ConA. Surprisingly, each patient showed variable aneuploidy in PHA-stimulated blood cell cultures. Fifty metaphases were counted and at least five karyotypes prepared for each patient.

Age	Clinical condition	IgA	abnormal karyotypes
11	chronic Trichophyton infection	303	3/9
15	severe mental retardation	302	5/5
49	TB plus pulmonary Aspergillus	370	2/6
73	tuberculosis	428	2/5

Three patients displayed aberrations such as translocations, quadriradial formation, chromosome additions and deletions, affecting no specific group; one patient showed 18p- in all cells, provoking interest because of reports of IgA decrease in association with 18p-. Chromosome aberrations and profound immunodeficiency occur in Bloom's syndrome, Fanconi's anemia, ataxia telangiectasia and xeroderma pigmentosum. The high IgA values reported here may therefore reflect a basic stem cell defect, manifested as lymphoid cell aneuploidy.

CELL CULTURE STUDIES ON CLASSIC AND VARIANT FORMS OF TYPE II GLYCOGEN STORAGE DISEASE (GSD). S. Shanske, A. Shanske and H. M. Nitowsky, Depts. Ped. and Gen., Albert Einstein Coll. Med., Bronx, N. Y.

Studies have been carried out on acid α -1,4 glucosidase (α -glu) activity, glycogen content, and uptake of exogenous partially purified α -glu from placenta and urine by fibroblast cultures from skin of patients with infantile (classic) and adult (variant) forms of type II GSD. Using 4-methylumbelliferyl α -D-glucoside as substrate, about 10% of normal activity was observed in cell extracts from 2 adults, whereas no activity was demonstrable in cells from infantile type II GSD. No evidence was obtained for complementation following cell fusion and formation of heterokaryons using Sendai virus. Increase in glycogen content was observed in confluent cultures, but there was no consistent difference between normal and mutant cell strains. For enzyme incorporation studies, human α -glu was partially purified from urine or placenta by NH_4SO_4 precipitation and isoelectric focusing. Incubation of mutant cells in medium containing partially purified α -glu resulted in restoration of normal cell enzyme activity. The kinetics of increase and persistence of cellular α -glu activity following removal of exogenous enzyme suggests that cells are capable of incorporating enzyme. Cell cultures may provide a useful model for an approach to *in vivo* enzyme replacement therapy.

THE NATURE OF RESIDUAL ARYLSULFATASE ACTIVITY IN LATE INFANTILE METACHROMATIC LEUKODYSTROPHY (MLD). Emmanuel Shapira* and Henry L. Nadler. Northwestern Univ. Med. Sch., Children's Mem. Hosp., Dept. of Pediatrics, Chicago.

Late infantile MLD is a familial degenerative neurologic disease presumably caused by a mutation of arylsulfatase A (ASA). In order to study the residual arylsulfatase activity in MLD, the two lysosomal isoenzymes, ASA and ASB, were purified from human liver and a specific antiserum to ASA prepared. The IgG fraction of the antiserum was covalently bound to CNBr-activated Sepharose 4B. Liver homogenates from normal and MLD patients as well as purified ASA gave an identical precipitin line when examined by double gel diffusion. The ASA activity of the preparations was determined and were then adsorbed with the insoluble anti-ASA antibodies. After adsorption, no crossreacting material with anti-ASA antiserum could be demonstrated. The ASA activity after adsorption was 17% of the original for the normal liver homogenate, 9% for the purified ASA, and 98.5% for the MLD liver homogenate. When purified normal ASA and ASB activities were determined, the ASB was found to have residual enzymatic activity (7%) in the A substrate determining assay. A synergistic effect of the normal and mutant ASA on the ASB activity determination assay was also observed. These data indicate that the mutant ASA in late infantile MLD has no enzymatic activity and the residual "A-like" activity is secondary to the ASB isoenzyme. Further studies are needed to determine whether or not the B isoenzyme in this form of MLD is enzymatically and antigenically identical to the normal B.