† **774** PRENATAL DIAGNOSIS OF A GIRL WITH MUSCULAR DYSTROPHY CAUSED BY DE NOVO t(X;4)(p21;q35). Jacquelyn Roberson, Daniel L. Van Dyke, Bernard Mandelbaum, and Lester Weiss. Henry Ford Hospital and Wayne State University, Detroit, Michigan.

In May, 1983 we obtained amniotic fluid for chromosome studies from a couple who were both 31 years old. The indication was parental anxiety because the mother worked closely with mentally retarded adults. The amniotic fluid cell karyotype was female with a balanced translocation: 46,X,t(X;4)(p21;q35) with the normal X preferentially inactivated. Alpha fetoprotein and detailed ultrasound examinations were normal. Chromosome studies of the parents were normal, so the translocation apparently arose as a new mutation.

Two special circumstances complicated the counseling. First, a de novo rearrangement ascertained by amniocentesis carries roughly a 5% increased risk of birth defects over the general 3-5% population incidence of birth defects, but the available risk estimates do not appear to include the risk of mental retardation without malformation, since follow-up has been sporadic of such cases identified prospectively. Second, in a balanced X/autosome translocation the structurally normal X is genetically inactivated, which allows expression of any abnormal genes on the translocation X. There are at least 13 other girls with Duchenne muscular dystrophy who carry a de novo X/autosome translocation with a breakpoint at Xp21. In the absence of a family history of muscular dystrophy, these findings suggest a point mutation due to the break at Xp21.

We advised the parents that the fetus was at some increased risk (of uncertain magnitude) for having malformations, retardation, or muscular dystrophy. The couple continued the pregnancy. At age 3 months, the infant has a normal appearance, developmental milestones and neurologic exam. However, at 24 hours of age her serum CPK was 21,450 IU/L. Subsequent values were 1,260 and 3,100 at 1 and 3 months, respectively. Such neonatal and infancy levels of CPK are strongly suggestive of Duchenne's muscular dystrophy.

777 ISOCHROMOSOME 9q IN AN INFANT EXPOSED TO ETHANOL PRENATALLY. Karen J. Sanders, Lytt I. Gardner, James Coplan, Douglas P. Kalinowski and Navnit Mitter. SUNY-Upstate Medical Center, Depts. of Pediatrics and Pathology, Syracuse, New York.

A two year old girl with several dysmorphic features was found to have an isochromosome for the long arm of number 9: 46,XX,-9,+i(9q). We could find no previous report of this chromosome abnormality. Furthermore, the mother reported that she "drank 3 to 6 beers a day, plus occasional binge drinking" up until pregnancy was diagnosed at 7 weeks gestation. Birth weight was 2.2 kg (below 3rd percentile). Placenta was small, with thin cord and only 2 vessels. The baby was "malnourished" and "peeling", with blood glucose values as low as 15 mg/dl. At age 19 months there was global developmental delay, with skills at 9-10 month level and mild hypotonia. At 23 months she exhibited a small midface, narrow palpebral fissures, slight epicanthal folds, mild ptosis, pectus excavatum, bilateral simian creases, clinodactyly V, syndactyly toes 2-4 and dystrophic toe nail V. There was a bicuspid aortic valve and slight aortic insufficiency. It is difficult to sort out phenotypic effects of i(9q) and ethanol embryopathy. Ethanol (via acetaldehyde) has been shown to interfere with the spindle apparatus (Harsanyi et al. Mutation Res. 48:51, 1977). Acetaldehyde is clastogenic in man, causing chromosomal aberrations and sister-chromatid exchanges (Obe & Ristow Mutation Res 65:229, 1979) Our patient may have suffered both clastogenic and teratogenic effects of prenatal ethanol toxicity.

● **775** GENE DELETION AND RESTRICTION FRAGMENT LENGTH POLYMORPHISM (RFLP) AT THE HUMAN ORNITHINE TRANSCARBAMYLASE (OTC) LOCUS. R. Rozen, A. Horwich, W. A. Fenton L. E. Rosenberg. Depts. of Human Genetics and Pediatrics, Yale Medical School, New Haven, CT

OTC, the second enzyme of the urea cycle, is a mitochondrial protein encoded on the X chromosome. Inherited OTC deficiency, which typically leads to neonatal ammonia intoxication and early death in hemizygous affected males, cannot currently be detected prenatally by amniocentesis because OTC is not expressed in amniocytes. To develop such diagnostic capability by examining directly the OTC gene, a rat OTC cDNA was used to screen a human liver cDNA library. Several clones containing human OTC sequences were isolated. A plasmid was constructed containing the entire human OTC coding sequence (1500 bp), and was used as probe in Southern blot analysis of DNA prepared from control human cells and from cultured fibroblasts of 7 patients with lethal OTC deficiency. Studies with Eco RI and several other restriction enzymes indicated that the human OTC gene normally spans ∿30 kb and contains at least 8 introns. Blots from 6 of 7 OTC-deficient patients were indistinguishable from controls. In the 7th, however, whose liver contained no detectable OTC activity or cross-reacting material, restriction with Eco RI or Hind III revealed the absence of a 3.0-3.5 kb band; no new bands were seen. This OTC gene deletion was localized to the 3' end of the OTC coding sequence. Furthermore, we have observed an RFLP, using Msp I, in 2 of 10 female controls, and are searching for other RFLPs which may be useful in counselling those families at risk whose genetic defect does not involve gene deletion.

● **778** DETECTION OF A NOVEL DNA POLYMORPHISM IN THE ß-GLOBIN CLUSTER AND EVIDENCE FOR SITE-SPECIFIC RECOMBINATION. Gregg L. Semenza, Padmini Malladi, Mortimer Poncz, Kathleen Delgrosso, Elias Schwartz, and Saul Surrey. University of Pennsylvania School of Medicine and Children's Hosp. of Phila.

Within the εγδß-globin gene region a non-random association of polymorphic restriction sites 5' and 3' to the δ globin gene has been observed. Between these two clusters lies a 9 kb region including the δ-globin gene which may contain sites of increased recombination. Analysis of DNA from an Albanian family revealed a novel Rsa I site 550 bp 5' to the ß-globin gene within the 9 kb region. One maternal and one paternal chromosome were identical at 9 polymorphic sites but differed at the Rsa site. This finding suggests that this polymorphism is randomly associated with previously defined haplotypes. Population screening showed the presence of this site in people of northern European, Mediterranean, Middle Eastern, African, Southeast Asian and Asian Indian descent, with an overall frequency of 0.39. DNA regions with $ß^A$, $ß^S$,$ß^E$ and ß-thalassemia alleles carrying and lacking the Rsa site were also identified. In one individual sequence analysis showed 28 alternating purine-pyrimidine dinucleotides in the region containing the Rsa site, rather than the 26 previously found in other individuals, suggesting that unequal crossing-over in this immediate region may lead to randomization of 5' and 3' polymorphic clusters.

776 INTRAUTERINE DIAGNOSIS OF SEX CHROMOSOME ANOMALIES: PROGNOSIS AND MANAGEMENT. Arthur Robinson. University of Colorado School of Medicine and National Jewish Hospital and Research Center, Department of Pediatrics and Department of Biochemistry, Biophysics and Genetics, Denver.

Intrauterine diagnosis places upon the physician the responsibility for making a diagnosis and a prognosis for an individual he has not seen or examined. Prognostication for a fetus with sex chromosomal aneuploidy (SCA) is particularly difficult and varies tremendously in various centers and in various parts of the world. As a result, the message patients get from their counselors and what action patients take varies greatly in different parts of the country. The author has received 86 telephone consults either from counselors or patients from various parts of the U.S.A. and Canada and has followed up the actions taken by these consultands. Two-thirds of couples, who represent a biased selection, have continued the pregnancy, irrespective of the fetal karyotype. The nature of the prognosis and future management of these high risk fetuses, especially the impact of environmental factors and long-term support, will be discussed.

779 PRENATAL DIAGNOSIS OF THE FRAGILE X CHROMOSOME. Lawrence R. Shapiro and Patrick L. Wilmot. Depts. of Pediatrics and Pathology, New York Medical College and Westchester County Medical Center, Valhalla, N.Y., and Genetics Laboratory, Letchworth Village, Thiells, N.Y.

The development and validation of prenatal testing for the fragile X chromosome [fra(X)] is important because of the estimated high prevalence of the disorder.

In order to confirm the validity of the successful prospective prenatal diagnostic techniques which we reported in 1982, a plan was designed for the use of amniocytes in tissue culture which included: tissue culture medium 199 for the last 72-96 hours of culture and medium RPMI-1640 to which FUdR in various concentrations, trimethoprim, or methotrexate was added.

To date, a total of 18 amniotic fluid specimens have been tested for fra(X) with the following results: 2 male fetuses positive for fra(X), 8 negative males, and 8 negative females. One of the males positive for fra(X) was confirmed by fetal blood testing prior to termination. The second positive male was confirmed by peripheral blood testing after birth. Follow-up confirmation has been accomplished in 5 of the negative females with 4 cases awaiting delivery and 7 pending.

Additional cases are required for further validation and experimental efforts should continue.