

THE EFFECTS OF TERATOGENIC ANTISERA ON PROTEIN SYNTHESIS AND DEGRADATION BY THE CULTURED RAT CONCEPTUS.

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Rat embryo culture was initiated on the 10th day of gestation to study embryonic site protein synthesis in normal and pathologic states. Three culture media were employed: rat serum, serum plus teratogenic sheep anti-rat visceral yolk sac (VYS) serum, or rat serum plus normal sheep serum. Two studies were performed: a) ^3H -leucine was added to produce incubation periods of 20 min. to 24 hr.; and after an initial period of culture in the presence of ^3H -leucine to obtain a constant precursor specific radioactivity, culture was continued in the absence of ^3H -leucine for a total of 1-30 hr. Embryos, VYS and culture media were analysed for total radioactivity and ^3H -leucine specific radioactivity in the protein-bound and free amino acid fractions. The results suggest that: a) anti-VYS serum inhibited protein synthesis by the embryo and VYS but had no detectable effect on protein degradation; b) anti-VYS serum increased intracellular labeled leucine concentration. The teratogenic mechanism of anti-VYS serum appears to involve both the suppression yolk sac amino acid nutritive support of the embryo and the inhibition of the utilization of amino acids by the embryo for protein synthesis. These techniques provide us with the ability to determine the amino acid requirements which will support normal organogenesis and to quantitate the amino acid deprivation which will result in embryopathology. (Supported by NIH)

THE EFFECT OF TERATOGENIC ANTISERA ON RAT FETAL DEVELOPMENT WHEN ADMINISTERED LATE IN DEVELOPMENT.

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In 1961 we reported that heterologous antisera prepared in the rabbit against rat kidney proved to be teratogenic when injected into pregnant rats (Brent et al, Proc. Soc. Exp. Biol. Med.). The teratogenic antiserum localized in the yolk sac and yolk sac antisera proved to be a potent rat teratogen. Metabolic studies have indicated that the yolk sac dysfunction is due to the antiserum's ability to interfere with the endocytosis of macromolecules, thus depleting the embryo and yolk sac of required quantities of amino acids. Two important questions were asked. At what stage of rat gestation does teratogenic antiserum no longer have an embryotoxic effect on the developing embryo or fetus and does the teratogenic antiserum affect pinocytosis late in rat development. Pregnant rats were exposed to teratogenic antiserum and while the most dramatic effects were produced during early organogenesis, embryonic and fetal effects were observed during the early fetal period several days after trypan blue no longer affected the embryo. Mortality or growth retardation were not observed when pregnant rats were administered teratogenic antiserum the last 5 days of rat gestation, in spite of the fact that the antisera does depress pinocytosis in vitro in the yolk sac late in gestation. (Supported by NIH)

TUBULAR BONE ALTERATIONS IN FAMILIAL SHORT STATURE
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An anthropometric study was performed on 40 Caucasian children with familial short stature (FSS) and compared with 40 age-, race-, and sex-matched children with normal height (C-NH), and 250 adolescent girls with normal height (AG-NH). Anthropometric measurements were also obtained on 30 short parents of the FSS (P-SS) and compared with 26 normal height parents of the FSS (P-NH) and 33 normal height adults (Ad-NH). Brachymetacarpus V, rhizomelia, and short upper and lower limbs were highly prevalent among the FSS patients as compared to the control groups. Brachymetacarpus V was present in 75% of FSS whereas only 28% of C-NH and 33% of AG-NH had this trait ($P < 0.01$). Among the FSS patients 42% had rhizomelia, 38% had short arms, and 65% had short legs whereas in the normal height children only 15% had rhizomelia, 12% had short arms and 30% had short legs ($P < 0.01$). Brachymetacarpus V was also more prevalent among the P-SS than among the Ad-NH (73% vs 33%) ($P < 0.05$). Rhizomelia and short limbs also appeared to be more prevalent in the P-SS than in the two other adult groups. The concomitant presence of more than one type of tubular bone alteration was more commonly seen in the FSS groups than in the control groups. All affected FSS patients had one or two affected parents suggesting a possible autosomal dominant mode of inheritance. The high prevalence of tubular bone alterations in FSS patients suggests that an altered tubular bone elongation or endochondral ossification is probably responsible for short stature in a large proportion of these families.

GENITOURINARY TRACT DYSMORPHOLOGY AND MATERNAL COCAINE USE. Ira Chasnoff and Gay Chisum (Spon. by James Stockman III). Northwestern Univ. Medical School, Dept. of Pediatrics, Chicago.

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Specific fetal dysmorphology associated with maternal cocaine use has not as yet been documented. In the first 23 pregnancies evaluated in our program for chemically dependent women, one infant with prune-belly syndrome and one infant with hypospadias were delivered to cocaine-using women. Subsequently, all infants delivered in our program have received a renal ultrasound at 2 to 3 days of life. Twenty-five infants born to polydrug (non-cocaine)-using women (Group I) and 25 born to cocaine-using women (Group II) have been evaluated thus far. The two groups are similar for maternal age, gravidity and race. All Group I women used marijuana and/or alcohol, and 5 women were additionally addicted to narcotics. All Group II women were cocaine users; 15 used alcohol and/or marijuana in addition. Mean birth weight of the two groups was similar. No infant in Group I had observable malformations except one infant with fetal alcohol syndrome, and all ultrasounds were normal. In Group II, two infants had a similar cluster of abnormalities: hydronephrosis, unilateral claw hand deformity and genital abnormalities (a female with ambiguous genitalia and absent uterus and a male with hypospadias and chordee of the penis with undescended testes). Renal ultrasound examination revealed 4 cocaine-exposed infants in Group II with hydronephrosis, one of whom had a 2^o hypospadias. From this preliminary study, it appears that infants delivered to cocaine-using mothers should be evaluated for abnormalities of the genitourinary tract.

VALPROIC ACID EMBRYOPATHY. David A. Chitayat, Kevin Farrell, Linda A. Anderson and Judith G. Hall
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We describe three children born to an epileptic woman who received carbamazepine (CBZ) and methosuximide (MT) during one pregnancy and valproic acid (VPA) and CBZ during the other two pregnancies. The children exposed to VPA and CBZ showed craniofacial abnormalities including prominent forehead, epicanthal folds, hypoplastic zygomatic arches, shallow philtrum, depressed nasal bridge, posterior angulation of the ears and infraorbital creases while the child exposed to only CBZ and MT did not.

In addition to the previously described features, both patients exposed to CBZ and VPA had lateral displacement of the medial origin of the eyebrows and a carrying angle of zero degrees. One of them also had hypoplastic nails and teeth. This unique family enabled us to compare sibs with the same parents who were exposed to a different combination of antiepileptic drugs and evaluate potential teratogenic effect.

The findings in this family would support the previous observation that valproic acid may be associated with a pattern of dysmorphic features in addition to the 1-2% risk for neural tube defect it is known to have when taken during the early part of pregnancy.

PRENATAL DIAGNOSIS OF POLYSPLENIA SYNDROME. David A. Chitayat, Agnes E. Lau, Judith G. Hall and K. Douglas Wilson, University of British Columbia, Department of Medical Genetics, Vancouver, B.C. Canada

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We report prenatal diagnosis of polysplenia syndrome in two cases of fetal bradycardia associated with complex cardiac abnormalities. Both cases were found during pregnancy to have congenital heart block and to have on ultrasound no spleen demonstrable. At autopsy, both cases were found to have polysplenia syndrome with complex cardiovascular anomalies.

Polysplenia is one of the syndromes which presents as a defect of lateralization. The most frequent manifestations besides polysplenia are pulmonary isomerism of the left lung, abdominal heterotaxia and complex congenital heart disease. The mortality rate is very high. Only 10% of the patients live to adolescence. In the subgroup of polysplenia, which presents with congenital heart block, the mortality is even higher. Although most of the cases of polysplenia are sporadic, there are reports of familial clustering of defects of lateralization (e.g., polysplenia, asplenia, situs inversus totalis and Kartagener syndrome) which raise the possibility of autosomal recessive transmission, thus the availability of prenatal diagnosis is desirable for subsequent pregnancies.

Our cases were found by careful pregnancy monitoring during which congenital heart block was observed. Ultrasound can usually delineate complex cardiac anomalies and documentation of an absent spleen can enable more accurate diagnosis, prognosis and management.