●1260 EFFECTS OF VALPROIC ACID ON THE FETUS. James W. Hanson, Holly H. Ardinger,*John DiLiberti,**Helen E. Hughes,°Mary Jo Harrod,°°Albert Schinzel, #Sterling Clarren, ##R. Dwain Blackston. (Sponsored by Samuel J. Fomon). Departments of Pediatrics, The University of Iowa College of Medicine, Iowa City, *University of Oregon, Portland Oregon, **Toronto Sick Children's Hospital, Toronto, °Texas Southwestern, Dallas, °°Institute for Medical Genetics, Zurich, #University of Washington, Seattle, ##Emory University, Atlanta.

Valproic acid is a recently identified human teratogen now clearly associated with neural tube defects in offspring of exposed pregnant women. Other recent studies have suggested an increased risk for congenital heart disease and facial clefts. We report 13 infants with prenatal valproate exposure for maternal epilepsy. The facial features in this group of children suggest a characteristic appearance including midfacial hypoplasia, telecanthus, and broad, low, nasal bridge with short nose. Two of the children have neural tube defects, 3 have cardiac defects, and 1 a cleft lip. In addition, several show growth or developmental disturbances. Taken together, these observations suggest a broader pattern of abnormalities which may be attributable to valproic acid. These may range from mild effects to a more serious fetal valproate syndrome.

1261 INCIDENCE OF MAJOR CONGENITAL MALFORMATIONS IN OFFSPRING OF ALCOHOLICS AND POLYDRUG ABUSERS

A study was carried out comparing the incidence of major anomalies: severe microcephaly (>3SD), hydrocephalus, cleft palate, congenital heart disease, scoliosis, club feet, constriction bands and cryptorchidism in the offspring of mothers who abused alcohol only (group I), versus alcohol and heroin or methadone and/or cocaine (group II). The average age of the mothers, ethnic background and amount of alcohol abused during pregnancy (3 oz of absolute alcohol/day) were similar.

In the first group, comprising 92 children with FAS, 30 malformations were found, 8 patients had congenital heart disease and 2 died in the first year of life. In the second group, comprising 36 patients with FAS, 6 major anomalies and no deaths were recorded (1 case of congenital heart disease).

Major congenital anomalies, including severe cardiac malformations, were significantly more frequent in group I. It seems that for yet unexplained reasons the combination of ethanol and opiates is less teratogenic than alcohol alone.

1262 EMBRYO CONSIDERED AS A VECTOR FIELD

Charles H. Klippel, Jr.

Technical limitations have deprived embryology of quantitation and have led to several untenable concepts. A vector study based on uniformly magnified embryo photographs, centered on biologically and topologically acceptable coordinates has improved the situation and opened the way for four dimensional mathematical treatment of the problem and development of the equations is presented.

1263 MALIGNANT HYPERTHERMIA AND NOONAN VERSUS KING SYNDROME. Boris G. Kousseff, (Spon. by Lewis A. Barness), University of South Florida College of Medicine, Department of Pediatrics, Tampa.

Malignant hyperthermia (MH) is a heterogeneous pharmacogenetic disorder; it has been reported as autosomal dominant and recessive traits, and with myotonia congenita, Duchenne and Barnes muscular dystrophies, Evans myopathy, central core disease, Kniest, Noonan and King syndromes.

The recognition of Noonan syndrome has helped the differentiation of the Turner-like phenotypes. Variable expressivity and pleiotropism characterized this syndrome and two types may exist. Patients with Noonan-like phenotype, myopathy and MH have been referred to as having King syndrome; 2/5 patients reported by King et al had contractures.

Two unrelated children diagnosed elsewhere as having Noonan syndrome and congenital arthrogryposis appeared to have King syndrome; both had Noonan facies, webbed neck, average intelligence, normal karyotypes and no heart anomaly. The female has had two episodes of MH. She also had hypomimic facies and winged scapules. Muscle biopsy showed evidence of myopathy. The mother of the male was of average stature and intelligence, but had Noonan facies and webbed neck.

Myogenic arthrogryposis, average intelligence and lack of heart defect may allow differentiation between King and Noonan syndromes. The screening platelet bioassay and the caffeine contracture test may be of help in identifying the patients at risk for MH; once identified, these patients should wear Medic alert bracelets.

†1264 CONGENITAL MALFORMATIONS AND EXPOSURE TO EXOGENOUS FEMALE SEX HORMONES, Edward J. Lammer, Jose F. Cordero, Godfrey P. Oakley, Jr., Center for Environmental Health, Public Health Service, U.S. Department of Health and Human Services, Atlanta, Georgia 30333.

We conducted a case-control study of maternal sex hormone exposure and the risk for major malformations. Using population-based surveillance data from the Metropolitan Atlanta Congenital Defects Program, we analyzed interviews from 1970-1979 for first trimester exposures to sex hormones among mothers of children with the following defects: oro-facial clefts; Down syndrome; diaphragmatic hernia; limb reduction defects; and esophageal, intestinal, or anal atresia. During the study period, 1,396 children with at least one of these defects were born in the surveillance area and 79% of the mothers were interviewed. For each defect category, the other defect categories served as the comparison group. We found no associations between any defect and oral contraceptive exposures; however, we did find an association between esophageal atresia and sex hormone exposure (odds ratio (OR) = 2.8, p = 0.009). Sex hormone exposures were subdivided, and associations persisted between esophageal atresia and 1) progestins and non specified sex hormones combined, and 2) hormonal pregnancy tests. Our findings suggest a relationship between esophageal atresia and non contraceptive sex hormone exposures. If causal, however, exposure would have a low absolute risk, on the order of 6/10,000 exposed live births.

1265 FETAL HYDROCEPHALUS AND EAR ANOMALIES ASSOCIATED WITH THE MATERNAL USE OF ISOTRETINOIN. Ira T. Lott, Henry W. Pribram, Marc Leitner. University of California Irvine, Medical School, Departments of Pediatrics and Neurology.

A 16 year old mother took 40 mg of isotretinoin (13-cis retinoic acid) daily for cystic acne during the first 130 days of pregnancy. An enlarged fetal head necessitated Caesarian section. The live born infant showed an increased cranial-facial ratio, low set and simplified auricles and an atretic ear canal A.D.. Neurological responses were depressed with poor visual tracking and minimal pupillary constriction to light. At age 5 months there had been no developmental progress. Brain stem evoked responses were abnormal on the right and non-elicitable on the left. An intravenous pyelogram was negative. The CT findings included aqueductal stenosis and an area of cerebral tissue loss in the right occipital region. The right hemicranium was enlarged compared to the left. In rats and rabbits, isotretinoin is similar to vitamin A in producing teratogenic effects involving the ears and brain. Taken together with our observation on the outcome in this human infant, it is suggested that sexually active women under treatment for acne not be given isotretinoin unless an effective form of contraception is utilized and the potential risk to the fetus is described. Should conception ensue, the physician and patient should discuss the desirability of continuing the pregnancy.