was in excess of 6 years. Additional features of this syndrome are significant motor and mental retardation, and an unusual facies including coarse eyebrows, prominent eyes, and low, upturned nose. Respiratory infections have been a major clinical problem. One patient died at 20 months of age from a hemorrhagic pneumonia and his autopsy did not reveal any cellular explanation for his condition. The other patient is having severe respiratory infections at 11 months of age. Both patients have been extensively investigated for the presence of endocrine or storage disorders, and no cellular or biochemical abnormalities have been detected. Although the etiology of this disorder remains unknown, the mechanisms underlying this syndrome may enhance our understanding of control mechanisms beside androgen, estrogen, or thyroid hormone which affect the rate of skeletal maturation.

Presented at the Western Society for Pediatric Research meetings. This material is of sufficient importance to be presented to a national audience.

- 23 *Genesis and Significance of Palmar and Digital Creases.* GREGORY A. POPICH and DAVID W. SMITH. Dept. of Ped., Univ. of Washington Sch. of Med., Seattle, Wash.

Our studies of skin creases in the early developing hand and in a variety of malformed hands show that these creases, which develop between 7 and 14 weeks of fetal life, are secondary to the early flexion planes in the developing hand. Thus with lack of development or flexion of a digital joint no underlying digital crease was found; and with lack of formation or oppositional function of the thumb there was no thenar palmar crease. The normal distal palmar sloping crease was found to be related to the sloping flexional plane of the 3rd, 4th, and 5th metacarpal-phalangeal joints and the usual mid-palmar crease represents the plane of skin folding between the sloping distal crease and the thenar crease. The occurrence of a single horizontal palmar crease, the simian crease, was found by roentgenographic studies to be related to a diminished slope of the 3rd, 4th, and 5th metacarpal-phalangeal joints such that only a single early horizontal plane of flexion existed in the skin of the upper palm.

Thus hand creases provide a record of the early flexional planes of function in the developing hand and any crease abnormality should always be interpreted as an indication of a more primary defect in form and/or function of the early developing hand.

- 24 *Severe Pyridoxine Deficiency: A Model for Ataxia Telangiectasia.* THOMAS E. NELSON, STARKEY D. DAVIS and THOMAS H. SHEPARD, Univ. of Wash. Sch. of Med., Dept. of Ped., Seattle, Wash.

The association of neural, vascular, and immunologic abnormalities in ataxia telangiectasia is unexplained. We studied the teratogenic effects of B_6 as an experimental model because it is associated with (1) neonatal convulsions and (2) impaired immunologic response in rats. Pregnant rats were given a B_6 -deficient diet and 4-desoxypyridoxine, an inhibitor of B_6 . The control group had the same plus excess pyridoxine. The fetuses were examined at 20 days. Treated rats developed clinical signs of B_6 deficiency and gained less weight than the controls. Mean weight of 108 B_6 -deficient fetuses was 1.63 g; mean crown rump length was 28.3 mm. The 61 control fetuses had a mean weight of 3.24 g and a mean length of 37.0 mm; no anomalies were found in the control group. Of the treated group, 48%

had digital defects, 20% had cleft palates, 12% had omphaloceles, 8% had micrognathia, and 6% had exencephaly.

Organ weights (as g % formalin fixed body weight)

Fetus	Kidney	Thymus	Spleen
Treated (21)	0.88	0.19	0.03
Control (25)	0.85	0.24	0.14

Though the thymus and spleen are both significantly smaller ($p < 0.001$) in the treated group, only the spleen is strikingly hypoplastic. We anticipate that intra-uterine B_6 deficiency will cause a lifelong immunologic defect.

- 25 *The Production of Multinucleated Lymphocytes by Cytochalasin B. An Electron Microscopic Study.* G.F. SMITH, P.O'HARA and M.A.C. RIDLER, Dept. of Ped., Loyola Univ. Stritch Sch. of Med., Maywood, Ill., and Kennedy-Galton Lab., St. Albans, England.

The cytochalasins are newly derived from moulds and are useful in studying nuclear division. Multinucleated fibroblasts were produced by CARTER [Nature 213: 261, 1967] and lymphocytes by us [Nature 216: 1134, 1967]. Lymphocytes with up to eight nuclei were seen. Progressive nuclear addition [1, 2, 3, etc.] was found instead of a doubling of the nuclei (1, 2, 4, etc.). The term 'pseudomitosis' was proposed for the process of synchronous mitosis, but which results in the division of only one nuclei.

Our observations, using the light microscope shows the nuclei of binucleated cells to be similar in size and shape; however, in cells with more than two nuclei there is marked variation in size and shape of each nucleus. What might have appeared, in many instances, as separate nuclei are seen by electron microscopy to be lobes of a rather large and irregular nucleus. In other instances, small nuclear bridges connected what might appear as separate nuclei. Variation exists in nuclear size from rather large nuclei to very small micronuclei. Serial sectioning of cell nuclei verified the morphological variability seen in single sections. Spindle fibers and kinetochore attachment to the chromosomes revealed no unusual features. Electron microscopy showed synchronous division of nuclei. Golgi apparatus remained as a single large unit. There was a doubling of centrioles in binucleated cells. What appears as separate nuclei under the light microscope were connected by nuclear bridges. The finding suggests that as nuclei accumulate that the spindle bridge is unable to accurately divide the large numbers of chromosomes present.

- 26 *Phocomelia With Mandibular Hypoplasia: A New Syndrome.* SALMA REGINA ASSEMAN, TADASHI KAJI and LYTT I. GARDNER, State Univ. of New York, Upstate Med. Center, Dept. of Ped., Syracuse, NY.

We have observed the association of non-thalidomide phocomelia and hypoplasia of the mandible (Pierre-Robin syndrome) in two unrelated infants. Baby boy C was born at term after a normal gestation. The mother was 29 and denied either illness or medication during pregnancy. Five months postpartum she had no glucosuria. The baby showed multiple deformities: both hands were hypoplastic with no visibly separate fingers. The right hand was more primitive than

the left. X-ray revealed absence of the tubular bones of the metacarpals and phalanges bilaterally. The feet showed similar abnormalities. There was micrognathia, glossoptosis, cleft soft palate and tracheomalacia. Eyes and fundi were normal. The baby expired after numerous apneic spells associated with cyanosis.

Baby boy D was born at term to a 29-year-old mother who was hospitalized for schizophrenia during the pregnancy; she showed intermittent glucosuria. The infant exhibited micrognathia, shortening of the right femur and bilateral club feet. X-rays showed the cortex of the femurs to be abnormally thick, and defects were noted in the vertebral bodies of the lower lumbar column. Ocular fundi were normal. The baby expired after a gastrostomy and repeated apneic episodes.

Cytogenetic studies on both patients were normal. Our two patients, together with the previously reported two cases [PASSARGE, *Lancet* *i*: 324, 1965; CENTA and ROVEI, *Pathologica* 57: 245, 1965] appear to represent a distinct syndrome.

- 27 *Development of Transsulfuration in the Human Fetus, Premature and Newborn: Clinical Implications.* GERALD GAULL, JOHN STURMAN and NIELS RAIHA, Dept. of Ped. Res., N.Y.S. Inst. Basic Res. Ment. Retard., Dept. Ped., Mt. Sinai Hosp. Sch. Med., New York, and Depts. Clin. Chem. and Obst. and Gyn., Univ. Helsinki (introduced by Horace Hodes).

In the human adult, 90% of ingested methionine is converted to cystine, a nonessential amino acid. The ability to make this conversion was investigated in the developing human. Enzymes on the pathway of conversion of methionine to cystine in the liver of 24 fetuses (2.5–20.5 cm crown rump length), three prematures and one full-term newborn were assayed. *Cystathionase* activity was undetectable, and administration of massive doses of vitamin B₆ to the mother had no effect on this activity in three fetuses. Cystathionine, the substrate of cystathionase, not normally present in measurable quantities in adult human liver (which has considerable activity of cystathionase) was present in large concentrations. Considerable activity of methionine-activating enzyme was present ($\frac{2}{3}$ of adult); cystathioninesynthase activity was also present ($\frac{1}{3}$ – $\frac{1}{2}$ of adult). A similar pattern of transsulfuration enzymes was seen in brain, but there are no antemortem adult controls for comparison. The concentration of cystathionine in whole brain was constant during this period and, in contrast to the adult, well below the concentration in liver. The placenta cannot subserve the transsulfuration function for the fetus, since the enzymatic mechanism was absent. Fetal rat liver, in contrast, is able to convert methionine to cystine. Thus, cystine may be an essential amino acid until sometime after birth, and the human fetus is entirely dependent upon the mother for its supply of cystine for protein synthesis. The implications for infant nutrition and metabolic screening will be discussed.

- 28 *Chloramphenicol Causes Ultrastructural and Biochemical Alterations in Developing Chick Liver.* J. B. WARSHAW, Harvard Med. Sch., Massachusetts Gen. Hosp., Children's Service and the Shriners Burns Institute, Boston.

Chloramphenicol (Ch) administration has been associated with the fetal 'gray baby syndrome' and depression of the hematopoietic system. Ch also causes alterations of mitochondrial morphology and inter-

feres with mitochondrial energy metabolism in a variety of species. We have investigated the effects of Ch on mitochondrial energy metabolism and structure in the developing chick liver. Ch and ¹⁴C-leucine were injected through shell windows into 12 to 17 day chick embryos. After 3 days of exposure to the drug the livers were fixed for electron microscopy and were also used for biochemical studies. Electron micrographs of the Ch treated livers showed major ultrastructural alterations characterized by profound mitochondrial swelling and distortions of mitochondrial structure. There was also a great abundance of free ribosomes. The cytochrome oxidase activity of the treated liver homogenates and the mitochondrial yields from Ch treated livers were approximately 40 to 50% of those of the controls. Mitochondrial profiles of Ch treated liver homogenates on sucrose density gradients were greatly diffused when compared with controls, presumably because of the ultrastructural abnormalities. ¹⁴C-leucine incorporation into the Ch treated liver mitochondria separated on a sucrose density gradient was significantly less than observed with controls. Those mitochondria which were isolated had some biochemical activities similar to the controls (isocitric dehydrogenase, malate dehydrogenase) but rates of oxidation with NADH limited substrates were less than control values. These data suggest that Ch may interfere with energy metabolism in rapidly proliferating tissues because of its effects on protein synthesis and mitochondrial structure and function.

- 29 *The Metabolism and Transplacental Passage of 3H-Vitamin D3 in the Pregnant Primate, Macaca mulatta.* HENRY RIKKERS, Univ. of Wisconsin Med. Sch., Dept. of Ped., Madison, Wisc. (introduced by C. C. Lobeck).

In animal systems excessive maternal ingestion of vitamin D during pregnancy has been shown to cause in the offspring most of the bony and arterial pathology seen in idiopathic hypercalcemia of infancy. This disease is felt by some to be due to altered responsiveness of the fetus and/or mother to vitamin D. Mammals, including man, convert vitamin D to 25-hydroxy vitamin D before the vitamin has its characteristic effects. A previous study demonstrated nonspecific antirachitic activity in cord serum of rabbits whose mothers had been given massive vitamin D doses during pregnancy. The current study demonstrates not only how much, but also, in what metabolic form the vitamin traverses the placenta.

C-sections were performed 6, 24, 48 and 100 h after IV administration of 3H-vitamin D3 in non-physiologic doses to pregnant rhesus monkeys. All tissues within the fetal compartment were studied for the amount and metabolic state of the vitamin present. Results show that the placenta acts as a barrier and storage organ from which the fetal serum somewhat selectively supplies fetal tissues with, mainly, 25-hydroxy vitamin D. Fetal tissues do not appear to convert vitamin D to 25-hydroxy vitamin D. The data suggest that at physiologic doses the fetal tissues would probably not be exposed to unaltered vitamin D. This suggests that the teratogenicity of vitamin D is due to undue exposure of fetal tissues to the unaltered vitamin.

- 30 *Early Mammalian Development: Nucleoside Transport and RNA Synthesis.* DONNA L. DAENTL and CHARLES J. EPSTEIN, Univ. of California, Dept. of Ped., San Francisco.