Gross edema formed at higher differential pressures. Thus the pups developed minimal PE at lower TPAWP than would have been expected from their T.P. and COP. The data do not permit a choice of the several factors that might explain this finding. Similar susceptibility of the human fetus and newborn in relation to the adult would favor the development of PE during the perinatal period and might thus play a role in the pathogenesis of pulmonary problems of the newborn.

- 173 *The Effect of Thyroxine on Fatty Acid Biosynthesis in Brain.* JORGE GRIPPO and JOHN H. MENKES, UCLA Sch. of Med., Los Angeles, CA.

Fatty acid synthesis by chain elongation occurs in microsomal and mitochondrial fractions of rat brain. With myelination (13–16 days of age) the rate at which microsomal particles incorporate malonyl-CoA into saturated fatty acids characteristic for myelin is increased. The present study was undertaken to study control mechanisms of fatty acid synthesis in brain.

Daily injections of triiodo thyronine ($60 \mu\text{g}/100 \text{ g}$ body wt.) were given from age 1 day to 2 h prior to sacrifice. In the microsomal system incorporation of malonyl-CoA into fatty acids in 5–6-day-old animals was increased from $0.91 \pm 0.52 \text{ m}\mu\text{M}/\text{mg}$ protein to $2.25 \pm 0.39 \text{ m}\mu\text{M}/\text{mg}$ protein. The increase in precursor incorporation occurred almost entirely into saturated fatty acids. Thyroid had no significant effect on fatty acid synthesis by microsomal particles derived from animals sacrificed at other stages of development or from adult rats.

Incorporation of acetyl-CoA into both saturated and unsaturated fatty acids by mitochondria was slightly increased by thyroid in adult animals and at 3–6 days of age, but the differences were not significant.

These studies suggest that thyroid accelerates the normal maturational increase in microsomal fatty acid synthesis. This probably occurs by stimulating the synthesis of the enzyme system involved in the production of fatty acids characteristic for myelin.

- 174 *Mechanisms Responsible for the Sensitivity of New-born Rats to Pregnanolone.* LESTER F. SOYKA, LASZLO GYERMEK and PATRICIA CAMPBELL, Stanford Univ. Sch. of Med., Palo Alto, CA.

The minimum lethal dose of pregnanolone, a potent pharmacologically active metabolite of progesterone, increased about 60-fold from birth to weaning. This was greater than the increase seen with non-steroid hypnotic drugs. The brain concentration of pregnanolone at the onset of hypnosis was $0.35 \mu\text{g}/\text{g}$ in 3-day-old and $7\text{--}10\times$ higher in 23-day-old rats, indicating an elevated receptor threshold. Similarly, older rats awoke at a brain concentration $6\times$ higher than that maintaining sleep in younger animals. Hepatic biotransformation to sulfate and glucuronic acid esters and more polar steroids was extremely rapid, even in 3 day olds. Seven minutes after i.p. administration of pregnanolone with radioactive tracer only 29 and 37% of the total cpm in blood and liver were present as free pregnanolone. Although metabolism was somewhat faster in older rats, the relative increase was not quantitatively important compared to the extent of newborn sensitivity. A number of metabolites were found in blood, brain and liver of which pregnanediol was a surprisingly small component. Esters in the liver (at 45 min post-injection) were predominantly sulfates. No conjugates were found in brain. Pregnanolone accumulation in brain, as a percentage of the injected dose, was slightly

greater in newborns, though far less than predicted assuming uniform distribution. In almost all previous developmental studies, impaired hepatic metabolism has been of sufficient magnitude to explain accentuated pharmacologic responses. These studies may be the first to experimentally verify the concept of altered receptor threshold in the brain as a mechanism for the sensitivity of newborn animals to drugs.

- 175 *Familial Neuromuscular Disease and Non-ketotic Glycinemia.* GRANT MORROW III, ASLAN AKSU, WILLIAM BANK, L. P. ROWLAND and L. A. BARNES, Dept. of Ped. and Neurol., Hosp. Univ. of Pennsylvania and Univ. of Pennsylvania Sch. of Med., Philadelphia, PA.

A family of Lebanese extract is described in which 3 of the 4 children (all males) have neuromuscular disorders and a primary aminoaciduria. The symptoms in those affected began in early childhood and are slowly progressive. In the 2 older siblings (age 22 and 24), the neurological disorder implied dysfunction of both spinal cord and peripheral nerves: weakness, wasting and loss of reflexes of distal muscles, combined with hyperactive reflexes, and spasticity of other muscles. EMG and muscle biopsy indicated denervation but conduction velocity of peripheral nerves could not be estimated because action potentials were not evoked by stimulation. Symmetrical upper motor neuron disease with clonus, spasticity, bilateral Babinski signs, and increased deep tendon reflexes were the clinical picture in the 10-year-old sibling. Examination and EMG in the mother and unaffected 14-year-old sibling were normal. The syndrome has features of both Friedreich's ataxia and Charcot-Marie-Tooth disease.

Urinary amino acids were measured on 6 members of the family. The combination of massive isolated glycinuria and neuromuscular disease was found only in the 3 affected males. Amino acid quantitation of the propositus revealed a plasma glycine of $0.817 \mu\text{M}/\text{ml}$ (normal $0.150\text{--}0.300$) and urinary excretion of $1720 \text{ mg}/\text{day}$ (normal <200). None of the patients were clinically acidotic and urinary organic acids were normal. Propionate metabolism in white cells of the entire family was normal. This is the first known example of an inherited neuromuscular disorder associated with a specific amino acid abnormality. (Supported in part by USPHS grants nos. AM-02231 and HD-04837.)

- 176 *A Syndrome of Hypopituitary Dwarfism, Hypoplasia of Optic Nerves, and Malformation of Prosencephalon: Report of 6 Patients.* SELNA L. KAPLAN, MELVIN M. GRUMBACH and WILLIAM F. HOYT, Dept. of Ped. and Ophthal., Univ. of California, San Francisco, CA.

We have suggested that 'idiopathic' hypopituitary dwarfism (IHP) is a heterogenous disorder of disparate pathogenesis [New Engl. J. Med. 278: 57, 1968]. Among a group of 36 children with sporadic IHP (16 isolated GH and 20 multiple pituitary deficiencies) in whom mass lesions were excluded, 6 patients (3F, 3M) had a distinctive clinical entity of dwarfism, optic nerve dysplasia, and midline abnormalities of the prosencephalon. The findings included: congenital diabetes insipidus in 2; bilateral hypoplasia of optic nerves with small optic discs in 6; pendular, dysjunctive nystagmus in 5; bilateral amblyopia in 3; inconstant, irregular field defects in 5; and documented growth