

For an update of antiepileptic drugs and teratogenicity, refer to Weber M. *Rev Neurol* (Paris) 1987;143:413. According to this report, the frequency of congenital malformations among children of epileptic mothers is twice that in the general population, genetic factors play a major role, and generally the teratogenic potential of antiepileptic drugs is low and does not contraindicate pregnancy in epileptic women. Many neurologists and certainly geneticists would advise stricter selectivity and caution in the choice of anticonvulsant for epileptic women contemplating pregnancy. Drugs with especially high or relatively frequent teratogenic potential (e.g. trimethadione, phenytoin) are usually contraindicated, those with moderate or unknown degrees of propensity (primidone, valproic acid, carbamazepine, clonazepam) are avoided when possible, and the drug of choice, least likely to induce malformations and most often recommended, is probably phenobarbital.

#### CONGENITAL MALFORMATION AND MATERNAL PHENYLKETONURIA

Infants born to women with PKU are frequently mentally retarded, microcephalic, of low birthweight, and have various malformations. The results of an international collaborative study (in UK, Europe, Australia) by the MRC/DHSS Phenylketonuria Register concerning the diet of pregnant women with PKU are reported from the Institute of Child Health, London:

(1) Normal birth weights and head circumferences and no malformations in 17 infants whose mothers received a strict low phenylalanine diet at conception; (2) below average birthweights and head circumferences and excess malformations a) in 29 infants whose mothers were on a relaxed or normal diet at conception and a strict diet during pregnancy, and b) in 18 infants whose mothers received no dietary treatment during pregnancy. Birth weights and head circumferences of the 64 infants were inversely related to the maternal phenylalanine concentrations at conception, and hyperphenylalaninemia in early gestation had a dose-dependent effect on the fetus. The authors estimate 2000 women with PKU of fertile age by 1990 in the UK and unless monitored closely through their reproductive lives, a substantial number of microcephalic and mentally retarded children will be expected. (Drogari E, Smith I (for correspondence), Beasley M, Lloyd JK. Timing of strict diet in relation to fetal damage in maternal phenylketonuria. *Lancet* 1987;2:927-930).

**COMMENT.** A National Collaborative Study of Maternal PKU was initiated in the US in 1984 and initial findings will be evaluated in 1991. Female PKU patients of fertile age receive education concerning risks to offspring and need for dietary and blood phenylalanine monitoring during pregnancies (O'Flynn M, Director PKU Clinic, Children's Memorial Hospital, Chicago, personal communication).

Levy HL and Waisbren SE (*N Engl J Med* 1983;309:1269) studied the effects of maternal PKU and hyperphenylalaninemia on 53 offspring from untreated pregnancies. Decreases in IQ, head circumference, and birth weight of the infants were correlated directly with the maternal IQ and inversely with maternal blood phenylalanine level. These authors concluded that maternal PKU has a substantial adverse effect on the fetus, and less severe maternal PKU may have subtle effects, resulting in slight reduction in IQ and intrauterine head growth. The UK report demonstrates that mothers with PKU who start a low phenylalanine diet before conception can give birth to normal infants despite variable phenylalanine blood levels during pregnancy. Congenital malformations

and irreversible impairment of brain and body growth are determined within the first trimester of pregnancy.

### METABOLIC AND DEGENERATIVE DISEASE

#### LEIGH SYNDROME AND CYTOCHROME OXIDASE

Mitochondrial enzymes were studied in 5 unrelated children with neuropathologically proven subacute necrotizing encephalomyelopathy (Leigh syndrome) at the College of Physicians and Surgeons, New York. Four patients showed psychomotor regression, ophthalmoparesis, nystagmus, optic atrophy, hypotonia, areflexia, ataxia, and abnormal breathing beginning in the second year and died after 3 to 4 years of an intermittently progressive course. The fifth child was floppy at birth, regressed at 5 mos, and died of congestive heart failure at 7½ mos. All had lactic acidosis and autopsies showed typical symmetrical necrotic and cystic lesions in the brain stem and cerebellum. Muscle biopsy was normal by light microscopy but showed mitochondrial changes on ultrastructural examination. A decrease in cytochrome c oxidase (COX) activity was found in brain, muscle, kidney, heart, liver and in cultured fibroblasts. The authors conclude that COX deficiency is an important cause of Leigh syndrome (DiMauro S et al. Cytochrome c oxidase deficiency in Leigh syndrome. Ann Neurol 1987;22:498-506).

COMMENT. The family history was negative in these patients but previous reports of autosomal recessive inheritance and occurrence in siblings are common. In one family from Quebec, 7 members in two generations had a mitochondrial encephalopathy and COX deficiency. Diverse clinical and pathological expressions of Leigh's disease in this family was explained by maternal transmission of varying proportions of mutant mitochondrial DNA. (Berkovic SF et al. Neurology 1987;37 (Suppl 1):223). Leigh syndrome, previously termed Leigh's disease and first described in 1951, appears to be nonspecific biochemically as well as clinically. In addition to the COX deficiency described above, defects of the pyruvate dehydrogenase multienzyme complex and pyruvate carboxylase have been reported. An inhibitor of the brain enzyme that catalyzes the formation of thiamine triphosphate has been found in the urine but the test is not diagnostic. Consistent early clinical features in the infantile cases are a quiet immobility with lack of crying and hypotonia.

#### REYE SYNDROME AND ASPIRIN

Twenty-six cases of Reye syndrome occurring between 1973 and 1982 have been reviewed in relation to aspirin ingestion at the Children's Hospital, Camperdown, Australia (formerly the Royal Alexandra Hospital for Children in Sydney), where Reye first described his syndrome of encephalopathy and fatty degeneration of the viscera in 1963. The ages ranged from 3 mos to 7 yrs (median 22 mos). Only 5% of patients had ingested aspirin and 30% acetaminophen. For the period of this study, aspirin accounted for 0.3% and acetaminophen for 99.7% of all pediatric analgesic/antipyretic sales. Despite this lack of association of Reye syndrome with aspirin use, Reye syndrome has been as common in Australia as in the US (9 cases per/million children c.f. 10-20 cases/mil in US and 3-7/mil in UK). The authors conclude that the purported association of