low concentration of copper, although albumin-bound copper is present in marked excess; there is also a great increase in the rate of excretion of copper in the urine. Studies with ^{64}Cu have shown that as the disease progresses the liver steadily loses its ability to concentrate the metal until, in advanced cases, there is virtually no uptake of injected copper. Once treatment has been established and the patient adequately 'decoppered' the liver will regain its ability to concentrate the metal (Osborn & Walshe, 1967). This has been interpreted as evidence that the binding sites for copper in the liver become progressively saturated until, late in the disease, the metal spills over and is deposited in other tissues, principally the brain and kidneys. The suggestion that the impaired hepatic uptake of copper is a consequence of non-specific liver damage unrelated to the genetic defect (Levi & Williams, 1968), is based on inadequate data and failure to understand the natural history of the illness.

Treatment of Wilson's disease. If the theory that Wilson's disease is related to copper toxicity is correct then the mobilization of copper should result in reversal of the disease process. This has proved to be true so that the neurological, hepatic and renal lesions have all been shown to be reversible once negative copper balance has been established (Walshe, 1968). This is achieved by oral administration of penicillamine (Walshe, 1956), which renders copper available for filtration at the glomerulus. The copper so lost from the plasma is presumably replaced from the excess stored in the tissues; this can be demonstrated by observing the resorption of the copper deposits in the cornea. However, for treatment to be effective it is necessary to establish and maintain a negative copper balance over long periods of time. Of the large number of chemicals studied only penicillamine has so far proved able to do this.

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Inherited Abnormalities Affecting the Nervous System: Genetic and Psychiatric Aspects

By J. STERN and VALERIE COWIE. (*Queen Mary's Hospital for Children, Carshalton, Surrey*)

The biochemistry of a number of inborn errors of metabolism affecting the nervous system is well understood. However, even in so extensively studied a disorder as phenylketonuria, little is known about the mechanism by which brain function is disturbed (Menkes, 1967). In phenylketonuria the basic defect is largely extracerebral; the organ primarily involved is the liver. However, recent work suggests that phenylalanine may also be oxidized in the brain. Factors affecting the minor fraction of phenylalanine metabolized in the brain might well have a disproportionate effect on intellectual function (Pauling, 1968). A wide spectrum of psychiatric symptoms is found in untreated phenylketonurics, although these may be obscured by the severe impairment of the intelligence. The picture is further complicated by the genetic heterogeneity of the disease. Four alleles probably exist at the locus for phenylalanine 4-hydroxylase: the normal (wild type) allele, the silent typical allele for phenylketonuria and two further alleles, one of which gives rise to an enzyme susceptible to substrate inhibition and the other coding for an enzyme of low activity which is not, however, susceptible to substrate inhibition (Justice, O'Flynn & Hsia, 1967; Woolf *et al.* 1968).

The interplay of genetic heterogeneity and variability in neuropsychiatric involvement is also found in histidinaemia. In most cases skin L-histidine ammonia-lyase activity is absent. Woody, Snyder & Harris (1965) found, however, that the enzyme was present in the skin of three siblings with the disease. In one family histidinaemia was found to be accompanied by alaninaemia (Auerbach, DiGeorge, Carpenter, Black & Reusch, 1967). The majority of patients are mildly or moderately mentally retarded. The evidence for a specific speech defect is not convincing. There is no simple relation between the biochemistry and brain damage. Waisman (1967) studied four siblings with obesity, mental retardation and a degenerative brain disease. Three only of the children also had histidinaemia. Corner, Holton, Norman & Williams (1968) found antenatal lesions in the brain of their patient. We have recently seen a 3-year-old girl with histidinaemia who is clinically perfectly well and has a I.Q. of 120.

Mental retardation is not always the most prominent neuropsychiatric symptom in inborn errors of metabolism. Thus a patient with hyperprolinaemia type 2, Δ^1 -pyrroline-5-carboxylic acid dehydrogenase deficiency, was only mildly retarded but had petit-mal epilepsy (Emery, Goldie & Stern,

1968). Encephalitis-like episodes have been described in patients with this disease (S. Berlow, personal communication). Symptoms are unlikely to be explained by the raised proline levels in the body fluids. The clinical picture in hyperprolinaemia type 1, proline oxidase deficiency (Efron, 1966), is quite different. Renal disease sometimes with deafness and photogenic epilepsy are found in affected families. Though the renal disease is transmitted from generation to generation, the hyperprolinaemia occurs only in sibs of one generation. Efron (1966) has suggested that the hereditary pattern is similar to that of haemoglobin H disease. Alternatively a mutation in an operator or regulator gene could affect more than one structural gene in the same operon.

A similar hypothesis has been proposed by Goedde (1967) for the genetics of maple-syrup-urine disease. Oxidative decarboxylation of the three keto acids corresponding to the branched-chain amino acids is mediated by three distinct enzyme systems. It is postulated that in this disease mutation of one operator gene affects three structural genes for three distinct enzyme proteins. Goedde (1967) suggests that a three-allele model on these lines could also account for the intermittent variant of maple-syrup-urine disease (Kiil & Rokkones, 1964), in which normal development for months or years is followed by an acute episode of fever, vomiting, lethargy or ataxia, accompanied by the biochemical picture of maple-syrup-urine disease.

In disorders of the Krebs urea cycle (Efron, 1967), ammonia intoxication appears to be responsible for the lethargy, vomiting, coma, seizures and ataxia observed in affected patients. The enzyme blocks are only partial and urea synthesis does take place. In citrullinaemia the enzyme responsible for the synthesis of argininosuccinic acid is present but is structurally altered. It has low activity and a high K_m value (Tedesco & Mellman, 1967).

The trans-sulphuration pathway is active in brain as well as liver. Metabolic blocks occur along this pathway in homocystinuria, above cystathionine, and in cystathioninuria, below cystathionine. Mental disorder is therefore associated with a deficiency of cystathionine in homocystinuria and an excess of cystathionine in cystathioninuria, although normal intelligence may be found in both disorders. Massive doses of pyridoxine by mouth and pyridoxal phosphate *in vitro* lead to increased activity of cystathioninase, suggesting a defect in the binding of coenzyme. A minority of homocystinurics also respond to pyridoxine therapy.

At least one case of cystathioninuria (Frimpter, 1966) and two cases of homocystinuria (Spiro, Schimke & Welch, 1965; A. C. Kaeser, R. Rodnight & B. A. Ellis, 1969) have been associated with

psychoses. We have seen a patient who had been in hospital for many years as a chronic schizophrenic. Increased incidence of psychiatric illness in relatives of homocystinurics has been reported (Carson, Dent, Field & Gaull, 1963; Dunn, Perry & Dolman, 1966). A role has been suggested for methionine in the pathogenesis of some forms of schizophrenia (Kety, 1967; Smythies, 1967).

Careful evaluation of the psychiatric features in patients with phenylketonuria and homocystinuria may give clues to the biochemical mechanisms of thought disorders. In higher-grade patients behaviour problems and psychotic features may respond to treatment even if started at the age of 3 years or later (J. Cowie, personal communication).

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