correlation between the changes that occur and the pathogenesis of the disease can only be speculative at this time.

B. Metabolism of Catecholamines

The possibility of defective catecholamine biosynthesis (Fig. 4) in phenylketonuria was suggested by the observation of decreased concentrations of catecholamines in the plasma[286,287] and urine[287] of these patients. The excretion of normal amounts of catecholamines, but the excretion of decreased amounts of the metabolite vanillylmandelic acid, also has been reported.[288] On a low-phenylalanine diet there were increases in plasma and urine catecholamines,[287] in urinary vanillylmandelic acid,[288] and in the accumulation of the metabolite homovanillic acid in cerebrospinal fluid after the administration of probenecid.[93] Curtius *et al.*[289] administered deuterated L-tyrosine to patients with phenylketonuria and found a lower excretion of metabolites of dopamine and norepinephrine when the patients had a high plasma phenylalanine concentration than when the plasma phenylalanine concentration was low. Although such findings do not necessarily reflect the situation in the brain, the recent analysis by McKean[93] has shown that the norepinephrine content of the caudate nucleus, the brain stem, and the

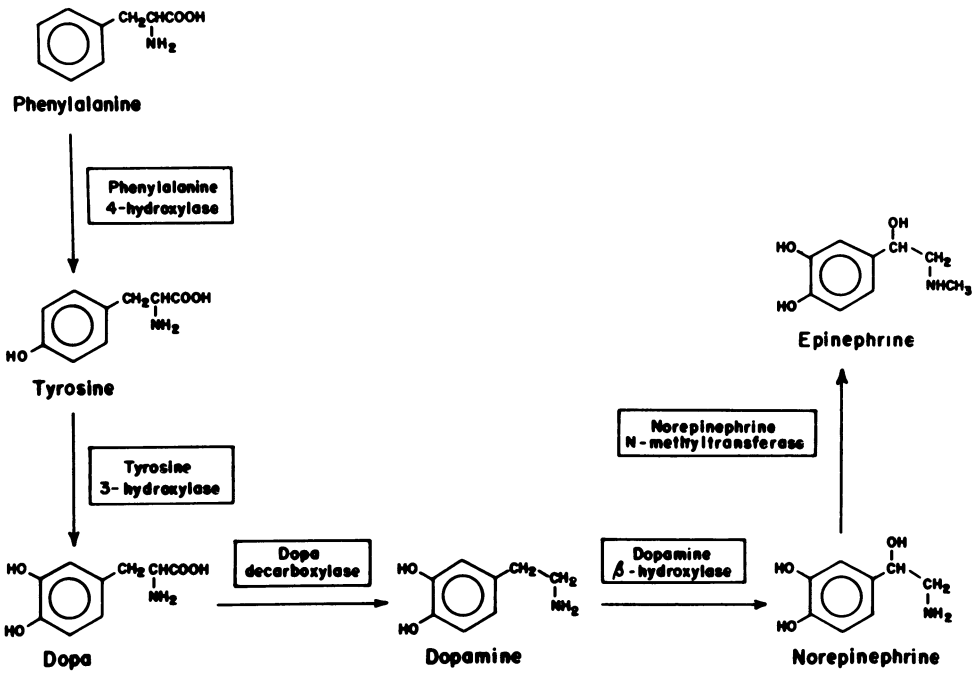

Fig. 4. Steps in the synthesis of the catecholamines.

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per.[49] In almost every patient with Wilson's disease the capacity of this excretory route is limited, since he cannot synthesize normal amounts of ceruloplasmin.[50]

Second, evidence from several independent studies indicates that the biliary excretion of copper is considerably diminished in Wilson's disease, apparently because of a defect in hepatic lysosomes.[51]

Little attention has been paid to how remarkably small a positive balance of copper is sufficient to result in the accumulations seen in patients with Wilson's disease: no more than 10–20 mg, out of well over a gram of copper eaten each year, is retained, a 1% positive balance.

A. Pathology

The effects of copper on the structure of the liver and the brain of patients with Wilson's disease have little specificity to distinguish them from the changes induced by other toxins. In the liver the copper is associated with a sequence of stages—fat accumulation; inflammation; the appearance of delicate, and then of coarse, fibrous bands; and hepatocellular necrosis resulting in collapse of parenchyma and regeneration—which eventuate in classical postnecrotic, nodular cirrhosis,[52,53] unique only in two histopathological respects. First, histochemical stains demonstrate that the excess hepatic copper in children with Wilson's disease is diffusely distributed throughout the cytoplasm of liver cells, in contrast to its localization in lysosomal granules in hepatocytes of normal newborn babies,[54] in whom physiologically large hepatic copper concentrations do not cause pathological consequences, probably because copper sequestered by hepatic lysosomes is innocuous.[53]

Second, electron microscopic study of biopsy samples of liver from patients with other types of liver disease, with Wilson's disease, and with no hepatic disorder has shown that specific mitochondrial changes—enlargement, bizarre shapes, changes in matrix density, presence of vacuoles and inclusions, and separation of the normally apposed inner and outer membranes—are seen only in patients with Wilson's disease (Fig. 1).[55] They are found only during the early stages of the disease and not when the cirrhosis is established.[53]

In the brain the distribution of copper and its pathological effects can be seen only in fatal cases and not in biopsy tissue, so that the natural sequence of pathological events and the effects of therapy, rather well known for the liver, are much less so for the brain.

The ventricular system is usually enlarged because of atrophy of basal ganglia. The lenticular nuclei show symmetrical atrophy and yellow or reddish brown discoloration. Gross cystic changes, noted by Wilson,[56] are seen in the putamen and globus pallidus (Fig. 2) Despite the name given it by Wilson, the cerebral degeneration in this disease is not limited to the lenticular nuclei, but it may invade the cerebral hemispheres and the cerebellum, so that the term *hepatocerebral degeneration* is more appropriate (Fig. 3),[57] though even that omits reference to several instances in which central pontine myelinolysis has been seen.[58]

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