THE BIOCHEMICAL DEFECT IN FARBER'S DISEASE

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In 1967 Prensky et al. reported the accumulation of ceramide in the postmortem tissues of a patient with Farber's disease (1), and in 1971 Samuelsson and Zetterström reported such an accumulation in a second case (2). In 1972 Sugita, Dulaney and Moser demonstrated the deficient activity of an acid ceramidase in the tissues of the case reported by Prensky et al. (3). Since this same enzymatic defect has now been demonstrated in three additional unrelated patients, it appears likely that the deficient activity of acid ceramidase represents the basic defect in this disease, and makes it appropriate to appraise our current knowledge about this striking rare disorder.

The clinical and pathological features of Farber's disease were very well described in the original report of three cases by Farber, Cohen and Uzman (4), and in the review by Crocker, Cohen and Farber which formed part of a previous symposium held at this Institute (5). The characteristic feature is a granulomatous lesion which contains a varying number of foam cells. The granulomas involve the joints, subcutaneous tissues (usually at points subject to pressure), the larynx, the lungs, often the kidney, and less commonly the heart, liver and spleen. The changes in the joints and subcutaneous nodules lead to striking deformities and those in the larynx to hoarseness and aphonia. These features make the diagnosis in classical cases unmistakeable. The main abnormality in the nervous system is the accumulation of storage material in the neuronal cytoplasm. This material is PAS positive and for the most part extractable with lipid solvents (6, 7), although some histochemical studies also suggested that there was polysaccharide accumulation (8). Neuronal storage is most
prominent in the anterior horn cells of the spinal cord, the large nerve cells of the brain stem nuclei, in the posterior root cells, and the autonomic ganglia. Cortical neurones also show storage, but less so than in other parts of the nervous system. While few ultrastructural studies have been performed, their results suggest that there is intralysosomal accumulation of lipids and possibly polysaccharides (9, 10, 11).

Farber's disease usually is rapidly progressive; of the 14 reported cases 10 died before age 2 years (4, 6, 8, 9, 12, 13, 14, 15). One patient who was already severely involved during his first year survived until age 16 years (2, 16). A one year old child, who is now severely disabled, is at present being followed by one of us (Sidbury). In addition, two patients have been reported who are more mildly disabled; one is a French girl who was 13 years old when she was reported in 1973 (10), and the other a boy of Portuguese extraction, reported by Crocker, Cohen and Farber at the previous symposium here (5). This boy, now 12 years old, is doing well in school and is only very mildly disabled by joint changes. While the clinical and pathological features in the mild and severe cases suggest strongly that they represent the same disease process, the biochemical studies to be reported here have been carried out only in the severely involved cases. Genetic data about Farber's disease are very limited; among the 14 reported cases 9 were females and five males. There is only one instance in which a pair of sibs were affected. There were a total of 19 unaffected sibs. In one instance parents were first cousins; in eleven instances parents were reported not to be related to each other. No cases have been described in previous generations. Thus, while the limited genetic data are compatible with an autosomal recessive mode of inheritance, this is far from proven.

Changes in Levels of Tissue Components

The late Lahut Uzman reported the presence in Farber's disease tissues of an abnormal "lipoglycoprotein" complex, which accounted for 8 to 30% of total lipids (4). This material was not fully characterized. Increases in neutral glycolipid or in ganglioside levels were reported by Clausen and Rampini (17) and by Moser et al. (6). In one case there was a considerable increase in the level of tissue mucopolysaccharides and a moderate increase in urinary polysaccharides (12), but this has not been found in other cases (2, 5, 6, 13). The most striking abnormality has been the accumulation of ceramide. It should be noted that ceramides are normally only present in small quantity ranging from 0.05% of total lipid in plasma to 1% in brain. Quantitation of ceramide levels often is not attempted when tissue components are analyzed, and had not been performed in the Farber's disease cases studied.