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15. Since preparation of this manuscript an abstract has appeared which reports the occurrence of extracellularly recorded bursts of action potentials in lateral geniculate neurons during interictal activity in a penicillin-induced epileptogenic focus in visual cortex. The authors of the abstract suggest that these spikes are antidromic [A. D. Rosen and E. F. Vastola, *Trans. Amer. Neurol. Ass.* **96**, 297 (1971)].
16. This investigation was supported by PHS grant NS 06477 to D.A.P. and PHS postdoctoral fellowship No. 42766 to M.J.G. We thank D. Kennedy and P. Schwartzkroin for helpful suggestions and comments on the manuscript and Pamela Vario for secretarial assistance.

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Deficiency of α-L-Fucosidase

Abstract. *A new form of α-L-fucosidase deficiency has been found in a 20-year-old severely retarded male. Additional signs include angiokeratoma corporis diffusum and anhydrosis. The skin lesion is due to an accumulation of residual bodies, presumably containing oligosaccharides and glycoproteins, in endothelial cells and fibrocytes. The enzyme activity in blood relatives indicates that the disease is inherited as a simple autosomal recessive trait that segregates according to Mendelian principles. Because the enzyme activity in the heterozygotes was consistently below that of normal controls, the carriers of the trait in this family could be ascertained.*

A significant decrease in, or absence of, activity of a lysosomal hydrolase in all tissues of an individual is the biochemical hallmark of lysosomal diseases. In some of these diseases, the predominant or exclusive substrate for the defective enzyme accumulates selectively, such as in acid maltase deficiency (Pompe's disease) (*1*) and in many of the sphingolipidoses (*2*). In other lysosomal diseases, for example the mucopolysaccharidoses, the defective enzyme normally hydrolyzes several biological substrates, and therefore different nondegradable biochemicals accumulate in residual bodies. The α-L-fucosidase deficiency presumably belongs in the latter category. Four children with this biochemical defect have been described: two with the clinical picture of Hurler's syndrome, and two with symptoms that were less distinct (*3*, *4*). All four suffered from severe mental and physical retardation, and a hyperhidrosis.

We now report on a patient with a deficiency of α-L-fucosidase, who also suffers from severe mental and physical retardation. However, although our patient is afflicted with angiokeratoma corporis diffusum, a skin lesion characteristic of Fabry's disease, the α-galactosidase activity in our patient is normal whereas it is below normal in Fabry's disease (*5*).

The patient, a 20-year-old white male, was the product of an uneventful pregnancy and delivery. His parents are not known to be related to each other by blood, nor are his grandparents. His early development was unremarkable, but at the age of 14 months mental and motor retardation became obvious with his failure to walk and talk; he did not learn to understand the spoken word. At the age of 24 months, muscular weakness and hypotonia were noted, and his physical growth, being within normal limits up to this time, began to slow down. At age 16, he weighed only 75 pounds, was 4 feet tall, and showed severe kyphoscoliosis and a pigeon chest. He never displayed organomegaly nor did he present radiographic evidence of skeletal abnormalities compatible with mucopolysaccharidoses. Since the age of 2 years the patient has been bedridden, and has experienced frequent episodes of respiratory tract infections.

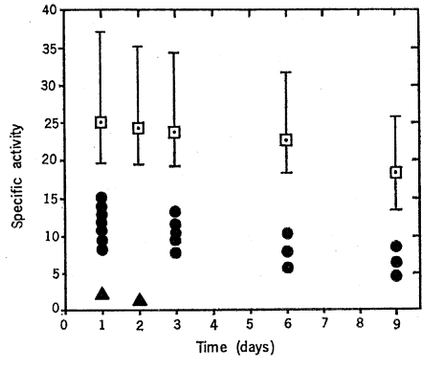

Fig. 1. Effect of storage time at 4° to 5°C on leukocytic α-fucosidase activity (nanomoles of *p*-nitrophenol liberated per milligram of protein per hour). ⊡, mean of ten controls with total range indicated by bar; ●, carriers; ▲, patient. No significant age-dependent differences (from 2 to 60 years) for leukocytic α-fucosidase activity were observed.

At age 4, he developed blue-brown, pinhead-sized, raised skin lesions, first over the abdomen and back, and then involving the lower, and finally the upper extremities, producing the characteristic picture of angiokeratoma corporis diffusum. Histological examinations revealed multiple teleangiectasias. Anhidrosis and inability to control body temperature developed synchronously with the skin lesions and necessitated confinement of the patient to an air-conditioned room for the last 10 years. For the past 2 years, the patient has suffered from convulsions at the rate of approximately one per month. The electroencephalographic tracings showed low voltage activity throughout with occasional paroxysms of 3- to 4-hz rhythmic waves, but no spike-wave discharges.

Because of the characteristic clinical and histological aspects of the skin lesion, a tentative diagnosis of Fabry's disease was made. However, we recognized that the severe mental and physical retardation did not fit this diagnosis nor did the normal renal functioning.

We measured (*6*) the activity of various lysosomal hydrolases in leukocytes, prepared according to a minor modification (*7*) of the procedure of Snyder and Brady (*8*). Urinary hydrolases were assayed as follows. Urine was collected over a period from 12 to 24 hours and was filtered; the proteins were precipitated with ammonium sulfate in a molal concentration between 1.5 and 4.5, were dissolved in 5 m*M*

tris(hydroxymethyl)aminomethane at *p*H 6, and were dialyzed for 6 hours against several changes of the same buffer. The dialyzed material was used for measuring hydrolase activity; undialyzed proteins, however, appeared to possess the same degree of activity. Concentrations of leukocytic and urinary proteins were determined by the method of Miller (*9*).

Leukocytic (Fig. 1) and urinary α-fucosidase activity of the patient was less than 10 percent of normal controls, whereas other lysosomal hydrolase activities were either normal or slightly increased. The activity of α-fucosidase decreased as a function of storage time at 4° to 5°C, in about equal decrements for patients, carriers, and controls. Because it was initially so low, the α-fucosidase activity of the patient was not measurable after 48 hours of storage. The leukocytic enzyme activities of parents and several blood relatives ranged from 30 to 60 percent that of normal controls. Although the activity in the controls varied between 19 and 37 units, there was no overlap with the activity of the carriers, all of whom showed an activity of 15 units or less. We conclude tentatively that leukocytic α-fucosidase activity is a diagnostic tool to determine the carrier state for this disease.

Electron microscopy of a punch biopsy of the skin revealed massive alterations of all endothelial cells and most fibrocytes (Fig. 2). The characteristic feature of these cells is the cytoplasmic distention, by numerous putative tertiary lysosomes, in the form of small vacuoles. In contrast to the superficially similar situation in Fabry's disease where these "storage lysosomes" contain lamellated membranous bodies consisting predominantly of ceramide trihexoside, in our patient no such lamellae were present. The material contained in the vacuoles appears to be partly eluted by fixation, or by dehydration procedures, or by both. The electron microscopic appearance of these storage vacuoles is reminiscent of that seen in mucopolysaccharidoses (*1*); the vacuoles are bound by a unit membrane derived from the Golgi–endoplasmic reticulum–lysosome system.

In three of the other known patients, the lysosomal enzyme defect was fatal when the patients were between the ages of 3 to 5½ years; our patient has survived much longer and also does not

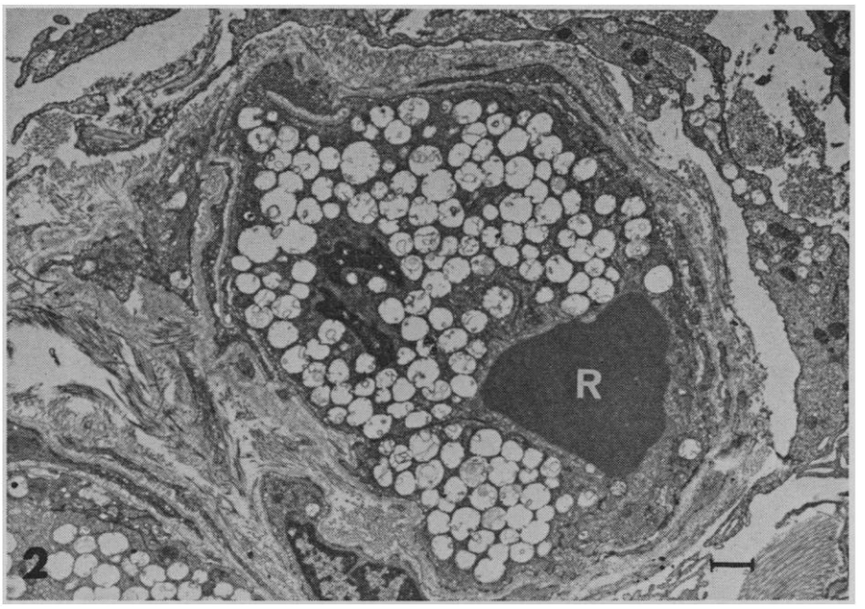

Fig. 2. A blood capillary in the dermis showing swollen endothelial cells due to presence of numerous cytoplasmic vacuoles. The neighboring fibrocytes contain similar vacuoles. Micron marker inserted; *R*, red blood cells (× 5200).

sweat, whereas the others exhibited a severe hyperhidrosis. Three of the patients were products of first-cousin marriages, but no consanguinity has been demonstrated for our patient.

Whether the enzymatic defect in our patient is different from those previously reported is not quite clear, but is possible by analogy to other lysosomal diseases, such as β-galactosidase and β-hexosaminidase deficiency where components of the respective enzymes are deficient in different degrees (*10*). This assumption is suggested by the clinical differences between our patient and others reported in the literature.

It is interesting that Freitag *et al.* (*4*) observed two types of residual bodies in a liver biopsy. The Kupffer, biliary epithelial, and vascular endothelial cells harbored largely empty vacuoles containing a granulofloccular material and sparse membranous profiles similar to those shown in dermal fibrocytes and endothelial cells (Fig. 2). The residual bodies in hepatocytes, however, were dense and osmiophilic due to multilayered lamellar structures arranged in fingerprint patterns. Because of previous experiences with lysosomal diseases involving the accumulation of glycolipids, we assume that the glycosphingolipid tentatively identified as fucose (1→2)–galactose (1→3)–*N*-acetylglucosomine (1→4)–galactose (1→4)–glucose-ceramide, and isolated from this patient by Dawson and Spranger (*11*), originated from the latter type of residual bodies. The nature of the material contained in the former type remains unknown; from its appearance in electron micrographs, and from the known substrates for α-L-fuscosidase, we assume that it represents oligosaccharide chains, either free or bound to polypeptides.

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