GENETIC DISEASES OF MUCOPOLYSACCHARIDE CATABOLISM; SINGLE-ENZYME DEFICIENCY DISORDERS. E. F. Neufeld (Bethesda, MD, USA)

The biochemical basis of the mucopolysaccharidoses due to failure to degrade dermatan sulfate and/or heparan sulfate is now clear in concept, if not in all details. Within lysosomes, exoglycosidases and exosulfatases hydrolyse the carbohydrate chains sequentially, and absence of any one of the required enzymes results in accumulation of undegraded polymers (1,2). The well-established enzyme deficiencies are those of α-L-iduronidase (Hurler and Scheie syndromes), iduronate sulfatase (Hunter syndrome), N-acetylgalactosamine 4-sulfatase (Maroteaux-Lamy syndrome; this enzyme is the same as arylsulfatase B); β-glucuronidase (β-glucuronidase deficiency); heparan N-sulfatase (Sanfilippo A syndrome); and α-N-acetylglucosaminidase (Sanfilippo B syndrome). Deficiencies of β-N-acetylgalactosaminidase, α-glucosaminidase and N-acetylglucosamine 6-sulfatase have also been reported. Among the unresolved questions are the role of endoglycosidases, the relationship of the enzymes of dermatan sulfate degradation to the degradation of chondroitin sulfates, and the wide spectrum of severity within any one enzyme defect. Two enzyme deficiencies have been found associated with keratan sulfate degradation and the Morquio syndrome: N-acetylgalactosamine 6-sulfatase (2) and N-acetylglucosamine 6-sulfatase (3).

As convenient assays become available, they are put to use for diagnosis, including prenatal diagnosis. Heterozygote identification is impractical for the rare autosomal recessive disorders, but is of great importance to families of patients with the Hunter (X-linked) syndrome. Iduronate sulfatase activity in hair follicles (which are almost clonal in origin) may be of value.

Several of the above deficiencies were elucidated not by direct enzyme analysis, but by purification of "corrective factors" in fibroblast secretions and human urine, and identification of their enzymatic activities. For example, the Hunter corrective factor was found to have the activity of iduronate sulfatase. In addition to enzymatic activity, the factors have a structural feature, or "recognition marker" for efficient, receptor-mediated entry into fibroblasts. The marker for β-glucuronidase (4) and for α-L-iduronidase (5) has been shown by indirect evidence to be phosphorylated mannose or some sterically related residue. The corrective factors secreted into culture medium are thought to be intermediates in the transport of glycosidases and sulfatases to their eventual destination within lysosomes (5).

1. Neufeld, E.F., Lim, T.W., and Shapiro, L.J., Ann. Rev. Biochem. 44: 357-376 (1975).
2. Dorfman, A. and Matalon, R., Proc. Nat. Acad. Sci. U.S.A. 73: 630-637; 2165 (1976).
3. Ginsberg, L., DiFerrante, D.T., Caskey, C.T., and DiFerrante, N., Clinical Research 25: 471A (1977).
4. Kaplan, A., Achord, D.T., and Sly, W.S., Proc. Nat. Acad. Sci. U.S.A. 74, 1977 (in press).
5. Neufeld, E.F., Sando, G.N., Garvin, A.J., and Rome, L.H., J. Supramol. Struct. 6, 1977 (in press).