Editorial

The Genetic Mucopolysaccharidoses

It is mainly in the last decade that the Hurler syndrome (gargoyleism) has been identified as an inborn error of mucopolysaccharide metabolism. Heterogeneity (i.e., separate entities that were lumped under the same diagnostic label), previously suspected on clinical and genetic grounds, has been substantiated with additional evidence provided by biochemical studies. Other clinically similar conditions have been distinguished. Thus far, five distinct hereditary disorders of mucopolysaccharide metabolism can be identified by combined clinical, genetic, and biochemical study.1 Others will probably be delineated by the continuing investigations.

Cardiovascular involvement is a significant feature of four of the five mucopolysaccharidoses now recognized. The skeleton, eye, and central nervous system are also affected to a variable degree. The central nervous system manifestations seem to be in part indirect effects through involvement of the meninges or toxic effects on the brain cells but are probably also the result of a defect in metabolic processes which the brain cells share with connective tissue.

Many of the clinical manifestations of the mucopolysaccharidoses are natural consequences of the fact that the mucopolysaccharides are important constituents of connective tissue, e.g., that of cartilage, blood vessels, and cornea. They are macromolecules with repeating units of a hexuronic acid and a hexosamine, as outlined in table 1. Chondroitin sulfate B, heparitin sulfate, and keratosulfate are mucopolysaccharides that have been implicated in the several mucopolysaccharidoses.

The present status of nosography of the mucopolysaccharidoses is summarized in table 2. More or less arbitrarily, numbers have been assigned to these disorders, MPS I to V, following the practice, in connection with the glycogenoses (glycogen-storage diseases). Eponyms have much to recommend them over numbers. Who, for example, remembers the characteristics of type III glycogen-storage disease? It seems likely that students of the mucopolysaccharidoses tend to think of the X-linked variety as the Hunter syndrome, because of the famous teen-age boys reported by Charles H. Hunter in 1917. The Morquio eponym is well established. The priority of Sanfilippo and his colleagues in describing the heparitinuric type of mucopolysaccharidosis is appropriately recognized by the eponym, and the designation Scheie's syndrome serves a similar useful function.

The Hurler syndrome is the prototype mucopolysaccharidosis. Its manifestations in the skeleton, eye, heart, and central nervous system are severe, and death occurs before 10 years of age in most cases.

The Hunter syndrome is a sex-linked (X-linked) recessive, whereas all the other four mucopolysaccharidoses are autosomal reces-

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Table 1

Mucopolysaccharides of Connective Tissue

<table>
<thead>
<tr>
<th>Type</th>
<th>Hexosamine</th>
<th>Hexuronic acid</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-sulfated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chondroitin</td>
<td>Galactosamine</td>
<td>Glucuronic</td>
<td>Cornea, Vitreous</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>Glucosamine</td>
<td>Glucuronic</td>
<td>synovial fluid</td>
</tr>
<tr>
<td>Sulfated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratosulfate</td>
<td>Glucosamine</td>
<td>None</td>
<td>Cornea, Cartilage</td>
</tr>
<tr>
<td></td>
<td>Galactose</td>
<td></td>
<td>Nuclei pulposus</td>
</tr>
<tr>
<td>Heparitin sulfate</td>
<td>Glucosamine</td>
<td>Glucuronic</td>
<td>Aorta</td>
</tr>
<tr>
<td>Chondroitin sulfate A</td>
<td>Galactosamine</td>
<td>Glucuronic</td>
<td>Cornea, Cartilage</td>
</tr>
<tr>
<td>Chondroitin sulfate B</td>
<td>Galactosamine</td>
<td>Iduronic</td>
<td>Skin, Heart, Aorta</td>
</tr>
<tr>
<td>Chondroitin sulfate C</td>
<td>Galactosamine</td>
<td>Glucuronic</td>
<td>Cartilage, Tendon</td>
</tr>
<tr>
<td>Heparin</td>
<td>Glucosamine</td>
<td>Glucuronic</td>
<td></td>
</tr>
</tbody>
</table>

Table 2

The Mucopolysaccharides

<table>
<thead>
<tr>
<th>MPS</th>
<th>Clinical</th>
<th>Genetic</th>
<th>Biochemical</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Hurler syndrome)</td>
<td>Early clouding of cornea, grave manifestations</td>
<td>Autosomal</td>
<td>Ch S-B</td>
</tr>
<tr>
<td>II (Hunter syndrome)</td>
<td>No clouding of cornea, milder course</td>
<td>X-linked</td>
<td>Ch S-B</td>
</tr>
<tr>
<td>III (Sanfilippo syndrome)</td>
<td>Mild somatic, severe mental effects later</td>
<td>Autosomal</td>
<td>Heparitin S</td>
</tr>
<tr>
<td>IV (Morquio syndrome)</td>
<td>Severe bone changes, cloudy cornea, intellect +/-, aortic regurgitation</td>
<td>Autosomal</td>
<td>Keratosulfate</td>
</tr>
<tr>
<td>V (Scheie syndrome)</td>
<td>Stiff joints, coarse facies, cloudy cornea, intellect +/-, aortic regurgitation</td>
<td>Autosomal</td>
<td>Chondroitin sulfate B</td>
</tr>
</tbody>
</table>

sives, like almost all inborn errors of metabolism. Milder manifestations with longer survival and particularly absence of corneal clouding also distinguish the Hunter syndrome from the Hurler syndrome. Curiously, no definite quantitative or qualitative difference in urinary excretion of mucopolysaccharides has been found distinguishing the Hurler and Hunter cases. Cardiovascular manifestations are often conspicuous in cases of both types. These are reviewed elsewhere in this issue by Krovetz, Lorincz, and Schiebler. Occlusive coronary artery disease and valvular involvement resulting in regurgitation are the main characteristics. Severe pulmonary hypertension was present in a 33-year-old case of the Hunter syndrome we recently observed. The Sanfilippo syndrome is distinguished by the combination of severe mental retardation with only mild somatic features.2 Clouding of the cornea does not occur, and coarsening of facial features, stiffness of joints, and radiologic changes in the skeleton are relatively mild. It is possible that many of these patients are institutionalized for mental retardation without recognition of the metabolic nature of the problem. Unfortunately no definitive treatment is yet available for this and
the other mucopolysaccharidoses. This is the only one of the five mucopolysaccharidoses in which no cardiovascular involvement has yet been detected clinically. Large amounts of heparitin sulfate are excreted in the urine. Chondroitin sulfate B is notably absent.

The Scheie syndrome has clouding of the cornea, stiff joints, and coarse facial features as do the Hurler, Hunter, and Sanfilippo syndromes. Mental retardation is not a feature, however. Aortic valve disease, usually aortic regurgitation, has been a feature in all the cases we have studied, including the brother and sister first investigated by Scheie.

In 1929, characteristic “osteochondrodys trophy” was described independently by Morquio in Uruguay and by Brailsford in Birmingham, England. In the next 30 years a variety of entities, which we would now classify differently, were reported under the Morquio eponym. Largely because of a “trash can” state of the nosology of Morquio’s syndrome, it was proposed that Morquio-Ullrich syndrome is a better designation for the cases in which corneal clouding was detected and in which excessive amounts of keratosulfate were demonstrated in the urine. It is the conclusion of my collaborators and me, however, that the true Morquio syndrome, i.e., the entity present in the originally described patients, was precisely that in which we now recognize extraskeletal manifestations and keratosulfaturia. Simply “the Morquio syndrome” is used for these cases. Aortic regurgitation has been present in most of the teen-aged (or older) cases of the Morquio syndrome that we have had an opportunity to study.

In the Hurler syndrome, heavy deposits of mucopolysaccharide in the intima of the coronary arteries, aorta and pulmonary artery produce a pseudoatherosclerosis. The involvement may be extreme even in children only a few years old at death. Almost certainly, this produces clinical manifestations in some, although the intellectual status of the patients usually does not permit evaluation. The changes are reminiscent of those induced in rabbits by intravenous injection of macro-
molecular substances such as pectin or methyl-cellulose.3

In some cases thickening of the ventricular endocardium is marked. Presumably fibrosis is stimulated by the deposited mucopolysaccharide. In vitro studies of collagen formation suggest a stimulating effect of mucopolysaccharides.

The valvular damage may be both a matter of mucopolysaccharide deposition and collagen derangement secondary to the disturbed mucopolysaccharide metabolism.

The diagnosis of a mucopolysaccharidosis is confirmed by demonstration of excessive amounts of mucopolysaccharide in the urine. As indicated in Table 2, differential diagnosis is possible by qualitative and quantitative assay of urinary mucopolysaccharides, with the exception that the Hurler and Hunter varieties cannot be distinguished by this means. Precise characterization of urinary mucopolysaccharides is moderately complex. Urinary screening tests, however, have been developed in recent years, particularly the bovine albumin turbidity test, and the toluidine-blue filter-paper metachromasia test. The recently introduced cetyl tri-methyl ammonium bromide test promises to be particularly useful because of both its sensitivity and its specificity.

The excretion of two mucopolysaccharides in excess in the Hurler and Hunter syndromes is perplexing but does not necessarily offend the notion of one-gene-one-enzyme, or the newer version of that concept—one-cistron-one-polypeptide. It must mean simply that the gene-determined defect involves a metabolic step shared in common by the two mucopolysaccharides. An intriguing suggestion by Dorfman is that the primary defect resides in the protein to which mucopolysaccharide is bound. In this view overproduction of mucopolysaccharide occurs in a blind attempt to satisfy the requirements for normal protein-mucopolysaccharide complexes.

Therapy directed at the primary defect, certainly at the gene defect, will not be easily achieved. However, because the mucopolysaccharidoses are progressive disorders with-
out significant features present at birth, it may well be possible to devise methods for manipulating metabolism before damage to vital structures, particularly the brain and heart, have occurred.

Victor A. McKusick, M.D.

References


Natural Laws

Natural laws there probably are, rigid and unchanging ones at that. Understand them and they are beneficent; we can use them for our purposes and make them the slaves of our desires. Misunderstand them and they are monsters who may grind us to powder or crush us in the dust.—Henry A. Rowland.
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