Correction. In the article "Free energy levels and entropy production in muscle contraction and in related solution systems," by Terrell L. Hill and R. M. Simmons, which appeared in the February 1976 issue of Proc. Natl. Acad. Sci. USA 73, 336–340, the authors have requested the following change. On page 340 the second integral in Eq. 19 should be deleted. The correct form is

\[
\frac{1}{d} \int_{d/2}^{-d/2} J_i \Delta \mu_i', dx \geq 0. \tag{19}
\]

Correction. In the article "The mucopolysaccharidoses (A Review)," by Albert Dorfman and Reuben Matalon, which appeared in the February 1976 issue of Proc. Natl. Acad. Sci. USA 73, 630–637, the authors have requested the following changes. On page 634, in Table 2, the enzyme deficiency for Mucopolysaccharidosis IV Morquio should be N-acetylhexosaminidase 6-SO₄ sulfatase and that for Mucopolysaccharidosis VI Maroteaux-Lamy should be N-acetylhexosamine 4-SO₄ sulfatase.
The mucopolysaccharidoses (A Review)*

(glycosaminoglycans/glycosidases/genetic disease, prenatal diagnosis)

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Contributed by Albert Dorfman, October 9, 1975

ABSTRACT The mucopolysaccharidoses are a group of genetic diseases characterized by storage of incompletely degraded glycosaminoglycans. Such storage causes marked distortion of many tissues with consequent severe somatic changes and mental retardation. Storage of glycosaminoglycans results from markedly diminished activity of specific hydrolases requisite for the normal degradation of glycosaminoglycans. The specific enzymic defects have been identified in nine different diseases. In some cases evidence has been obtained indicating the existence of additional allelic diseases based on the same enzyme. The knowledge obtained from these studies has made prenatal diagnosis possible and has led to the possibility that therapy may be undertaken utilizing enzyme replacement.

The role of the study of human genetic disease in the elucidation of biochemical pathways has been widely recognized since the classical writings of Sir Archibald Garrod (1). His keen insight led to the first indication of the one gene-one enzyme concept. Study of sickle cell disease by Pauling et al. (2) firmly established the relationship of genetic disease to aberrant protein structure. Less dramatic but of increasing general interest has been the elucidation of the fundamental defects that result in storage diseases.

In the case of the mucopolysaccharidoses, study of the structure and biosynthesis of the mucopolysaccharides has aided in the determination of the metabolic basis of this group of diseases, while study of the diseases has increased our knowledge of the pathways of degradation of the mucopolysaccharides. More recently the term glycosaminoglycans has been adopted for these compounds and will be used in this paper.

Detailed reviews of historical aspects and clinical characteristics have been published elsewhere (3–5). Briefly, the first description of a case of mucopolysaccharidosis probably was that of Thompson in 1900, which was published by Henderson in 1940 (6). The original photograph strongly resembles patients now diagnosed as afflicted with Hurler disease. In 1917, Hunter (7) described two brothers whose features fit the X-linked form of mucopolysaccharidosis that is identified with his name. Gertrud Hurler (8), in 1919, described in detail two unrelated boys with a syndrome characterized by markedly distorted facies, multiple skeletal abnormalities, corneal opacities, hepatosplenomegaly, and cardiac disease. This description became the prototype of a number of syndromes which were erroneously grouped under the general name gargoilism by Ellis (9) because of supposed similarity to the figures on medieval cathedrals. For a number of years gargoylism was considered a lipid storage disease because of the appearance of histological sections prepared by standard fixation procedures.

Although several early investigators questioned whether the storage material was truly lipid, chemical identification of this material did not occur until, in 1952, Brante (10) isolated a fraction from livers of afflicted patients which contained hexosamine, uronic acid, and sulfate. He concluded that the substance was a mucopolysaccharide and proposed the term mucopolysaccharidosis. Subsequently, Stacey and Barker (11) isolated a glycosaminoglycan fraction from the liver of an affected patient.

In 1957, Dorfman and Lorincz (12) isolated, from the urine of a patient with Hurler disease, large quantities of heparan sulfate and dermatan sulfate. This identification was confirmed by Meyer et al. (13, 14), who isolated both polysaccharides from several tissues, while Brown (15) detected low-molecular-weight heparan sulfate in the liver of Hurler patients. The excretion in urine and storage in tissues of glycosaminoglycans has been widely confirmed and reviewed elsewhere (3). Determination of the level and qualitative distribution of glycosaminoglycans is now a routine clinical diagnostic procedure.

With increasing chemical knowledge regarding the nature of substances deposited and stored in these diseases, a number of more careful clinical-chemical correlations began to appear which eventually led to the identification of specific syndromes. The existence of more than one entity was apparent from the description of an X-linked and an autosomal recessive form of the disease. The findings by Lorincz (16), Harris (17), and Sanfilippo et al. (18), that certain patients afflicted with an autosomal recessive form of the disease excreted only heparan sulfate while others excreted heparan sulfate and dermatan sulfate, indicated the existence of more than one autosomal recessive syndrome. Sanfilippo et al. (18) correlated the excretion of heparan sulfate with severe mental retardation. The reports of Scheie et al. (19), and Maroteaux et al. (20) differentiated yet other mucopolysaccharidoses. The complexity of these diseases was elegantly pointed out by McKusick et al. (21), who first proposed a systematic classification of mucopolysaccharidoses. More recently, McKusick (4) has modified and expanded this classification.

The study of mucopolysaccharidoses, like many other genetic diseases, began to progress rapidly with the use of tissue culture techniques. In 1960 Krooth and Weinberg (22) showed that cultured skin fibroblasts exhibit the enzymic defect of galactosemia. However, tissue culture was not widely applied to the study of human genetic diseases until Danes and Bearn (23) observed that fibroblasts cultured from the skin of patients with Hurler disease show striking metachromasia. Independently, we demonstrated that fibroblasts from patients with Hurler, Hunter, and Sanfilippo diseases accumulated glycosaminoglycans (24). Schafer et al. (25) found that the extent of dermatan sulfate accumulation depended on ascorbic acid concentration.

* By invitation. From time to time, reviews on scientific and technological matters of broad interest are published in the PROCEEDINGS.
The basis of polysaccharide accumulation in these diseases was first suggested by van Hoof and Hers (26). In contrast to the accumulation of glycogen in cytoplasm in other glycogen storage diseases, Type II glycogen storage disease is characterized by glycogen accumulation in lysosomes. This accumulation was shown by Hers (27) to result from the deficiency of an acid maltase, a lysosomal enzyme. It was proposed that there exists a category of diseases characterized by the absence of specific lysosomal hydrolases, which results in the accumulation of incompletely degraded macromolecules within lysosomes (27). Electron microscopic study (26) of the livers of patients with the Hurler syndrome showed the presence of markedly distended lysosomes. It was therefore suggested that Hurler syndrome, like Type II glycogen storage disease, is due to the absence of a specific hydrolase required for the degradation of glycosaminoglycans.

Fratantoni et al. (28) concluded that mucopolysaccharides were due to defective degradation of polysaccharides on the basis of the kinetics of $^{35}$SO$_4$$^2-$ accumulation in cultured fibroblasts obtained from skin biopsies of patients with Hurler and Hunter syndromes. They also found that cocultivation of Hurler and Hunter cells led to mutual correction of the abnormal accumulation of $^{35}$SO$_4$$^2-$ glycosaminoglycans (29). Subsequent studies (30) showed that correction of the metabolic defect of fibroblasts could be achieved by use of media or extracts of various tissues and urine (31). Material obtained from normal subjects and patients with other syndromes correct the defect in fibroblasts derived from each of the specific mucopolysaccharidoses. Using this cross-correction technique, it was established that the Hurler and Scheie syndromes may be allelic (32) and that there exists two genetically distinct Sanfilippo diseases, which were designated Sanfilippo A and Sanfilippo B (33). On the basis of the "corrective factor" assay, Neufeld and coworkers partially purified several of the factors (34–36).

The evidence that accumulation of intracellular glycosaminoglycans results from degenerative defects led us to seek hydrolases specific for the cleavage of linkages in the stored polysaccharides. Fig. 1 illustrates a portion of the structure of various glycosaminoglycans stored or excreted in the mucopolysaccharidoses and the enzymatic steps necessary for their degradation. Heparan sulfate and dermatan sulfate (as well as heparin) share $\alpha$-L-iduronosyl linkages not present in chondroitin 4/6-SO$_4$ or keratan sulfate. Since both dermatan sulfate and heparan sulfate are excreted and stored in the Hurler, Hunter, and Scheie syndromes, a deficiency of an enzyme acting on $\alpha$-L-iduronosyl linkages could account for these diseases. The lack of suitable substrates for the postulated $\alpha$-L-iduronidase made a search for this enzyme difficult. As a first approach, desulfated dermatan sulfate was digested exhaustively with testicular hyaluronidase (which hydrolyzes N-acetylgalactosaminy-D-glucuronic acid linkages) and $\beta$-glucuronidase. Since the enzyme extracts were known to contain considerable $\beta$-N-acetylatedhexosaminidase activity, it was postulated that such a substrate should have available a maximum number of nonreducing terminal $\alpha$-L-iduronosyl residues. When extracts of normal fibroblasts were incubated with this substrate, $\alpha$-iduronolactone was released, demonstrating for the first time the existence of an $\alpha$-L-iduronidase. In contrast, incubation of this substrate with extracts of Hunter fibroblasts released only traces of iduronolactone (37). A more specific substrate, the disaccharide $\alpha$-L-iduronosyl-anhydromannose, was prepared by the nitrous acid cleavage of desulfated heparin. Once again, in contrast to

![FIG. 1. Pathway of degradation of glycosaminoglycans stored in mucopolysaccharidoses. The defects in various syndromes are indicated by numbered steps with line across arrow. The known diseases of degradation are: 1, Hurler and Scheie diseases; 2, Sanfilippo A disease; 4, Sanfilippo C disease; 5, Hunter disease; 6, Sanfilippo B disease; 7, $\beta$-glucuronidase deficiency; 8, Maroteaux-Lamy disease; 9, Sandhoff and Tay-Sachs diseases; 10, Morquio disease; and 11, GM1-gangliosidosis. No known disease has been shown for step 3. The enzyme involved in step 12 is not clear.](image)
glycosaminoglycans by a bacterial endo-N-acetylatedehexosaminidase, produces a 4,5-unsaturation in the adjacent uronic acid (O-glucuronic acid or L-iduronic acid). Accordingly, hydrolysis of dermanal sulfate with chondroitinase ABC prepared from Proteus vulgaris results in the release of both unsaturated and saturated products, as illustrated in Fig. 2. The saturated products are derived only from the nonreducing end of the polysaccharide. If an absence of L-idurono-sulfate sulfatase was responsible for Hunter syndrome, terminal disaccharide (saturated) released by chondroitinase treatment of dermatan sulfate stored in Hunter fibroblasts would be expected to contain idurono-sulfate groups. When such experiments were carried out, the results confirmed the speculation, indicating that Hunter disease is due to a deficiency of L-iduronosulfate sulfatase. Independently, Bach et al. (46) and Coppa et al. (47) reached a similar conclusion using different methods. Bach et al. showed that when L-iduronosulfate-anhydromannose was incubated with either Hurler or Hunter corrective factor, no iduronolactone was liberated, but when the disaccharide was incubated with a mixture of the two, L-idurone release could be demonstrated. More recently Lim et al. (48) have used a more convenient substrate, O-(α-L-idopyronosyluronic acid) 2-sulfate-(1→4)-2,5-anhydro D-1-[3H]mannitol sulfate. Coppa et al. (47) presented evidence for the occurrence of L-iduronosylsulfate N-acetylgalactosamine in the urine of patients with the Hunter syndrome.

The existence of allelic forms of the Hunter syndrome has been indicated by Lichtenstein et al. (49). Hunter syndrome in a female has been reported (50). It was proposed that this might be due to the in vivo selection of cells in which the maternal X-chromosome is expressed. Punnett (51) has suggested that a more likely explanation might be that the patient is homozygous as a result of a new mutation in the fa-

ther.

The fact that patients with Sanfilippo A and B diseases excrete and deposit only heparan sulfate suggested that enzymic defects in these diseases involve linkages unique to this glycosaminoglycan. Inspection of Fig. 1 reveals that heparan sulfate (as well as heparin) contains α-N-acetylgalactosamine and sulfamide linkages not present in other glycosaminoglycans. Kresse and Neufeld (36) first proposed that Sanfilippo A disease was due to a deficiency of sulfamidase. Direct proof of this enzyme defect was furnished by utilizing as a substrate [35S]heparin specifically labeled in the sulfamide group. Extracts of fibroblasts of patients with Sanfilippo A disease failed to release significant amounts of 35SO4, whereas extracts of fibroblasts derived from normal subjects or patients with mucopolysaccharidoses hydrolyzed this substrate (52, 53). These findings were confirmed by Kresse (54).

Predictions on the basis of the chemical structures were substantiated when O'Brien (55) demonstrated the deficiency of α-N-acetylgalactosaminidase in Sanfilippo B disease. This finding was confirmed by Von Figura and Kresse (56). Maroteaux et al. (20) described a group of patients with marked somatic defects and no mental retardation except that which occurs secondary to the frequent hydrocephalus. Although similar in appearance to children with the Hunter syndrome, these patients excrete predominantly dermanal sulfate. Morquio disease is characterized by severe skeletal deformities and excretion of keratan sulfate and chondroitin sulfate (57, 58). Fig. 1 illustrates the structure of the compounds involved in these two syndromes. Chondroitin 6-SO4 and keratan sulfate share common 6-O-SO4 linkages to N-acetyllactosamines; additionally, keratan sulfate contains 6-O-SO4 linkages to galactose. Since the polysaccharides excreted in this syndrome appear to have common 6-O-SO4 linkages, a substrate containing such linkages was sought.

After incubation of minces of 13-day-old chick embryo epiphyses of tibiae and femurs with 35SO4, chondroitin 4/6-

SO4 was isolated and used as a substrate for extracts derived from fibroblasts of normal subjects and individuals with a variety of storage diseases. As compared to normal extracts, there was a marked decrease in release of radioactivity by extracts of both Morquio and Maroteaux-Lamy fibroblasts (59, 60). When a labeled heptasaccharide was prepared by treatment of chondroitin 4/6-SO4 with testicular hyaluronidase and β-glucuronidase, virtually no release of radioactive sulfate was observed by Morquio extracts, although release of 35SO4 by extracts of Maroteaux-Lamy fibroblasts was equivalent to that produced by normal extracts (60). This result was somewhat difficult to interpret since it was anticipated that the heptasaccharide would contain the same distribution of 4-SO4 and 6-SO4 as the parent polysaccharide. Somewhat surprisingly it was found that although the parent polysaccharides contained 59% 4-SO4 and 37% 6-SO4, the heptasaccharide contained 37% 4-SO4 and 63% 6-SO4. Since the 6-sulfate is much more active than the 4-sulfate on the heptasaccharide, the Maroteaux-Lamy defect cannot be demonstrated with this heptasaccharide. The reason for the difference between distribution of 4-SO4 and 6-SO4 linkages in the polysaccharide and the heptasaccharide is not clear, but may involve the selective action of testicular hyaluronidase.

When chondroitin 4,35SO4, prepared by utilizing a rat chondrosarcoma, was incubated with fibroblast extracts, there was a release of radioactivity by Morquio extracts but not by Maroteaux-Lamy extracts (60). A labeled heptasac-
charide was then prepared from chondroitin 4-SO₄ by the procedure indicated above. Radioactivity was released from this substrate by normal extracts and Morquio extracts but not by Maroteaux-Lamy extracts.

Table 1 summarizes the data obtained from the study of the degradation of the various chondroitin sulfates and heptasaccharides. The extent of degradation of the heptasaccharides was calculated on the basis of isolation of the degradation products after incubation with fibroblast extracts followed by incubation with chondroitinase AC.

These experiments demonstrate that Morquio fibroblasts are deficient in an N-acetylhexosamine 6-SO₄ sulfatase, while Maroteaux-Lamy fibroblasts are deficient in an N-acetylhexosamine 4-SO₄ sulfatase. Austin (61) had reported a deficiency of arylsulfatase B activity in Maroteaux-Lamy tissues, a finding that has been confirmed by Fluhrty et al. (62) and Beratis et al. (63). O'Brien et al. (64), using an end group analysis method similar to that which we used for study of Hunter syndrome, also reached the conclusion that the Maroteaux-Lamy syndrome was due to an N-acetylhexosamine 4-SO₄ sulfatase deficiency. Fluhrty et al. (62) found a deficiency of uridine diphospho-N-acetylgalactosamine sulfotransferase in fibroblasts of patients with Maroteaux-Lamy syndrome. Shapira et al. (65) demonstrated that Maroteaux-Lamy fibroblasts contain a protein that crossreacts immunologically with arylsulfatase B but shows no activity toward nitrocellulose sulfate.

Taken together, these studies indicate that the Maroteaux-Lamy syndrome is due to a deficiency of arylsulfatase B, the natural substrate for which, N-acetylhexosamine 4-SO₄, is present in dermalan sulfate and chondroitin 4-SO₄. Di Ferrante et al. (66) found a deficiency of arylsulfatase B in a patient with a mild form of the Maroteaux-Lamy disease, and suggested that this may be an allelic variant.

Another mucopolysaccharidosis was identified clinically by Sly et al. (67) and shown by Hall et al. (68) to be due to a deficiency of β-glucuronidase. Two additional patients exhibiting β-glucuronidase deficiency have been reported by Beaudet et al. (69). Although all three patients exhibited deficiency of β-glucuronidase in cultured fibroblasts and leukocytes, differences in clinical manifestations were noted in the three patients. An additional patient reported by Gehler et al. (70) appears to resemble more closely that reported by Sly et al. (67). Beaudet et al. (69) have suggested the existence of allelic forms of this disease.

The specific effect of β-glucuronidase deficiency on metabolism of glycosaminoglycans is not yet clear since there appears to be differences in the reports as to the identification of the polysaccharides excreted. Gehler et al. (70) reported the presence of dermalan sulfate in histochemical studies in a liver biopsy, while Sly et al. (67) reported chondroitin 4/6-SO₄ in the urine. Beaudet et al. (69) found dermalan sulfate and heparan sulfate in urine, including that of the patient reported by Sly et al. (67).

The studies thus far reviewed indicate that nine distinct genetic diseases based on eight different lysosomal defects have now been identified. These are summarized in Table 2, and the affected linkages are shown in Fig. 1. In addition to the allelism proposed for the Hurler and Scheie syndromes, there is evidence of allelism in Hunter, Maroteaux-Lamy, and β-glucuronidase deficiencies. Further variation in clinical characteristics may occur as a result of compounds of allelic genes. Such a mechanism has been proposed by McKusick et al. (71), who have pointed out that patients of this type might be expected to occur with twice the frequency of those that are homozygous for either allele.

The search for the enzymatic basis of the mucopolysaccharidoses has contributed sufficiently to an understanding of the pathway of degradation of glycosaminoglycans to attempt to portray these pathways. When this is done systematically, it becomes clear that certain problems remain unsolved. It seems likely that the solution of these problems may lead to the identification of other mucopolysaccharidoses.

The initial step(s) of heparan sulfate degradation not depicted in Fig. 1 remain uncertain. Present evidence indicates that heparin and heparan sulfate are initially synthesized as proteoglycans. It is possible that heparin chains are split from the proteoglycan by proteolytic enzymes or endoglycosidases before release from cells. Ogren and Lindahl (72) have reported the presence of a heparinase in transplantable mouse mastocytoma that apparently cleaves macromolecular heparin by an endoglycosidase activity. The existence of an endoglycosidase that splits heparan sulfate has been suggested by Hutterer (73). Further evidence of an enzyme of this type was indicated by Knecht et al. (74), since the degraded fragments of heparan sulfate found in urine and tissues of Hurler patients are of two types: one type is highly sulfated and contained large amounts of N-sulfate but no linkage region components (xylose, galactose, and serine), while the other type contained low sulfate, high N-acetylgalactosamine, and xylose, galactose, and serine in molar ratios of 1:2:1. These findings suggested that the latter fragments are derived from the portion of the chains proximal to the protein while the former fragments are derived from the distal portions of the chain.

The pattern of further degradation of heparan sulfate is now relatively clear. The removal of N-SO₄ groups by sulfatidase results in a terminal α-glucosaminide linkage which probably requires a specific enzyme other than the α-N-
The recent report by Kresse and von Figura (75) suggests that such an enzyme is absent in Sanfilippo C disease. Further data are required to characterize this step.

Studies on the structure of heparan sulfate indicate that a considerable number of N-SO$_3$-hexosamine residues also contain 6-O-SO$_4$ (76). Whether a critical order exists between steps 2 and 3 (Fig. 1) is unknown. In any case an enzyme must exist for the hydrolysis of the glucosamine 6-SO$_4$ groups. The studies reviewed above demonstrated that an N-acetylhexosamine 6-SO$_4$ sulfatase is deficient in Morquio disease. This enzyme presumably acts on both N-acetylgalactosamine 6-SO$_4$ linkages (that occur in chondroitin 6-SO$_4$) and N-acetylglucosamine 6-SO$_4$ linkages (that occur in keratan sulfate). If this same enzyme is responsible for the hydrolysis of the 6-SO$_4$ linkage in heparan sulfate, Morquio disease should be characterized by the excretion and storage of heparan sulfate. Increased quantities of heparan sulfate have never been reported in Morquio urine. These facts suggest that yet another sulfatase is required for the hydrolysis of the 6-SO$_4$ groups in heparan and heparan sulfate. The requirement for an enzyme that is different from that active on chondroitin 6-SO$_4$ (or keratan sulfate) may be due to the presence of N-SO$_3$, a free amino group if N-SO$_3$ is first removed, or a conformational difference that results from the $\alpha$-glycoside bond.

Step 7 of Fig. 1 refers to the action of $\beta$-glucuronidase which would be required for the complete degradation of heparan sulfate. The available data are confusing regarding the storage or excretion of heparan sulfate in the published cases of $\beta$-glucuronidase deficiency.

The role of $\beta$-N-acetylhexosaminidases (step 9) in degradation of glycosaminoglycans requires further investigation. The studies of Thompson et al. (77) indicated that extracts of fibroblasts derived from patients with Sandhoff and Tay-Sachs diseases fail to remove the nonreducing terminal N-acetylhexosamine group of a heptasaccharide derived from chondroitin sulfate. Since $\beta$-N-acetylhexosaminidase A is absent in Tay-Sachs disease and $\beta$-N-acetylhexosaminidase A and B are absent in Sandhoff disease, these data indicate that $\beta$-N-acetylhexosaminidase A is required for the degradation of chondroitin sulfate and presumably dermatan sulfate. Cantz and Kresse (78) have recently reported the accumulation of glycosaminoglycans in fibroblasts of patients with Sandhoff disease but not Tay-Sachs disease. Despite this finding, the failure of either of these two syndromes to exhibit the characteristics of mucopolysaccharidoses remains unexplained. It is possible that chondroitin sulfate and hyaluronic acid are primarily degraded by the endhexosaminidase, hyaluronidase, in certain tissues. However, hyaluronidase appears to be absent from cultured skin fibroblasts (79, 80); hyaluronidase has been reported in skin (81).

Step 11 refers to $\beta$-galactosidase activity. There is evidence of more than one $\beta$-galactosidase involved in degradation of gangliosides (82). The $\beta$-galactosidase responsible for degradation of $\text{GM}_1$ ganglioside appears to be involved in the degradation of keratan sulfate in view of the storage and excretion of a keratan sulfate-like material in $\text{GM}_1$-gangliosidosis (83).

A number of problems remain concerning the degradation of keratan sulfate. There is no available evidence regarding the enzyme responsible for hydrolysis of the galactose 6-SO$_4$ linkage present in keratan sulfate. The large number of variants of spondioepiphyseal dysplasia offer many more disease possibilities for a deficiency of such an enzyme. It should be pointed out that 3-O-SO$_4$ linkage occurs in cerebroside sulfate and is presumably hydrolyzed by arylsulfatase A. The absence of this enzyme leads to metachromatic leukodystrophy. The storage of keratan sulfate in this disease has not been reported, although the storage of mucopolysaccharides in the metachromatic leukodystrophy variant characterized by multiple sulfatase deficiencies has been observed. Fibroblasts from this unusual disease show reduced amounts or absence of arylsulfatases A, B, C, cholesterol sulfatase, and dehydroepiandrosterone sulfate sulfatase. On the basis of correction studies, there also appears to be a deficiency of iduronosulfate sulfatase and sulfamidase. The basis for this multiple sulfatase deficiency is unclear (84).

In addition, a number of problems regarding the pathogenesis of the mucopolysaccharidoses remain. It is still difficult to correlate the enzyme deficiencies with clinical manifestations of disease. Kaplan (85) originally suggested that

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Table 2. Summary of enzymic defects in mucopolysaccharidoses

<table>
<thead>
<tr>
<th>Mucopolysaccharidosis</th>
<th>Accumulated product</th>
<th>Enzyme deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurler</td>
<td>Heparan sulfate</td>
<td>$\alpha$-L-Iduronidase (EC 3.2.1.76)</td>
</tr>
<tr>
<td>Hunter</td>
<td>Heparan sulfate</td>
<td>$\alpha$-L-Iduronidase (EC 3.2.1.76)</td>
</tr>
<tr>
<td>Sanfilippo A</td>
<td>Heparan sulfate</td>
<td>Sulfamidase</td>
</tr>
<tr>
<td>Sanfilippo B</td>
<td>Heparan sulfate</td>
<td>$\alpha$-N-Acetylglucosaminidase (EC 3.2.1.50)</td>
</tr>
<tr>
<td>Sanfilippo C</td>
<td>Heparan sulfate</td>
<td>$\alpha$-Glucosaminidase (?)</td>
</tr>
<tr>
<td>Morquio</td>
<td>Keratan sulfate</td>
<td>$N$-Acetylhexosaminidase 4-SO$_4$ sulfatase</td>
</tr>
<tr>
<td>Morquio</td>
<td>Chondroitin sulfate</td>
<td>$N$-Acetylhexosaminidase 6-SO$_4$ sulfatase</td>
</tr>
<tr>
<td>Maroteaux-Lamy</td>
<td>Dermatan sulfate</td>
<td>Arylsulfatase B (EC 3.1.6.1)</td>
</tr>
<tr>
<td>Maroteaux-Lamy</td>
<td>Heparan sulfate</td>
<td>$\beta$-Glucuronidase (EC 3.2.1.31)</td>
</tr>
</tbody>
</table>
increased excretion of heparan sulfate was correlated with mental retardation. This correlation is striking in Sanfilippo syndrome but is difficult to apply to the Scheie syndrome and the milder form of Hunter syndrome. Whether the clinical symptoms can be correlated with the extent of activity of different allelic mutant enzymes remains to be determined.

The information derived from the study of the mucopolysaccharidoses has already had important implications in the practice of human genetics. Perhaps the most striking of these has been the development of methods of prenatal diagnosis for these and other diseases (86). This method as now practiced should make possible the prenatal diagnosis of all the syndromes discussed. It is limited in scope, however, since it can only be applied to families in which previous cases are known. Theoretically, the method would have a much greater efficiency if combined with heterozygote screening. Although such screening should be possible for all of these diseases, with improved assays and substrates, it seems unlikely that it will be practical in view of the low gene frequency of these syndromes. Conceivably at some future time technological improvements may make screening for rare genes economically feasible, but such mass screening programs raise serious ethical, legal, and emotional problems.

Recently considerable interest has developed in the possibility of treatment of lysosomal storage diseases by enzyme replacement therapy. In general these attempts have followed two lines, transplantation of tissues and injection of enzymes. The latter procedure stems particularly from the studies of Neufeld and coworkers (54–56) reviewed above, which showed the correction of metabolic defects in tissue cultures by exogenous factors now known to be the specific missing enzymes. That uptake of such enzymes may depend on specific markers that are recognized by cell receptors has been indicated by studies of Hickman et al. (87) and Hickman and Neufeld (88). The reported studies of enzyme replacement therapy are as yet too fragmentary to determine whether current investigations will lead to practicable methods of treatment.

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Thompson, J. N., Stoolmiller, A. C., Matalon, R. & Dorfman,


