Hurler's Disease

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AT FIRST GLANCE few diseases appear as unrewarding of study as Hurler's disease. Yet few other diseases hold the potential key to the solution of so many physiologic and pathologic mysteries as does this uncommon problem. Victor A. McKusick, in the preface to his classic text "Heritable Disorders of Connective Tissue" quotes a letter of William Hardy in which he noted that "nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of Nature by careful investigation of cases of rare forms of disease. For it has been found, in almost all things, that what they contain of useful or applicable nature is hardly perceived unless we are deprived of them, or they become deranged in some way."[1]

As a mucopolysaccharidosis, Hurler's disease presents an opportunity to elucidate certain of the mysteries surrounding collagen diseases, allergic phenomena, and some of the metabolic disorders which depend for their final explanation on an understanding of the ground substance of connective tissue. This amorphous, extracellular, mucopolysaccharide dominated matrix assumes a role far more important than one expects from its deceptively simple histologic appearance. We have long considered collagen fibrils a product of the fibroblasts.* The amorphous ground substance has been thought of as a cement substance holding the fibrils together. Gross, Hyberger and Schmidt[3] found that collagen is arranged into its typical fibrils outside the cell, in the ground substance, where adequate conditions must be maintained for this synthesis from smaller tropocollagen units elaborated by the cells. We must then consider the ground substance as participating in functions more complex than simple adhesion.

Of the constituents of ground substance, the mucopolysaccharides are most exciting. Dorfman,[4] considering the role of the mucopolysaccharides in physiologic and pathologic processes, lists the following possibilities:

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"called fibroblasts because they are generally believed to be instrumental in the elaboration of the intercellular fibrils".[2]

1. The control of the electrolytes and water in extracellular fluid
2. Calcification
3. Wound healing
4. Resistance to infection
5. Lubrication
6. Blood coagulation
7. Clearing activity
8. Maintenance of stable transparent media (the eye)

Thus the mucopolysaccharides may well supply answers in several heretofore unrelated areas. Dorfman's studies of the mucopolysaccharide levels in diabetic animals,[4] Krompecher's[5] work on thyroid disease and Winzler's[6] work on tissue disintegration suggest possible research avenues.

Hurler's disease presents unique investigative opportunities since in this syndrome mucopolysaccharides are produced in great excess, stored in tremendous deposits throughout the body and excreted in massive quantities. We can assume that somewhere an error exists which causes this over-production. We cannot, however, assume that any other abnormality exists regarding the metabolism of these muco-polysaccharides. Thus, we may look to these patients for an explanation of the normal mechanism of production, storage, and excretion of these products.

HISTORICAL

Although far from rare, Hurler's disease was not described until this century. Newell and Koistinen[7] give John Thompson of the Royal Infirmary, Edinburgh, credit for the first description. He referred to it as "Johnny McL's Disease" and noted it in three siblings seen between 1900 and 1913. These were not reported, however, until 1924. Charles H. Hunter, the late Professor of Medicine of the University of Manitoba, carefully described two brothers seen at the Winnipeg General Hospital in 1915 in the *Proceedings of the Royal Society of Medicine*.[8] At the time of his paper, Charles Hunter was an obscure Major in the Canadian Army Medical Corps stationed in England. Perhaps this explains why the syndrome is not called the Hunter syndrome.

In 1919, Professor Meinhard Von Pfaundler of the University Clinic of Pediatrics, Munich, urged Gertrude Hurler to publish two cases of this syndrome.[9] The Professor himself had previously presented these two cases to the Munich Society for Pediatrics on the 27th of June, 1919. Thus the syndrome became Hurler's syndrome or the Hurler-Pfaundler syndrome.

The work of Brante in 1952[10] showed that Hurler's disease is a mucopoly-saccharidosis. Prior to this it was considered a member of the lipid storage defects along with Niemann-Pick's, Gaucher's, Hand-Schuller-Christian, Tay-Sach's diseases.[11]

An index of the confusion which may prevail when non-eponymous names are used in describing poorly understood syndromes may be obtained by noting some

Figure 1

D. W., Note the typical facies, epicanthus, hypertelorism, thick lips and tongue, low ears and short neck.

Figure 2

D. W., Note the protuberant abdomen, flexion deformities of elbows and knees.

Figure 3

J. C., Note the "head on shoulders" appearance.

Figure 4

J. C., Note the massively enlarged liver.

of the names coined in behalf of the Hurler disease. Among them are lipochondro-dystrophy,[12] dysostosis multiplex,[13] lipochondrodysplasia,[14] gargoylism,[15] chondro-osteodystrophy,[16] and the Hurler-Pfoundler syndrome.

Two cases of Hurler's disease have been seen. Both were typical and illustrate the clinical and ocular manifestations noted below unless otherwise mentioned. The first case, D.W. a white female, was delivered at the Schilling AFB Hospital on March 14, 1957 (Figures 1 & 2). The family history, pre-natal course and delivery were not remarkable. The second case, J.C., Henry Ford Hospital #105-22-07 was first seen here at 21 months of age by Dr. P. J. Howard who referred him to the Ophthalmology Department for biomicroscopy (Figures 3 & 4).

Clinical Manifestations of Hurler's Disease other than Ocular: The child with Hurler's disease is usually of normal parents. Growth and development proceed along normal curves for the first few months. By six months of age the weird facial characteristics and some of the multiple skeletal malformative changes may be noted. The enlarged, scaphocephalic skull, enlarged ears and tongue are apparent. The tongue may also show transverse furrows (as did D.W.). The palate may be cleft and the teeth spaced at wide intervals. The lips are thick and heavy. The hair is coarse and usually of a gray blond color; the skin is coarse and thickened. Kyphosis, dwarfing and a shortened neck are characteristic. At 23 months D.W. was in the lowest 25 percentile for height and J.C. slightly lower than this. Examination of the neck reveals the classic "head on shoulders" picture. Despite multiple nasopharyngeal and respiratory infections there may be no palpable cervical lympha-denopathy. Flexion deformities of the extremities with marked limitation of extension produce a grotesque semi-crouched position. The hands are as wide as they are long and usually carried in a "claw" position. In one of the cases, D.W., the hands were a source of concern because of frequent dislocations of the thumbs.

The thorax is wider than normal and flared out below but is insulted physio-logically by thoraco-lumbar kyphosis. These problems coupled with an oropharynx crowded by a huge tongue, enlarged turbinates and a poorly constructed palate produce the characteristic noisy respirations and contribute to the frequent bouts of upper-respiratory infection. In both these cases multiple episodes of pneumonia have been treated. The heart is usually enlarged and a high percentage of these children have valvular defects. The abdomen is protuberant with hepatosplenomegaly and umbilical hernia present so constantly that they serve as a quick differential point in separating these children from cretins, in which disease the mental retard-ation, thickened skin and dwarfing are also prominent. In Hurler's disease mental retardation may or may not be present initially but may be slowly progressive when present.

OCULAR MANIFESTATIONS

Changes immediately apparent about the orbit are the prominent supra-orbital ridges and the depression of the bridge of the nose. This resemblance to the gargoyles of Gothic architecture is heightened by hypertelorism and by the frontal and temporal bossing. Both cases showed narrowing of the palpebral fissures with

some epicanthus. The lids, like the lips, are thickened and somewhat baggy. Visual acuity could not be determined in either case though both displayed central and steady fixation. Ophthalmoscopy is usually normal as it was in these cases. Corneal clouding is infrequent at birth, but by six months' of age should be visible by biomicroscopy if it is to appear. Although corneal changes are seen in 70 per cent of patients[17] and are the most common ocular abnormality, they are not necessarily present. It is this finding by which the genetic types of Hurler's disease may be differentiated at the earliest possible age.

Newell[7] notes the reduction in vision to be out of proportion to the corneal opacity and feels there might also be a defect of a cerebro-cortical or retinal nature. Histopathologic retinal changes have been described by Lindsay,[18] et al. Hydrocephalus is often seen and was thought by Hogan and Cordes[19] to account for the papilledema they noted in their first case. This finding was also noted by Walsh.[20] Other authors have added a potpourri of additional, relatively infrequent, findings. Among them, anisocoria,[21] narrowed palpebral fissure,[22] high hyperopia,[23] congenital cataract,[24] retinal detachment,[25] increased intraocular pressure,[26,27] and pupillary membrane,[28] are worthy of mention.

GENETICS

Halperin and Curtis[29] in 1942 pointed out a familial incidence of 52 per cent in a study of 85 families in which one or more member had Hurler's disease. They concluded that the defects were caused by a monomeric autosomal recessive gene. Shortly after this work, Millman and Whittick described a Hurler's variant without corneal opacities occurring in males only. In 1950, Jervis[30] pointed out the excess of affected males. Herndon[31] showed that the Millman-Whittick variant could be produced by a sex-linked gene and summarized his work in 1956 noting that Hurler's disease was caused by a recessive autosomal gene in approximately two-thirds of afflicted patients and a sex-linked gene in one-third.[32] The transmission of the sex-linked variant is through apparently normal females in a manner similar to hemophilia and red-green color blindness. Studying the two groups, Herndon[32] was the first to point out that among all the physical signs of Hurler's disease, only three were of importance in genotype differentiation. Corneal clouding, present in over 70 per cent of the autosomal recessive gene variant, was absent in those cases which were sex-linked. About the same number of the autosomal recessive group showed dwarfing, while only one-third of the sex-linked type did. Deafness was eight times as frequent in the sex-linked as in the autosomal recessive group[33] (Chart 1). Studies of these variations leads us to feel that our case, D.W., is probably an autosomal recessive and that J.C. is a sex-linked recessive.

Thus, two genotypes of Hurler's disease occur. In both of these there is urinary excretion of the mucopolysaccharides Chondroitin sulfate B and Heparitin S sulfate. Those patients with mucopolysacchariduria, but from whose urine only one of these can be recovered, are not considered here to be Hurler's disease.

Although we are unable to differentiate these two genotypes chemically by studying the materials deposited in the various tissues and excreted in the urine, certain differences may exist which explain the differences in phenotype.

Chart 1

GENOTYPES OF HURLER'S DISEASE

	Autosomal Recessive	*Sex-linked Recessive*
Sex	Males & females affected equally	Males only
Percentage of reported cases, 65	66%	33%
Corneal clouding	About 70%	Probably never
Dwarfing	About 80%	About 33%
Deafness	Infrequent	Frequent
Mental Retardation	Usual	Less common & less severe
Gibbus	Usual	Unusual
Progress	More rapid	Slower
Age of death	Usually under 20 years	Often over 40 years
Biochemical characteristics	No difference yet known between genotypes	

It now seems apparent that there are a group of mucopolysaccharidoses. Some of them can be separated both phenotypically and by variation in urinary muco-polysaccharides. Some can not. Two cases studied by Meyer and Hoffman[34,35] showed only Heparitin S in the urine. One of these at age four showed "only the widely set eyes and coarse hair suggestive of Hurler's syndrome, but no skeletal abnorm-alities, a slightly enlarged liver and only slight mental retardation". No mention of the corneas was made. These two cases undoubtedly represent a mucopoly-saccharidosis other than Hurler's disease. This may be said also of two cases of Morquio-Ullrich's disease described recently by Zellweger and his colleagues.[36] In these cases an increase in urinary mucopolysaccharides was noted which was then studied by fractional differentiation of the mucopolysaccharide components. The larger fraction of this was a mucopolysaccharide containing glucosamine.† In these two cases they noted skeletal characteristics similar to Morquio's disease* as well as corneal opacities and mental retardation.

In a recent paper Scheie[17] has described "A newly recognized forme fruste or variant of Hurler's disease." In these patients corneal clouding was clinically signi-ficant and a diagnosis of mucopolysaccharidosis was substantiated by a battery of laboratory studies, but the usual clinical picture was either obscure or absent. These cases were not analyzed as to differential urinary hexosamine content. Hexosamine contents were given for "crude mucopolysaccharide" in three day urine collections, but fractionation into Chondroitin sulfate B, Heparitin S, or other mucopolysaccharides was not done. It will be interesting to learn whether cases of this variant contain Chondroitin sulfate B and Heparitin S in ratios similar to the classic Hurler's disease or whether a new mucopolysaccharidosis has been described. It would seem much more likely that the cases of Scheie represent a new mucopolysaccharidosis, not a forme fruste.

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†In Hurler's disease the glucosamine fraction, Heparitin S, is much the smaller.
*There is no elevation of the mucopolysaccharides in the urine of patients with Morquio's disease.[36]

LABORATORY STUDIES

In 1941, Reilly[37] described abnormal leukocytes in four of eight patients with Hurler's disease. These cells contained dark lilac colored granules. Because of the similarity between the description by Reilly and a previous description by Alder[38] of similar azurophilic granules in several non-Hurler's patients this finding is variously called "Reilly Bodies" or "Alder's Phenomenon". Early investigators had difficulty showing this finding in more than about half their patients using a variety of staining techniques.[13,28,39,40] In 1959 Ursula Mittwoch,[41] using the May-Grunwald-Giemsa technique, was able to show abnormalities in the lymphocytes in each of six patients although the granulocytes were normal. In addition to granules she described vacuoles in the lymphocytes similar to those described in amaurotic idiocy and in Niemann-Pick disease. She noted also that several patients showed large inclusions within the lymphocytes similar to those seen in Chediak's anomaly. Last year she added 14 more patients with Hurler's disease showing the abnormality. Up to 50 per cent of all lymphocytes showed these granules with May-Grunwald-Giemsa stain and with toluidin blue stain.[42] She noted that "the fact that, as a result of an inborn error in mucopolysaccharide metabolism, human lymphocytes contain inclusions of acid mucopolysaccharides provides a simple diagnostic test for gargoylism. It also may throw a light on the function of the lymphocyte which, in spite of much literature devoted to it, is still unknown."[42]

Jermaine[43] studied the bone marrow of 12 patients in all of whom the presence of phagocytic clasmatocytes containing inclusions unique to this disorder was noted. These "Hurler's cells" were not found in bone marrow of unaffected relatives. The appearance of these cells in the bone marrow was shown to antedate the other manifestations of the disease providing a useful early diagnostic tool.

In 1947, Rebuck[44] devised a simple technique useful in the study of inflammation in which cover slips are fastened over dermal abrasions. Cells accumulating on these windows can be studied at intervals. Carlile[45] found that the two and four hour windows of patients with Hurler's disease did not differ from normal children but that "in the 16 and 24 hour stages the hematogenous macrophages in every field contained large basophilic granules which appear morphologically to be identical to those seen in some of the reticulum cells of the bone marrow in this disease . . . In both these cases the changes in the peripheral blood were very minimal."[45] Parents and one sibling of the two patients so studied did not show abnormalities using Rebuck windows. The second case presented in this paper was studied with such windows and the resulting inflammatory exudates were examined by Dr. Rebuck himself. He stated that "The inflammatory lesion on the male infant suffering from Hurler's disease revealed a sparse leukocytic exudate at the sixth hour of inflammation. The exudative cells were an admixture of neutrophilic leukocytes, macrophages with and without the characteristic metachromatic cytoplasmic inclusions of this disease[43,45] and an unexpected precocious migration of basophilic granulocytes. Even at this early stage, degranulation was accomplished by an explosive disintegration of some of the basophilic granulocytes. At the fourteenth hour, the customary influx of lymphocyte, hypertrophied lymphocytes and macrophages, of which representatives

of each were found to be bearing the metachromatic inclusions of Hurler's disease, was again complicated by a moderate but definite increase in basophilic migrations. At twenty-seven hours, many of the predominant macrophages bore the metachromatic inclusions as fine granules, as vacuolated structures with metachromatic borders, as amorphous metachromatic masses and as irregular angulated metachromatic crystalline structure. Periodic acid-Schiff reactions employed at the twenty-fourth hour of in-flammation reveal a positive reactivity in some, but not all of the cytoplasmic inclu-sions. Basophilic granulocytic migrations at the later stages were further increased and accompanied by cytoplasmic degranulation with the conversion of the exudative fluids in some areas to a lavender coloration."

The urine of patients with Hurler's disease contains excessive quantities of mucopolysaccharides.[46,47] This serves as a basis for the urine test of Dorfman. The high accuracy of this test as a screening procedure has been confirmed by Steiness.[48] The presence of both Chondroitin sulfate B and Heparitin S in urine is probably necessary for the diagnosis of Hurler's disease.[34] Barrey described a simple paper spot test using toluidine blue reagent to detect Chondroitin sulfuric acid in Hurler's patients.

Scheie[17] obtained conjunctival and skin biopsies from all ten of his patient's. With formalin fixation and toluidine blue staining, large vacuolated "gargoyle" cells could be found at the epidermal-dermal junction of the skin and in epithelial cells of the conjunctiva. These changes were thought to be diagnostic. Certainly their staining characteristics bore out a conclusion of mucopolysaccharide inclusion in these cells.

Changes of the cornea seen histologically in Hurler's disease have recently been reviewed by Forgacs and Franceschetti.[49] They summarized changes noted by several authors in the 21 eyes so studied up until that time. Scheie[17] has described similar changes in a new variant of this disease.

Berliner[50] originally described the epithelium to be normal and intact. Dystrophic changes which gave a diffuse staining with Fluorescein were later described by Sheldon[51] and although most histological studies show an intact epithelium changes have been noted in the cases of Zeeman[52] and Francois and Rabaey[53] which could account for this staining. In Zeeman's case fine granules were noted in the cytoplasm of the basal epithelium and the cells were displaced and vacuolated.

Bowman's membrane may be fragmented and interrupted by large cells whose cytoplasm is loaded with metachromatic granules.[17] In Newell's[7] cases he noted large vacuolated cells five and six layers thick which divided Bowman's membrane into thin lamella. These cells were also noted near the limbus.

Descriptions of the corneal lamella by Berliner,[50] Hogan and Cordes,[19] Newell,[7] Forgacs and Franceschetti,[49] and Scheie,[17] note the granules of Hurler's disease to distend and fill the corneal corpuscles; the interlamellar spaces usually being empty. Berliner[50] described the consequent slit-lamp changes as small punctate deposits of various sizes beginning in the anterior middle stromal layers and increasing in density

towards the posterior corneal surface; the corneal opacification usually being most noticeable near the center of the cornea. In addition to these granular deposits most authors have described edema of all corneal layers with consequent increase of the corneal thickness. Usually the corneal opacities preclude adequate fundoscopy.

Descemet's membrane is usually not remarkable. Lindsay,[18] et al, and Newell[7] describe granules of stored material in the endothelium causing some enlargement and vacuolation of these cells.

Analysis of the differential distribution of Chondroitin sulfate B and Heparitin S in various organs has been evaluated.[34,35] The liver usually contains a predominance of Heparitin[35] S while other organs, including the spleen, have more Chondroitin sulfate [35] B. In normal humans these two mucopolysaccharides occur together in high concentration only in the blood vessels. This may indicate that the site of origin of these products is vascular tissue. The deposition of mucopolysaccharide granules in many tissues is well reviewed by McKusick.[1]

CONNECTIVE TISSUE

Connective tissue consists of an amorphous ground substance of varying consistency in which collagen, elastin and reticulin fibrils are embedded. In addition, the ground substance is shot through with cells whose histologic simplicity cloaks a wide potentiality for differentiation and modulation. These cells consist of macrophages, mast cells, and the ubiquitous fibroblast. This latter cell, though similar in morphology from tissue to tissue, has a quite different role in synovial tissue than in cornea.

The role of the fibroblast in the formation of collagen has been shown by Jackson.[54] A stubby proteinaceous precurser called a tropocollagen unit is formed within the fibroblast and extruded into the media. When conditions are satisfactory, these bits are lined up like boxcars to form collagen fibrils.*[3] Gaines[55] has shown that tissue cultures of chicken embryo heart will synthesize both acid mucopolysaccharides and collagen. Although he did not use a clone system in these experiments he states that "almost without exception a single morphological cell type was present in these cultures, and this was a spindle shaped cell with long cytoplasmic processes, which is, in other words, the prototype of a fibroblast".

Pertinent to our study is the group of linear polyelectrolytes of high molecular weight called mucopolysaccharides (Chart 2). Eight of these have been isolated in mammalian tissue[56] and are found in the ground substance along with sugars, electrolytes, proteins, metabolites, fibrils, water, etc. They are made up of chains of disaccharide units containing an amino sugar such as glucosamine or galactosamine, and a uronic acid such as glucuronic or iduronic acid. There may be up to three sulfate moles per repeating unit (as there is in Heparin) or there may be no sulfate present. These chains of repeating units are wrapped about a protein core and held in place by covalent linkages to produce macromolecules with molecular weights of 4 million and up. The best known of these, hyaluronic acid, consists of glucosamine and glucuronic acid and is nonsulfated (Chart 2). The sulfate and carboxyl groups

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*It is interesting that such highly specialized organization is carried out in an extracellular area.

Chart 2

CONNECTIVE TISSUE MUCOPOLYSACCHARIDES

	Hexosamine	Hexuronic Acid	Source
Non-sulfated mucopolysaccharides:			
Chondroitin	galactosamine	glucuronic	cornea
Hyaluronic acid	glucosamine	glucuronic	vitreous
Sulfated mucopolysaccharides:			
Keratosulfate	glucosamine, galactose	none	cornea
*Heparitin sulfate (Hep S)	glucosamine	glucuronic	aorta
Chondroitin sulfate A	galactosamine	glucuronic	cornea cartilage
*Chondroitin sulfate B (ChS B)	galactosamine	iduronic	skin heart aorta
Chondroitin sulfate C	galactosamine	glucuronic	cartilage tendon
Heparin	glucosamine	glucuronic	

*Deposited in the tissues in Hurler's disease

on each repeating unit confer a high negative charge to these units and explain some of the roles of the acid mucopolysaccharides suggested in the introduction to this paper. Their high viscosity, high molecular weight, and complex molecular construction explain other roles on a purely physical basis.

Of interest to Ophthalmologists is the water binding by the mucopolysaccharides in the ground substance of the cornea. The role of osmotic, diffusional and hydro-dynamic factors in maintaining corneal deturgesence are well known. The role of the mucopolysaccharides, principally the non-sulfated chondroitin and keratosulfate, is less well known. Studies of corneal swelling by Smelser and Ozanics,[57] of the extracellular water in connective tissue ground substance by Day,[58] of the water binding capacity of the mucopolysaccharides by Hvidberg,[59] of connective tissue hyaluronic acid by Schiller,[36] and of the colloid-chemical nature of connective tissue gel, indicate that the mucopolysaccharides may be of major importance in the maintenance of corneal deturgescence.

PRIMARY METABOLIC DEFECT

Description of the primary error in Hurler's disease is not available. The complexity of the cellular production of any molecule as large as a mucopolysaccharide molecule would favor a variety of possible non-lethal variants.* Thus it would seem reasonable that a variety of mucopolysaccharidoses will be described.

Some will reflect qualitative, others quantitative errors. If the error in a mucopolysaccharidosis is in the construction of the mucopolysaccharide molecule itself, these diseases will be characterized by normal amounts of abnormal products. If the

*Consider the number of variants of the hemoglobin molecule which consists of only 150 amino acids; sickle cell disease being an error in only one of these amino acids.

error is in the quantitative expression of a product, then the disease will be characterized by abnormal amounts of a normal product. So far as is now known, the mucopolsaccharides produced in Hurler's disease are normal mucopolysaccharides. It is only necessary for a single pair of amino acids to be transposed in the nucleotide sequences of the nuclear DNA of certain fibroblasts to explain the excess production of a compound. This error is transferred to the ribosomal RNA by the base-pairing mechanism and one or several faulty enzymes are produced. These enzymes may either stimulate the formation of abnormal amounts of mucopolysaccharide or they may fail to inhibit the formation of these products. The specific enzyme at fault has not been isolated though Pogell and Koenig[60] have isolated an enzyme of importance in the formation of mucopolysaccharides which forms glucosamine-6-phosphate from D-glucose-6-phosphate and L-glutamine. These enzymes might also be degrading enzymes which in a mutant, ineffective, form fail to break down the specific mucopolysaccharide.† It has been argued[11] that the presence of other normal mucopolysaccharides in patients with Hurler's disease indicates that a clone system defect is necessary to explain these diseases. That is, an error in the differentiation of the fibroblast series occurs in which certain cells are arrested at the level of differentiation characterized by the specific mucopolysaccharide appearing in excess, while other cell lines proceed on to maturity.* It is more probable that fibroblast differentiation occurs along normal lines. If it did not, marked connective tissue collagen problems should also be expected since it has been shown[55] that both collagen and mucopolysaccharides are derived from the same connective tissue cells.** The connective tissue in Hurler's disease appears to be normal and other mucopolysaccharides, collagen fibrils, other proteins, etc., are satisfactorily produced.

We feel that in a mucopolysaccharidosis a mutant gene exists, capable of altering the effectiveness of an enzyme regulating mucopolysaccharide production. The presence of two mucopolysaccharides in Hurler's disease, Chondroitin sulfate B and Heparitin S, probably represents an error in the over production of only one of these. Uzman[11] hypothesizes that only one of these mucopolysaccharides is present as the direct responsibility of a genetically induced metabolic defect. The deposition of this first material so interfers with the normal functions of the involved cells that a second substance is formed.***

Summary

1. A brief review of Hurler's disease is presented.

2. Two illustrative cases are mentioned.

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†Meyer and Hoffman state that "the chemical dissimilarity of the two mucopolysaccharides (in Hurler's disease) makes it highly improbable that an enzyme specific for the two would exist."

*After the differentiation has been arrested, the cells producing Chondroitin sulfate B and Heparitin S, (in Hurler's disease, for example) would continue to divide at a normal rate but would differentiate no further so that at birth the total number of these cells would be abnormally large and the consequent production of Chondroitin sulfate B and Heparitin S would also be high.

**Immaturity of collagenous structure, were it not lethal, would produce defects such as seen in the Ehlers-Danlos syndrome, osteogenesis imperfecta, or pseudoxanthoma elasticum.

***This situation does occur in the lipid-storage diseases in which all lipid fractions are increased although the various diseases themselves are identified by increases in cerebrosides (Gaucher's disease) or sphingomyelins (Niemann-Pick's disease), etc.

3. Recent genetic, biochemical and histologic aspects of the problems of the muco-polysaccharidoses are briefly treated.

4. Further study of the mucopolysaccharides is of importance in explaining a variety of diseases in addition to the mucopolysaccharidoses per se.

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