

MORQUIO-ULLRICH'S DISEASE

AN INBORN ERROR OF METABOLISM?

BY

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Gargoylism or Hurler's disease was first described by Hunter (1917) and by Hurler (1919). This disease, which is also called dysostosis multiplex, is among other findings characterized by dwarfism and deformities of the spine and extremities. It has, during the years, caused diagnostic problems towards the disorder described by Brailsford (1929) and Morquio (1929) known as Morquio-Brailsford's disease or chondro-oste-dystrophy.

It has been emphasized that no diagnostic difficulties occur in typical cases of the two disorders, because essential differences are found. Gargoylism is most often accompanied by severe mental retardation and always affects a varying number of organs such as the brain, liver, spleen, heart, cornea and the inner ear, whereas the typical patient with Morquio-Brailsford's disease is intellectually normal and is lacking symptoms other than from the skeleton, where the spine and the epiphyseal ends of the long bones show the most pronounced changes.

In gargoylism microscopical examinations have shown storage in swollen, pale cells of abnormal metabolic products in different tissues such as cartilage, bone, liver, spleen and heart (Jervis, 1950). During the past decade it has been shown that there is an abnormal excretion of acid mucopolysaccharides in the urine, presumably the same metabolic products as found in the different tissues (Brante, 1952; Dorfman, 1958). Gargoylism is consequently now considered one of the known forms of inborn errors of metabolism. Such a defect has not been found in typical cases of Morquio-Brailsford's disease, but only a few reports have appeared on the pathological and chemical findings in this disorder (Einhorn, Moore and Rowntree, 1946; Benda, 1952; Zellweger, Ponseti, Pedrini, Stamler and von Noorden, 1961).

A great number of transitional forms between the two diseases has been reported over the years, and

some authors have questioned the differentiation (Eichenberger, 1954; Robinow, 1958). Others have felt that a separate disorder could be established between the two, a disorder called Morquio-Ullrich's disease as described by Zellweger *et al.* (1961) who reported the findings in two brothers with this disease. It is characterized by stunted growth and radiological changes as seen in Morquio-Brailsford's disease and without the ugly face seen in gargoylism. It differs from Morquio-Brailsford's disease in having extraskeletal changes, such as corneal opacities and mental retardation. Perhaps of greatest importance is the finding by Zellweger *et al.* (1961) of an excretion in the urine of mucopolysaccharides apparently somewhat different from that found in gargoylism. Maroteaux and Lamy (1961) have reported the presence of acid mucopolysaccharides in the urine of four cases of Morquio's disease, all with corneal opacities.

We have studied three siblings with an abnormal condition, which in our opinion must be Morquio-Ullrich's disease, and present our clinical findings as well as our preliminary biochemical studies.

Case Reports

The family lives in Greenland. The father and mother of our patients are related, the father being the mother's paternal uncle (Fig. 1).

The mother has polysyndactyly, but further radiographs and laboratory studies revealed no other abnormalities. A toluidine blue screening test for acid mucopolysaccharides was negative (Berry and Spinanger, 1960). Her height and intelligence were normal. In the generation with our patients there are eight siblings. The oldest is a girl 23 years of age, who is slightly retarded but manages to take care of herself. No. 2 is a healthy boy 21 years of age; No. 3 has polysyndactyly but is otherwise normal; No. 5 is a 13-year-old boy, and No. 7 an 8-year-old boy, and they are both healthy. The three siblings affected with the disease are No. 4, a boy of 15 years, No. 6, a girl of 11 years, and No. 8, a boy of

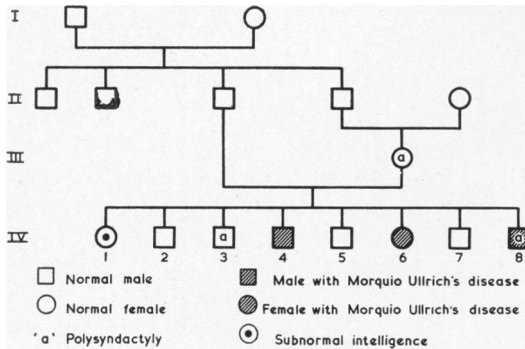


FIG. 1.—Family tree.

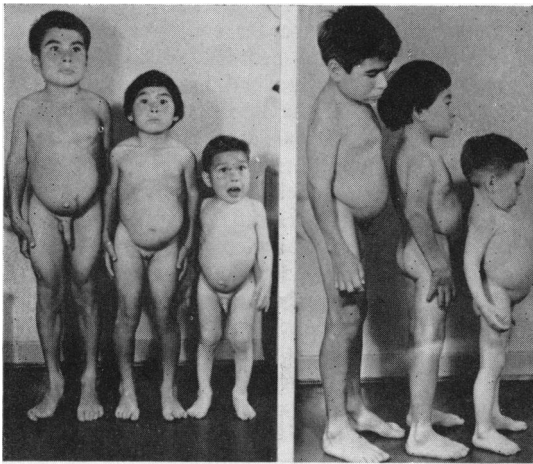


FIG. 2.—Morquio-Ullrich's disease in three siblings, 15, 11 and 4 years old (Cases 1, 2 and 3). The short necks, huncheri and femora as well as protruding sternum and abdomen and moderate knock-knees are seen.

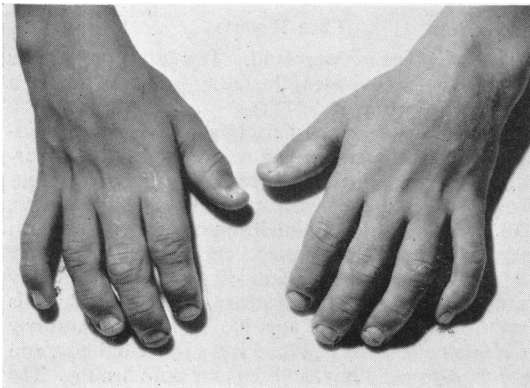


FIG. 3.—Hands of Case 1. The short broad fingers with slight extension defects are seen. Epidermis is thickened.

4 years (Fig. 2). Five of the eight siblings including our three patients have reddish-golden hair.

The father is said to be alcoholic. Sterilization was performed after the birth of the eighth child.

Case 1. Boy J.J., born March 11, 1946. Pregnancy and delivery seem to have been normal. He sustained a head injury at 18 months, after which he developed behaviour difficulties and only made slow progress intellectually.

At the age of 9 years he was admitted to the University Clinic of Paediatrics for mental evaluation. A developmental quotient was 34. He was 33 cm. below average Danish height, and radiological examination revealed changes of the spine as seen in gargylism or in Morquio-Brailsford's disease. Eye examination including slit-lamp examination was normal. He was operated on for rectal prolapse, and 12 cm. of the rectum was removed. Microscopical examination of the tissue showed no abnormalities and no storage of abnormal products. Electroencephalogram (E.E.G.) was normal except for some activity of low frequency.

The next years were spent at home in Greenland, but since the age of 11 years he has been a patient in a state institution for mentally retarded persons. His I.Q. was 27 at the time of admission. Radiological studies twice revealed the same changes as seen previously. The E.E.G. was normal and eye examination was normal. On admission to the State Institution he had grown only 4 cm. in two years, and the following two years he grew 5 cm. to 118.7 cm. His speech is very limited.

He was admitted to the University Clinic of Paediatrics at 15 years of age for further examinations. Apart from his stunted growth the most striking finding was the deformity of the spine with increased lordosis of the lumbar part. There was protrusion of the sternum and only a very short space between the thorax and the pelvis. His extremities were rather short, especially in the proximal parts. The arm span was 118 cm. The hands were broad and short with some extension defects of the finger joints (Fig. 3). The head circumference was 51.6 cm., the hair was reddish brown in colour, the features were eskimoic but normal. Eye examination including slit-lamp study was normal. Teeth and oral cavity were normal. Audiogram normal. There was no enlargement of the liver or spleen. The external genitals were of normal size but there was no pubic hair. His gait was a little waddling but his motor activities were unimpaired. Neurological examination was normal. The following examinations were carried out and revealed Hb 100%, sedimentation rate 3 mm. (Westergren); blood pressure normal; white blood cells 6,600-7,900 with a normal distribution, and no granulations or vacuoles were found. The bone marrow was normal. Wassermann reaction and serological test for toxoplasmosis were negative. Calcium, phosphorus and alkaline phosphatase as well as electrolytes in the serum were normal. Liver function was normal, blood creatinine and urea were normal. Fasting blood sugar and serum lipids and proteins were normal. Vitamin B₁₂ in serum normal. Sex chromatin negative and chromosomal studies normal. Urine excretion of 17-keto-

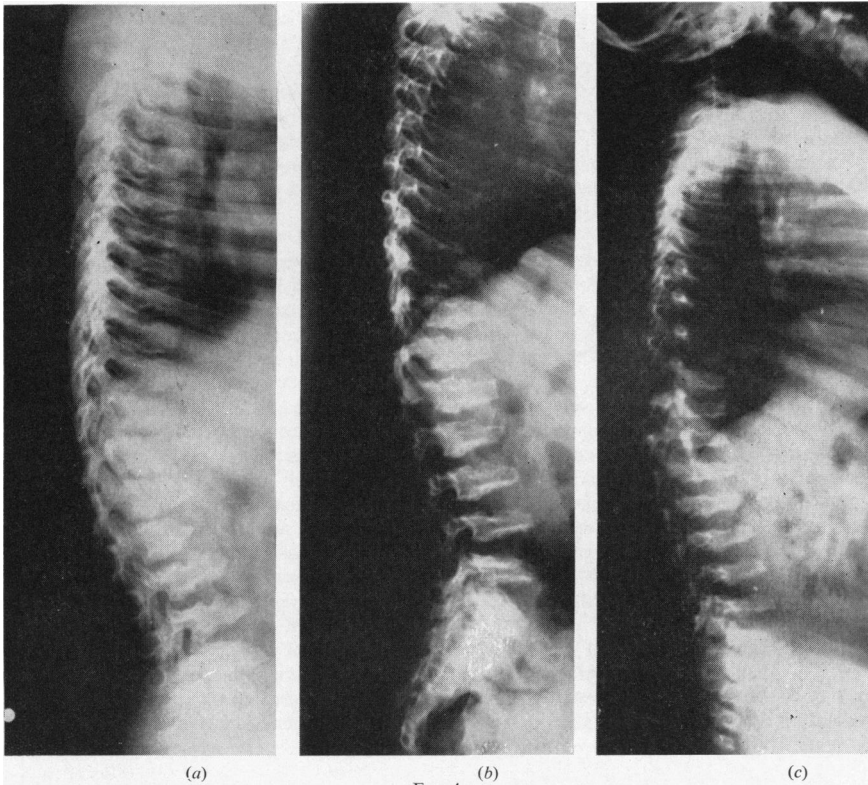


FIG. 4

FIG. 4.—Lateral view of spine. (a) Case 1, 11 years old (no further changes had taken place at 15 years); (b) Case 2 (11 years old); (c) Case 3 (4 years old). The changes in all three cases are the same. Note the flattened irregular corpora with a pointed end directed forwards. The changes are most marked in the lumbar part. The fusion of the pelvic corpora is delayed and the flattening of the thoracic corpora is most marked in Case 3.

FIG. 5.—Case 1: anterior view of pelvis. Note the deformation of the femoral head and neck and the irregularities in the iliac crest with swelling and demineralization.

FIG. 6.—Case 1: radiograph of upper part of left arm. The proximal epiphysis of humerus is broadened. The ossification centre of caput humeri is small and irregular. Humerus is short and its lateral margin is convex. Capitulum radii is rudimentary.

FIG. 7.—Case 1: radiograph of right hand. Note the shortening and broadening of the metacarpals and phalanges and the rather small and partially absent ossification centres of the wrist.



FIG. 5



FIG. 6



FIG. 7

steroids and gonadotrophic hormones normal. No amino acids were found in the urine. A screening test for urinary mucopolysaccharides was negative. A skin biopsy revealed considerable fibrosis and chronic oedema with perivascular sheets of lymphocytes and mast cells. The elastic tissue was scarce. The E.E.G. showed some fast activity frontally. Pneumoencephalography revealed symmetrical dilatation of the ventricular system (Evans ratio 0.30) with normal surface air distribution.

The spinal fluid contained 37 mg./100 ml. protein. Immuno-electrophoresis showed increased amounts of α_2 lipoprotein and of α_2 macroglobulin whereas the same study showed normal findings in the serum. This can be interpreted as a slight partial breakdown of the blood-C.S.F. barrier, but there was no evidence of intracranial immunization processes.

Radiological examination showed very pronounced changes in the vertebrae of the lumbar spine (Fig. 4a). It can be seen that the vertebral bodies are flattened and tapering forwards. Changes were also present in the hip joints with flattening of the acetabulum. Furthermore, Fig. 5 shows a broadening and swelling of the iliac crest. In the extremities changes were found in the epiphyseal zones (Fig. 6), and in the wrist lack of development of some of the small bones is seen (Fig. 7). Urography revealed no malformations.

Psychological testing gave a mental age of 3 years, a quotient of 20. Doll's test for social maturity corresponded to 4 to 5 years. Compared with the previous tests no intellectual development had taken place during the last 6 years, but some social improvement had occurred. The boy is good-natured and easy to deal with.

Case 2. Girl H.J., born July 7, 1950. No information on abnormalities during pregnancy and delivery. Because of slow mental development she was admitted to the same State Institution as her older brother when she was 7 years old. At the time of admission her developmental quotient was 40. During her stay she had several respiratory infections. She has been easy to take care of, is friendly and is good-natured as are her two brothers. There has been no intellectual progress during her four years stay in the Institution.

Radiological examination revealed the same skeletal changes as found in Case 1. During her stay she had grown 13 cm. Electroencephalograms taken on two occasions revealed no abnormalities.

She was admitted to the University Clinic of Paediatrics at the age of 11 years. She was found to be 104 cm. in height (35 cm. below average Danish height), and had the same deformities of the spine, thorax and extremities as were found in Case 1, except that her hands and feet were less deformed. Her hair was reddish-golden in colour. Head circumference was 48.2 cm. and arm span 95 cm.

The same examinations as were performed in Case 1 were carried out except for the pneumoencephalogram and chromosomal studies. The results of the blood and urinary laboratory studies were normal as in the case of the older brother. The only difference was that no

abnormalities could be found by immuno-electrophoretic studies of the spinal fluid. Eye examination and audiogram were normal.

Psychological testing gave an I.Q. score of 32. The social maturity was above the intellectual level.

Radiological examination of the bones revealed the same changes as in Case 1. The spine can be seen in Fig. 4 and pelvic irregularities in Fig. 8.

Case 3. Boy L.J., born May 23, 1957. Pregnancy and delivery were normal, birth weight 3,050 g. At the age of 3 years he had symptoms of a rectal prolapse, and one year later he was operated on for this reason.

At 4 years of age he was admitted to the same State Institution as his older siblings because of lack of development; in particular he had no speech. At the time of admission his height was 81 cm. (22 cm. below Danish average), and his arm span was 87 cm. He was as good-natured as the two older children. E.E.G. showed some activity of low frequency, but was otherwise normal. Radiological examination showed the same changes of the bones as were found in Cases 1 and 2.

He was admitted to the University Clinic of Paediatrics when he was 4 years and 6 months of age. His appearance was very much the same as seen in the older siblings. He was much below normal height and had the same changes of the spine, thorax and the extremities. His facial expression was normal, his hair reddish-brown. Head circumference was 46.8 cm.

Polysyndactyly was present on the fifth toe on the right foot. The same examinations were performed as in Case 2, and the only difference was the finding of some abnormalities in the spinal fluid studied by immuno-electrophoresis. A slight increase of all proteins was present including small amounts of α_2 lipoprotein and α_2 macroglobulin, indicating a partial breakdown of the blood-C.S.F. barrier. No significant signs of an intracerebral immunization were seen.

Psychological testing revealed a developmental quotient of 50 and a social maturity above this.

Radiological studies of the spine (Fig. 4c) and of the pelvis (Fig. 9) showed that the changes in the pelvis were less marked than in Cases 1 and 2.

Special interest in the three cases is connected to the study of the urine with regard to acid mucopolysaccharides, and a more detailed description of this part of the study seems indicated.

Material and Methods

The demonstration of acid mucopolysaccharides (heparin, chondroitin sulphate and hyaluronic acid) was performed in the following way:

The urine was collected for a period of 24 hours (sodium azide 0.1% was added to prevent bacterial growth). A sample of urine (25 ml.) was concentrated 500 times by vacuum dialysis in an apparatus* constructed for vacuum dialysis of cerebrospinal fluid (Clausen, 1962).

The identification of acid mucopolysaccharides in the

* Membranfilter Gesellschaft, Germany.

urine was performed by electrophoresis either on filter paper (Schleicher and Schüll No. 2043 B) or on cellulose acetate paper (Veronal buffer, ionic strength $\mu = 0.05$ M, $pH = 8.6$). Filter paper was used as described by Heremans, Vaerman and Heremans (1960) (running time three hours at 110 volts). The patterns were stained with Alcian blue or mucicarmine.* This procedure has the advantage that it is possible to separate heparin (fast) from the slower-moving chondroitin sulphate. This is not so easily performed on cellulose acetate paper which on the other hand can demonstrate cathodically weak fractions in the areas of the chondroitin sulphate fraction, and furthermore it can demonstrate differences in mobilities of the chondroitin sulphate fractions.

On cellulose acetate paper the electrophoresis was performed in a modified LKB-apparatus as described by Clausen and Rosenkast (1962) (running time $1\frac{1}{2}$ hours at 200 volts). The paper was stained for acid mucopolysaccharides with mucicarmine.

By correlation with the electrophoretic pattern obtained from the children under investigation with those obtained from standard preparations (0.5% w/v in NaHCO_3 (0.1 M)) of hyaluronic acid (the State Serum Institution, Copenhagen), chondroitin sulphate (Sigma) and heparin (NOVO), it was possible by means of the mobilities to identify the fractions.

Furthermore, it was possible by means of electrophoresis of a concentrated urine from a patient with gargoylism to see the difference between the excretion of acid mucopolysaccharides in this disease and that described in the children investigated in the present publication. Also a correlation was performed with the pattern of normal, pooled and concentrated urine.

Results

Fig. 10 demonstrates the acid mucopolysaccharide fractions in urine separated by electrophoresis on filter paper. The patterns are run together with



FIG. 8.—Case 2: anterior view of pelvis. Deformation of the femoral head and neck. Pronounced changes of the iliac crest.

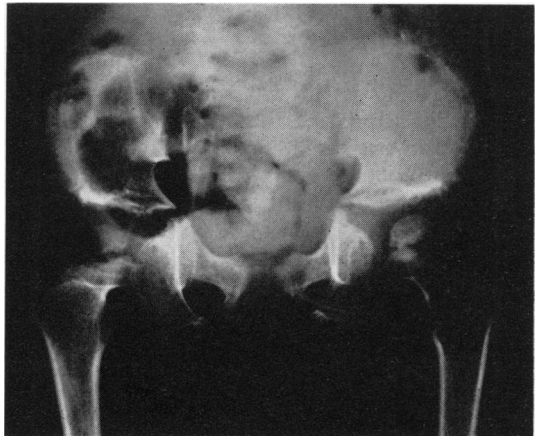


FIG. 9.—Case 3: anterior view of pelvis. Deformation of the femoral head and neck. Only slight changes of the iliac crest.

* Ciba Ltd.

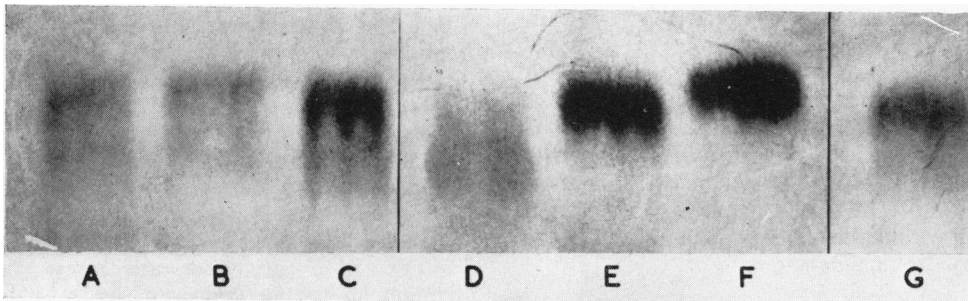


FIG. 10.—Alcian blue staining for acid mucopolysaccharides on Whatman No. 1 paper electrophoresis of urines concentrated 250 times.

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| <p>A. Paper electrophoretic pattern of urine, Case 3.
 B. The same as A from a normal urine.
 C. The same as A from Case 2.
 D. Paper electrophoretic pattern of hyaluronic acid, 0.5% in 0.1 M NaHCO_3.</p> | <p>E. Paper electrophoretic pattern of chondroitin sulphate, 0.5% in 0.1 M NaHCO_3.
 F. Paper electrophoretic pattern of heparin, 0.5% in 0.01 M NaHCO_3.
 G. The same as A from Case 1.</p> |
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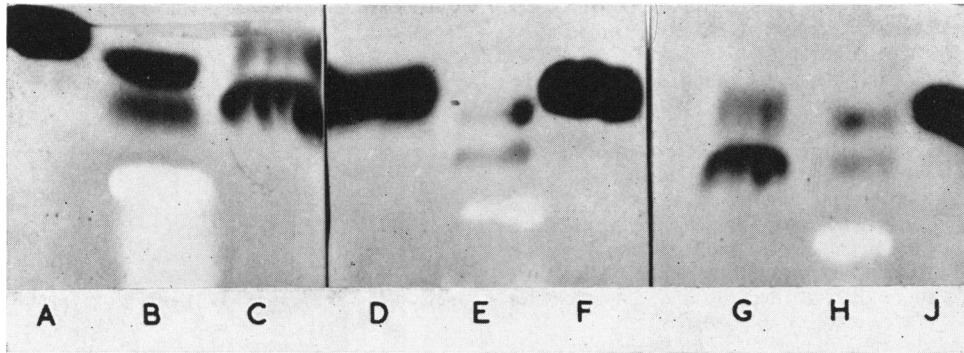


FIG. 11.—Mucicarmine staining for acid mucopolysaccharides on cellulose acetate paper electrophoresis of urines concentrated 250 times.

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|--|--|
| <p>A. Electrophoretic pattern of chondroitin sulphate standard.</p> <p>B. Electrophoretic pattern of urine from Case 2.</p> <p>C. Electrophoretic pattern of hyaluronic acid, standard.</p> <p>D. The same as A.</p> <p>E. Electrophoretic pattern of normal urine concentrated 1,000 times.</p> | <p>F. Electrophoretic pattern of heparin, standard.</p> <p>G. The same as C.</p> <p>H. Electrophoretic pattern of urine from Case 3 concentrated 500 times.</p> <p>J. The same as A.</p> |
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standard preparations of acid mucopolysaccharides and those of normal urine (all urines are concentrated 250 times). It is seen that the urine pattern of Case 2 is different from the pattern of normal urine, because it contains more acid mucopolysaccharide than normal. The mobility of the main fraction is somewhat slower than that of the chondroitin sulphate standard preparation (mainly containing chondroitin sulphate A, but mixed with a smaller part of B). Furthermore, a small fraction, with a mobility as hyaluronic acid, is present.

Fig. 11 shows the findings on cellulose acetate paper, demonstrating the same. Furthermore, a weak fraction is seen with a slower mobility than that of hyaluronic acid, but with a faster mobility than that of albumin.

In urine concentrated 2,000 times, several other fractions with mobilities between chondroitin sulphate and the albumin fractions can be seen (Fig. 12).

The urine from a patient with gargoylism, concentrated 500 times, demonstrated, on cellulose acetate paper, the presence of an increase of not only the chondroitin sulphate fraction and the fraction corresponding to the hyaluronic acid, but also the fraction just ahead of the albumin (Figs. 13, 14). On the other hand no fractions with a mobility somewhat slower than the main fraction of chondroitin sulphate were increased.

Discussion

Since the first reports of cases of gargoylism and of Morquio-Brailsford's disease a great number of papers concerning the differential diagnosis of these

two diseases has been published as well as descriptions of the typical findings in each condition. (de Rudder, 1942; Cocchi, 1950; Benda, 1952; Eichenberger, 1954; Hochheim, Körner and Liebe, 1955; Robinow, 1958; Zellweger *et al.*, 1961; van Pelt, 1961). Also a transitional form between the two disorders has been described several times and most recently by Zellweger *et al.* (1961) who proposed the name Morquio-Ullrich's disease. Already Wiedemann (1954) used the term Morquio-Ullrich's disease, but in a somewhat different way, meaning all cases of Morquio's disease, including Ullrich's cases of 'Spät-Hurler' who developed corneal changes when adult but otherwise had the appearance of Morquio-Brailsford's disease (Ullrich, 1943). The typical findings in the three disorders can be seen in the Table.

It can be seen that the common features are the retarded growth or real dwarfism, the short neck and the deformities of the back. Also the deformities in the vertebral bodies and in the epiphyseal zones of the long bones are found in all three diseases. The changes of the spine are most pronounced in the lumbar part with formation of beak-shaped corpora. It seems as if the flattened, compressed bodies are most marked in Morquio-Brailsford's and in Morquio-Ullrich's disease. The bones of the hands and feet are short and coarse, especially in gargoylism, and severe changes are found in the hip joints, particularly in Morquio-Brailsford's disease. The changes in the spine and the hip joints are according to Brailsford (1952) progressing in chondro-osteo-dystrophy and lead eventually to severe disablement. In the present cases these changes are evident but in addition

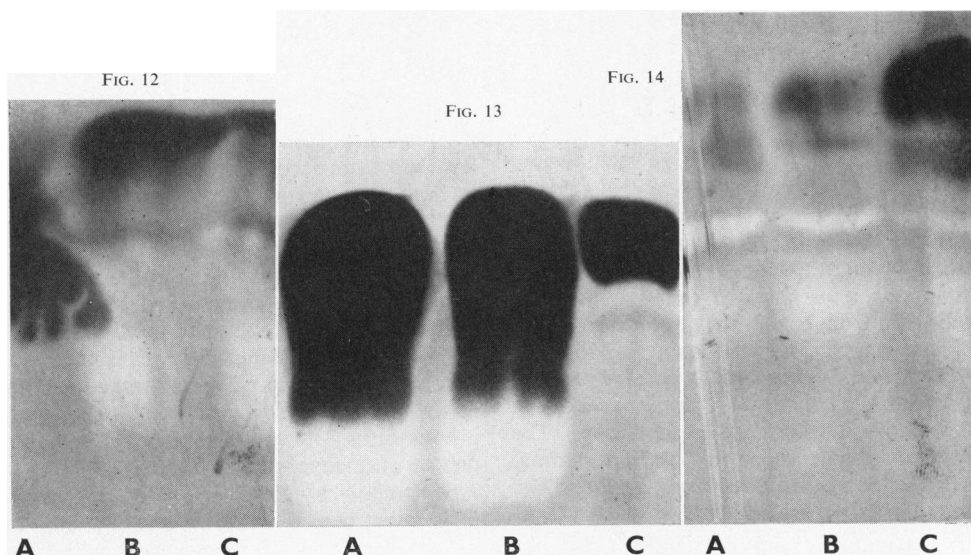


FIG. 12.—Mucicarmine staining for acid mucopolysaccharides on cellulose acetate paper electrophoresis.

- A. Electrophoresis of hyaluronic acid, standard.
- B. Electrophoresis of urine from Case 2 concentrated 1,000 times.
- C. Electrophoresis of urine concentrated 2,000 times from a normal individual.

FIG. 13.—Mucicarmine staining for acid mucopolysaccharides on cellulose acetate paper electrophoresis.

- A. Electrophoresis of urine concentrated 250 times from patient S with gargoylism.
- B. The same as A, but the urine was concentrated 500 times.
- C. Electrophoresis of chondroitin sulphate standard.

FIG. 14.—Mucicarmine staining for acid mucopolysaccharides on cellulose acetate paper electrophoresis. The urine from Case 2 is compared with the urine from the case of gargoylism.

- A. Case 2, the urine concentrated 250 times.
- B. Case 2, the urine concentrated 500 times.
- C. Patient S with gargoylism, the urine concentrated 250 times.

marked alterations of the iliac crest can be seen with irregularities and demineralization. In the reported cases we have only found this described once in a Morquio-Brailsford's case (Smith and McCort, 1958).

The further signs and symptoms characteristic of gargoylism are listed in the Table, and a detailed description can be found in the monograph by van Pelt (1961). Even by using the above proposed division into three well-defined clinical entities it can be seen from the literature that many cases do not fit into this scheme such as for instance cases of gargoylism with normal intelligence (van Pelt, 1961) and on the other hand cases of Morquio-Brailsford's disease with mental retardation (Farrell, Maloney and Yakovlev, 1942; Benda, 1952; White-side and Cholmeley, 1952; Robinow, 1958), but some of these patients might belong to the third group if re-examined.

We find that our cases belong to the group of Morquio-Ullrich's disease. The heredity of Morquio-Brailsford's disease and of gargoylism has been thoroughly discussed by Robinow (1958). As

previously reported in similar cases (Andersen, 1937; Farrell *et al.*, 1942; Hochheim *et al.*, 1955;

TABLE
DIFFERENTIAL DIAGNOSIS BETWEEN GARGOYLISM,
MORQUIO-BRAILSFORD'S DISEASE AND MORQUIO-
ULLRICH'S DISEASE

	Gargoylism	Morquio-Brailsford's Disease	Morquio-Ullrich's Disease
Retarded growth	+	+	+
Short neck and deformed back	+	+	+
Deformed and flattened vertebrae	+	+	+
Epiphyseal changes	+	+	+
Grotesque face	+	+	+
Coarse hands	+	(+)	(+)
Mental retardation	+	-	(+)
Hepatosplenomegaly	+	-	(+)
Corneal opacities	+	-	(+)
Reilly granulations	+	-	(+)
Deposits of abnormal metabolic products in various organs	+	?	(+)
Mucopolysaccharides in urine	+	?	+

(+) Symptom has been described in some patients.
? Unexplored.

Townsend-Coles, 1954; Eichenberger, 1954) we also found consanguinity between the parents. It might be of interest to notice that our family comes from Greenland, and that similar case reports have been published from the Sudan (Townsend-Coles, 1954), in a Japanese family in California (Smith and McCort, 1958), as well as in an Armenian family (Farrell *et al.*, 1942) and in a Negro family in the United States (Benda, 1952). A possible explanation could be a higher frequency of intra-familial marriages among more isolated populations.

As can be seen from Fig. 2, the appearance of our three siblings is typical of that seen in Morquio-Brailsford's disease. They are dwarfed with pronounced lordosis of the lower back, have some protrusion of the sternum and short necks. The extremities are characterized by short proximal parts, and the hands and feet are coarse. The features are normal Greenlandish, but it is remarkable that five out of eight children in this family have reddish-golden hair, among them the three affected children. This hair colour is extremely rare in Greenland.

Pronounced mental retardation is present in the three siblings. It is our impression that the mental development continues to a certain degree after which there is no further progress. This is particularly seen in Case 1, where I.Q. examinations with six years' interval showed no progress in intellectual age with a drop in I.Q. from 40 to 27, but where we found some social development over the same period of time. The degree of mental deficiency in the three siblings also indicates the same, the youngest child being retarded to a lesser degree than the older ones. As found by Benda (1952) in his case, our three patients were very kind, good-natured and easy to deal with.

The characteristic radiological findings are seen in Figs. 4-9. The most pronounced and typical findings are in the vertebrae of the lumbar spine, but it is worth noticing that the deformities have not progressed in the oldest child who has been followed up for six years. The hip joints are severely affected, but no real arthrosis or luxation has occurred yet. An interesting finding is the change in the iliac crest which is less marked in the youngest child and seems to increase with advancing age. As in the case reported by Andersen (1937) poly-syndactyly was present in some members of our family. In none of our children did we find any evidence of involvement of other organic systems, and we did not find corneal clouding, loss of hearing or Reilly granulations as described in two brothers by Zellweger *et al.* (1961).

The two affected boys in the present family had

severe rectal prolapse both needing operations. This symptom has apparently not been described before in such cases, whereas hernias are found frequently in cases of gargoylism.

In gargoylism pathological-anatomical studies have shown an accumulation of mucopolysaccharides in large vacuoles in cells of many different tissues, whereas microscopical examinations in the two forms of Morquio's disease are very limited. Compression of the medulla by the upper cervical vertebrae was the cause of death in a case of Morquio-Brailsford's disease published by Einhorn *et al.* (1946). No detailed description of the microscopical appearance of other organs was included in their report. Zellweger *et al.* (1961) performed a bone biopsy in one of their cases and found evidence of mucopolysaccharidosis.

The report by Zellweger *et al.* was particularly interesting because they found in one of their children abnormal excretion of acid mucopolysaccharides in the urine possibly of a somewhat different sort than the excretion found in gargoylism. The biochemical and chemical data revealed in the present report are only preliminary and detailed data will be published later (Clausen, Dyggve and Melchior, 1963). Paper electrophoresis, especially on filter paper or on cellulose acetate paper, appears to be the tool of choice as a screening test for an increased amount of acid mucopolysaccharides in the disease described here. The cellulose acetate paper electrophoresis can be performed within two hours after vacuum dialysis which takes about five to six hours (Clausen and Rosenkast, 1962) which means that this method can be performed within one day. Paper electrophoresis on cellulose acetate paper makes it possible to distinguish between several different acid mucopolysaccharide fractions with mobilities corresponding to those of chondroitin sulphate and hyaluronic acid. This can be done, when the electrophoresis is performed at pH 8.6, where these fractions possess a mobility distinctly different from that of the protein fractions, because the isoelectric point of the acid mucopolysaccharides is distinctly lower than that of the proteins. It is necessary to perform the electrophoresis together with those of the standard preparations of acid mucopolysaccharides on the same paper, in order to correlate the mobilities of the obtained pattern. Electrophoresis on filter paper can be performed within three to four hours (Heremans *et al.*, 1960). Both cellulose acetate and Whatman paper electrophoresis have to be performed. Thus it is not possible to stain with Alcian blue on cellulose acetate paper as on filter paper. This stain seems

to us superior to other staining materials, giving more clear-cut results. Furthermore, the filter paper seems to distinguish better between the chondroitin sulphate A fraction and the heparin fraction than cellulose acetate paper. The latter seems on the other hand to give a better result concerning the splitting of the pattern around the chondroitin sulphate fraction into independent subfractions. Thus often both the chondroitin sulphate A and B fractions can be visualized as well as still unknown fractions (Clausen and Rosenkast, 1962). In urine from the children under investigation only Case 2 showed an increase in fractions of acid mucopolysaccharides, stainable both with Alcian blue and with mucicarmine.

The fast fraction had a mobility distinctly slower than heparin, but quite similar to the chondroitin sulphate fraction. Since this fraction had a somewhat smaller mobility than the fast part of the chondroitin sulphate standard preparation (consisting mainly of fraction A with impurities of fraction B) it is rather tempting to suggest that the increased chondroitin sulphate is localized mainly in fraction B. Also the more slowly migrating fractions, of which one had a mobility corresponding to hyaluronic acid, were increased. On the other hand no heparin fraction was found in the urine.

By comparing the results from Case 2 with those from a clinically verified case of gargoylism (a 12-year-old boy (S), who is a patient in the same institution as the siblings) it is obvious that the electrophoretic feature is only partially the same. Thus Case S showed an increased fraction, localized in the area corresponding to the fast chondroitin sulphate and to the heparin fractions. The urine from Case 2 contains an increased amount of an acid mucopolysaccharide fraction with a mobility somewhat slower than the main fraction of the chondroitin sulphate, in contrast to the case of gargoylism where the fractions correspond in mobility to heparin and to the fast fraction of the chondroitin sulphate.

These results seem in agreement with the data given by Zellweger *et al.* (1961) who demonstrated that the clinical entity, Morquio-Ullrich's disease, was both clinically and biochemically a syndrome with properties intermediate between gargoylism and Morquio-Brailsford's disease. Thus it was reported that this disease was associated with an increase of an acid mucopolysaccharide, most probably keratosulphate, in the urine, but not mainly of chondroitin sulphate as in gargoylism, where both chondroitin sulphate and heparitin sulphate were found excreted in large quantities in the urine. Keratosulphate was not identified,

because this substance is relatively unknown and no data about its mobility on paper electrophoresis are available. Therefore it cannot be excluded that the most anodic of the fractions from Case 2 contains some keratosulphate.

Both the clinical findings and the biochemical data seem to indicate that Morquio-Ullrich's disease represents a familial, inborn error of metabolism with abnormal excretion of acid mucopolysaccharides in the urine closely related to but not quite identical with the biochemical changes found in gargoylism.

Besides this, certain abnormalities were found by immuno-electrophoretic examination of the cerebrospinal fluid in two of our cases. The hypothesis is put forward that there might be a correlation between the abnormal mucopolysaccharide metabolism and the changes in the cerebrospinal fluid and the mental deficiency.

Summary

The clinical and biochemical findings in three Greenlandish siblings with Morquio-Ullrich's disease are presented. The appearance and the radiological changes are similar to the findings in Morquio-Brailsford's disease, but in addition the three siblings were severely mentally retarded and had an abnormal excretion of acid mucopolysaccharides in the urine. The parents were closely related. The disease seems to be due to a recessively inherited enzymatic defect.

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