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Hurler's Syndrome: A Clinical Report on Two Cases

BY

L. JACOBSON, B.SC., M.B., CH.B. (Cape Town), M.R.C.P. (Lond.), D.T.M. & H.

AND

M. A. KIBEL, M.B., B.CH. (Witwatersrand), M.R.C.P. (Edin.), D.C.H.

Bulawayo, S. Rhodesia.

Dwarfism, hideous features, characteristic deformities of the skeleton and other abnormalities involving many systems typify this bizarre and rare condition.

It is said to have been first recognised by John Thomson, of Edinburgh, about 1900 (Henderson, 1940), but the first report was that of Hunter in 1917. Entitled, "A Rare Disease in Two Brothers," it described fully the deformed extremities, dwarfing, hepatosplenomegaly, cardiac involvement and facial appearance; yet corneal clouding, mental deficiency and gibbus, features which were later considered by many to be essential for the diagnosis of the syndrome, were absent.

Two years later, Hurler, at the instigation of Professor Pfaundler, of Munich, described cases in infants who had, in addition to the above features, corneal clouding, retardation of intellect and gibbus (McKusick, 1956). It is with the names of Hurler and Pfaundler that this condition is most commonly associated. In common with other diseases of obscure etiology, there are also several synonyms: "dysostosis multiplex" (Husler), "lipochondrodystrophy" (Washington), "gargoylism" (Cockayne, 1936; Ellis *et al.*, 1936). The latter is the term most generally used in the English literature, yet McKusick deprecates its use as unnecessarily cruel in a condition which is now recognised to be not unusually associated with normal intellect.

Since the classical writings of Hunter and Hurler there have been numerous reports of this disorder; Emanuel, in 1954, estimated the total number of reported cases at over two hundred. In recent years several fine reviews dealing with the clinical and pathological aspects, notably those of Reilly *et al.* (1948), Lindsay *et al.* (1948), Jervis (1950), Henderson *et al.* (1952) and McKusick (1956), have clarified the clinical limits of the syndrome and its morbid anatomy. Jervis drew attention to the "formes frustes" in which one or other of the typical features were missing in undoubted cases of Hurler's syndrome. Despite these advances, the basic metabolic defect which causes this bizarre picture is still unknown. Histologically there is an accumulation in tissues throughout the body—parenchymal, fibroblastic and reticulo-endothelial—of an unidentified substance which balloons the cells and interferes with their function. This was considered by earlier workers (Washington, Ellis and others) to be a lipid, but subsequent histochemical studies have failed to substantiate this (Lindsay *et al.*, 1948). These workers considered the substance to be glycogen or glycoprotein. Brante isolated a mucopolysaccharide from the liver of a case of Hurler's syndrome, and more recently Uzman has described two storage materials obtained from the liver and spleen of these cases: (i) a complex polysaccharide; and (ii) a glycolipid. Uzman refers to these as fractions P and S respectively.

The widespread deposition of this as yet unidentified material leads to the classical clinical picture. At autopsy the brain may show internal hydrocephalus or areas of cortical atrophy, and extensive changes in the leptomeninges have been described (Magee, 1950). The liver and spleen are commonly greatly enlarged. There is cardiac enlargement with left ventricular hypertrophy as a feature in a large proportion of cases, with patchy thickening of both endocardium and epicardium in some. The most constant abnormality is thickening and

opacification of valves and chordae tendineae, often sufficient to produce clinically evident stenosis or regurgitation. The incidence of involvement of the heart valves is precisely as occurs in rheumatic fever (McKusick, 1956). Affection of the intima of the coronary arteries leads to a narrowing to such an extent that almost complete occlusion may follow. The aorta and its branches, the pulmonary arteries, the cerebral arteries and other arteries have been described as being similarly affected. The tracheo-bronchial cartilages are abnormal, and this feature may be in part responsible for the especial liability to respiratory infections. The skeletal changes appear to be the direct result of abnormal storage in chondrocytes and osteocytes. Abnormal storage is also responsible for the corneal clouding. The kidneys and gonads may be involved. Enlargement of lymph nodes has been described. The pituitary gland may be enlarged and the sella tursica frequently is ballooned, producing a "shoe-shaped," "shell-shaped" or "bowl-shaped" appearance on X-ray.

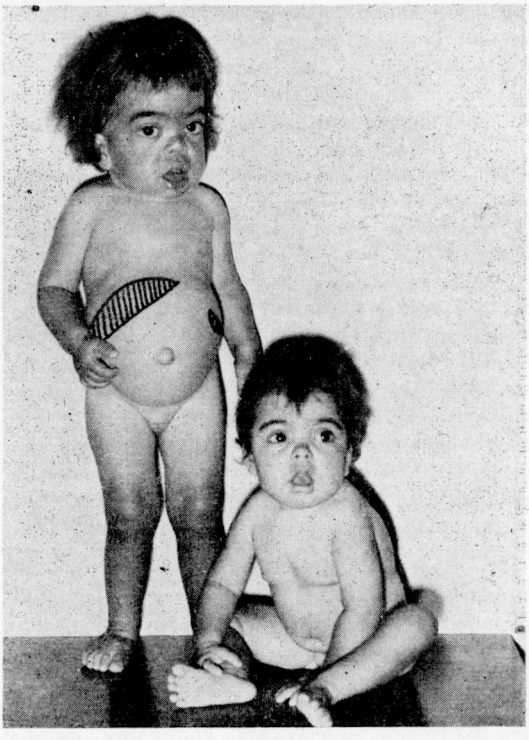

Fig. 1—The two sisters with Hurler's syndrome.

Since the first descriptions of this disease it has been known to display familial characteristics. There are frequently several affected siblings in one family, yet the parents are invariably normal. Parental consanguinity is often present. These factors point to inheritance by an autosomal recessive gene. There is no authentic report of minor manifestations of the syndrome in close relatives of patients with the disease to suggest that partial expression of the trait in the heterozygous state may occur (McKusick, 1956).

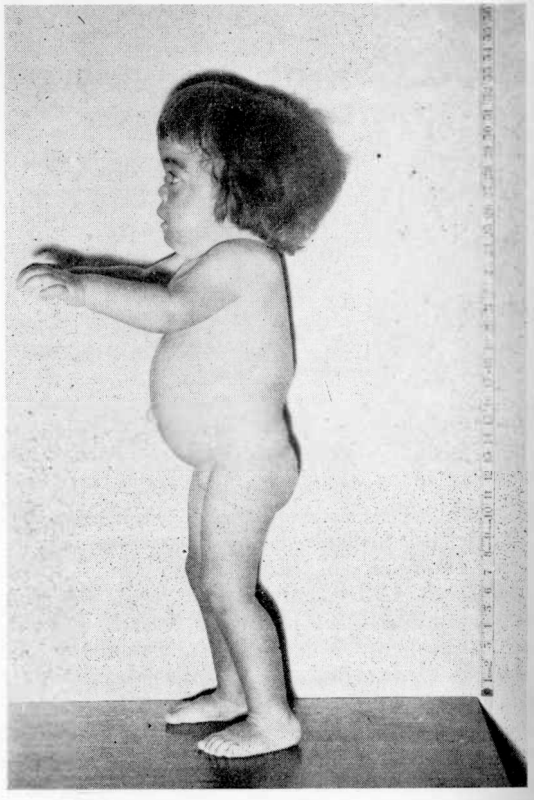

Fig. 2, Case 1—The large dolichocephalic head, depressed nasal bridge, protruberant abdomen with umbilical hernia, flexion of joints, clawed fingers, and kyphosis are well shown.

There are also several undoubted examples of the disease in a sex-linked pattern similar to haemophilia. Beebe and Formel (1954) described nine cases of Hurler's syndrome in four generations of a family of Dutch extraction living in the Catskill mountains. Of 19 males in this family, nine were affected; whereas of 16 female siblings of the affected males, none was affected. All were descended from a common female ancestor. This interesting report concords with Njà's opinion that the sex-linked form of the disease is different clinically from the autosomal recessive form (Njà, 1945-46).

McKusick, after reviewing the literature, elaborates this theme and is of the opinion that the sex-linked form manifests at a later date and the cases frequently have normal intellect and absence of corneal clouding and gibbus. He suggests that Hunter's original cases were of the sex-linked and Hurler's of the autosomal recessive type, and therefore there is historic justification for using the terms Hunter's syndrome and Hurler's syndrome respectively.

We describe here two undoubted examples of Hurler's syndrome occurring in siblings.

Case 1

Beverley W., European female, aged 2½ years, first came to our notice in June, 1956, when she was admitted to the Bulawayo General Hospital as an acute emergency with broncho-pneumonia. She was born on the 8th April, 1954, the first child of healthy parents, the father being 22 years and the mother 21 years at the time of the child's birth. There was no consanguinity between father and mother and none between any other members of the family in the preceding two generations. Apart from the sibling, born subsequently, to be described below, there has been no similarly affected relative in the traceable family tree.

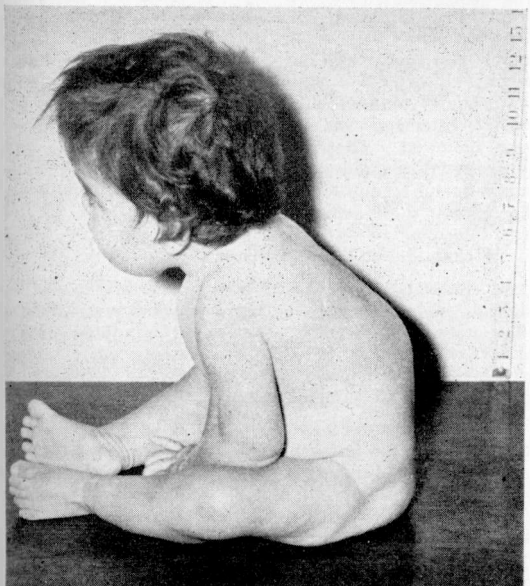

Fig. 3, Case 2—Note the typical kyphosis and lanugo hair over the back and limbs.

The pregnancy preceding Beverley's birth was normal, apart from rather severe morning sickness and an attack of influenza during the first three months, and delivery took place at full term, the infant weighing 7 lb. 1 oz. Snoring breathing and poor colour necessitated the use of oxygen during the first week. Continuous mouth-breathing and nasal catarrh persisted and became a constant feature, with frequent exacerbations and associated bouts of cough. Such an exacerbation was responsible for the admission to hospital. Deformity of the lower part of the anterior chest was noted at birth.

Progress during the first three months was unsatisfactory. Breast feeding was abandoned after three weeks and thereafter various dried milk formulae were tried. At all times she was noticed to be a poor sucker. In spite of this, she smiled at six weeks, cooed soon afterwards and reached for a rattle at four months.

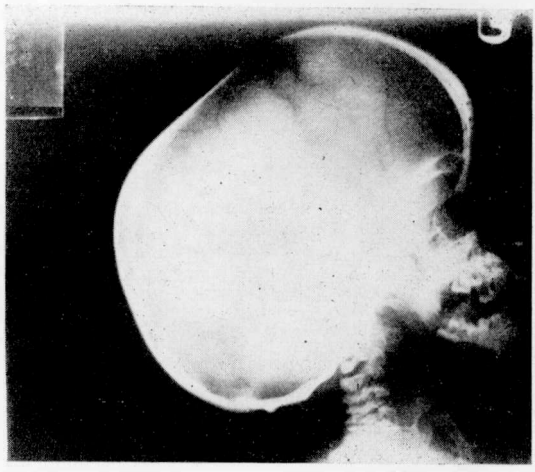

Fig. 4, Case 1—Note the large skull and pituitary fossa and suture separation.

At three months a deformity of the lower spine was noticed and medical opinion sought. A diagnosis of cretinism was then suggested. It was considered that there was some improvement on thyroid orally, but from this time onwards physical development was never satisfactory and weight and height have shown a progressive lag behind those of children of similar age—this despite a normal appetite and varied diet. She began walking unaided at 18 months and now walks well, though tending to fall easily. If she falls she cannot pick herself up. She says a few words, but cannot yet make herself understood. Her habits are still faulty, but the mother says she will indicate her needs in this respect. The first tooth erupted at 12 months. Eyesight and hearing appear normal. For the past nine months there has been progressive abdominal distension.

Examination revealed a grossly stunted child, 23 lb. 14 oz. in weight and 32½ inches in height. These measurements fall below the third percentile curve for growth and height (Nelson, 1955). The span was 27 inches and the crown rump measurement 20 inches, leaving a lower measurement of 12½ inches. These figures illustrate the shortening of the extremities in relation to the trunk. She showed most of the typical stigmata of gargoylism. The skull was large (circumference 24 inches), with great prominence of the frontal eminence. It was

scaphocephalic, with a prominent midline ridge extending down the forehead. The eyes were set far apart (hypertelorism) and there was well marked buphthalmos. The corneae showed fine homogeneous opacity easily obvious to the naked eye, but slit-lamp microscopy was not possible. There was no obvious impairment of visual acuity. The irides were of a dark brown colour. There were prominent epicanthic folds. The nose was broad, the alae nasae coarse and the bridge flattened. There was profuse mucoid nasal discharge and noisy, grunting breathing. The mouth was large, the tongue smooth and

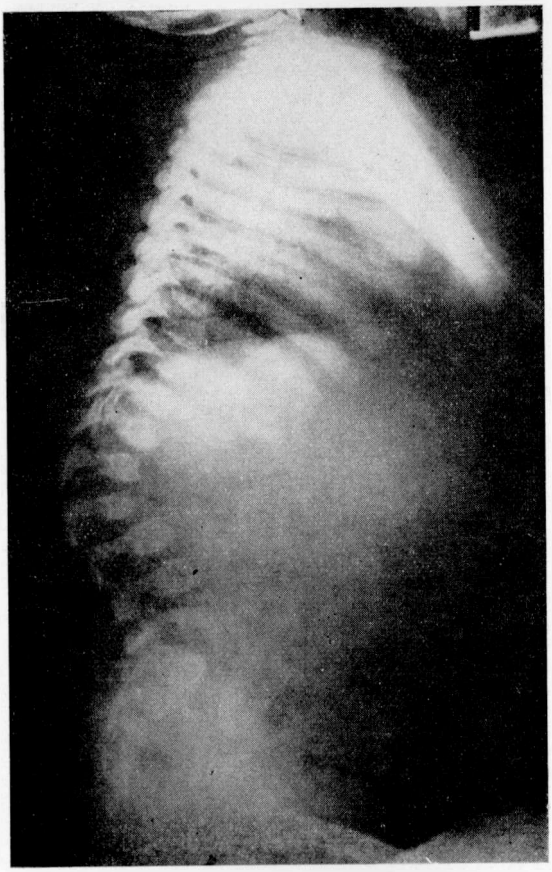

Fig. 5, Case 1—The lumbar spine shows angular kyphosis with deformed bodies. Note enlargement of the ribs.

partly protruded on to the lower lip. Papillae were normal. Only five teeth had erupted in the upper jaw and six in the lower. Only the tips of these were visible owing to a marked gingival hypertrophy. The ears were normal, but set low on the head, the top of the ear being below the level of the eyes (Figs. 1 and 2). Scalp hair was profuse and coarse, but there was conspicuous thinning over the occiput. There was fine, downy hair on the arms, legs, back and shoulders. The skin was sallow and waxy to the touch. When pinched between the fingers, gross thickening of the dermis was at once apparent. Even in areas normally thin and mobile in children—the inside of the arms and thighs—this thickening was evident. It was most marked over the face and especially over the chin, where it appeared fixed to the bony structures beneath. Because of this thickening, the scalp veins formed deep grooves in the skin easily palpable to the examining finger. The neck was almost non-existent, the head appearing to sit on the shoulders. The lower third of the sternum was pushed forward, with backward tilting of the xiphisternum. In the sitting position a deep cleft was formed between the protuberant abdomen and this sternal prominence. There was a moderate umbilical hernia. A firm, non-tender, smooth liver was palpable $2\frac{1}{2}$ inches below the xiphisternum. The spleen was just palpable.

Lungs, after the initial broncho-pneumonia, were normal. The heart was clinically normal and the blood pressure was 95/60. All joint movements were rather restricted, especially at the elbows and knees, where full extension was impossible. The fingers were continuously held in slight flexion, and here again full passive extension was not possible. The little fingers were incurved. There was bulging of the lower ends of radius and ulna. A marked kyphosis involved the lumbo-dorsal region. The ribs were palpably broad throughout their length. The clavicles could be felt from sternum to acromion. Neurological and fundoscopic examinations were unremarkable.

An accurate mental assessment proved difficult, but she was undoubtedly somewhat backward, even making allowances for the obvious physical handicap of her continually obstructed upper respiratory tract. However, she was attentive, interested in her surroundings and showed no gross mental defect.

She was admitted almost moribund with an extensive bilateral broncho-pneumonia. This responded rapidly to oral tetracycline. The erythrocytes were 4,000,000 per c.mm., the haemoglobin 11 gm. per cent. and the C.I. 0.98. The leucocytes were 5,000 per c.mm. (polymorphs 50 per cent., lymphocytes 46 per cent., monocytes 2 per cent. and eosinophils 2 per cent.). Abnormal granulation was not demonstrable in the white cells. Serum protein was 7.4 gm. per cent. (albumen 3.6 gm. per cent. and globulin 3.8 gm. per cent.). The blood cholesterol (total) was 176 mg. per cent. An electrocardiograph revealed no abnormality. The urine was normal.

Radiological Findings

Skull: There was enlargement of the skull, especially of the frontal region. The coronal suture was separated and the pituitary fossa

showed marked enlargement in its antero-posterior diameter, appearing boat-shaped (Fig. 4).

Spine: This showed an angular kyphosis of the upper lumbar region produced by backward displacement of lumbar 1 and 2. The bodies of these vertebrae were small and beaked anteriorly, due to concavity of the antero-superior margin. There was slight convexity of the superior and inferior surfaces of other lumbar and thoracic vertebral bodies (Fig. 5).

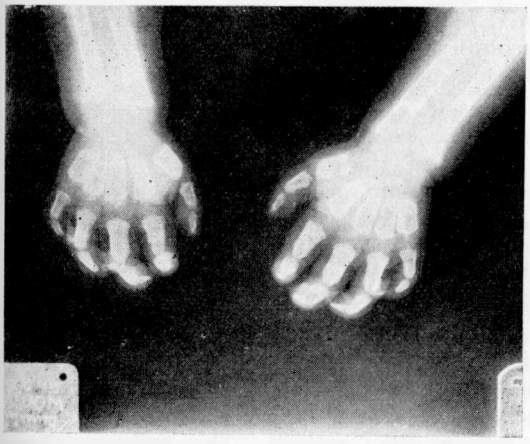

Fig. 6, Case 1—There is a typical deformity of the wrists and hand bones.

Pelvis: The acetabulae were shallow and shelving and a coxa valga deformity of the femoral heads was present. These were otherwise normal.

Chest: The ribs were enlarged, as were the medial halves of the clavicles and both scapulae. There was vara deformity of the humeral heads. There was slight generalised cardiac enlargement.

Hands: Angulation of the distal surfaces of the radius and ulna was present. These bones were widened, due to a large medullary cavity. The metacarpals and phalanges showed marked widening, with central cyst-like areas, and the bases of the second to fifth metacarpals were tapered. The bone age was normal (Fig. 6).

Long bones: There was localised increase in width of the upper third of both humeri.

Case 2

Cynthia W., Beverley's younger sister, was aged five months when first seen, and born on 29th February, 1956. Pregnancy and labour were uneventful and birth weight was 7 lb. 10 oz. Early infancy was not remarkable, apart from an attack of bronchitis at two months. Subsequent development was satisfactory, but at the age of three months snoring breathing, similar to Beverley's, became apparent. Apart from this the mother noticed no other abnormalities. She was breast-fed for six weeks and then fed with a mixture of Nutrine and cow's milk. Solids were introduced at three months.

On examination she was a well-covered infant, weighing 15 lb. 15½ oz. There was a resemblance to her sister, and even at this early age many of the stigmata were present.

The skull circumference was 18 inches. The anterior fontanelle was widely patent, measuring 3 inches by 1½ inches, and the posterior fontanelle closed. The eyes were normal and the irides of a similar dark brown colour to Beverley's. There was slight "steaminess" of the corneae. The skin over the chin, cheeks and upper arms was indurated, resisting movement, but elsewhere it showed a normal resilience. The bridge of the nose was flattened and there were prominent epicanthic folds. There was marked hypertrophy of the gums and mucosae of the hard palate. No teeth had erupted. The tongue was constantly protruded on to the lower lip. Heart and lungs were normal and there was no abdominal distension and no umbilical hernia. The scalp hair was dry and fine, being very sparse over the occiput. Fine dark lanugo-like hair was present on the small forehead, and there was similar hair on the arms and back.

The spleen was impalpable. The liver was felt 1½ inches below the right costal margin. There was a smooth kyphosis of the lower dorsal spine, and the neck was short. There was anterior bowing of the upper sternal segments, with depression of the lower half of the sternum. There was bossing of the lower ends of the radius and ulna. The hands and feet were normal. There was no restriction of joint movements.

A blood count revealed normal indices. The white cells were normal. The serum cholesterol was 160 mg. per cent. and serum proteins were 5.2 gm. per cent. total, with a normal albumen: globulin ratio.

Radiological Findings

Skull: There was no enlargement and the pituitary fossa was within normal limits. The coronal sutures were separated.

Spine: This showed a similar deformity to Beverley's, involving lumbar 2 (Fig. 7).

Pelvis: There was slight shelving of the acetabulae.

Chest: The ribs appeared slightly enlarged and there was club-shaped expansion of the upper ends of the humeri. The heart size was normal.

Deformity of wrists and hands similar to that in Case 1, but of a lesser degree, was apparent.

Discussion

The unmistakeable features of a fully developed case of Hurler's syndrome as exemplified in Case 1 are due to a widespread involvement of the skeleton. The grossly short neck, the dorsal kyphosis, the deformed thorax, the maldeveloped long bones and flexion deformities of all the joints combine to produce marked stunting. Involvement of the skull vault and facial bones with thickening of the skin and soft tissues

are responsible for the grotesque facies. The head is large, the bridge of the nose flattened and the eyes widely spaced. These features, together with the coarse lips, large protruding tongue, stridulent mouth-breathing and apathetic bovine expression serve to make cases of this disease resemble each other as closely as do mongols and microcephalics.

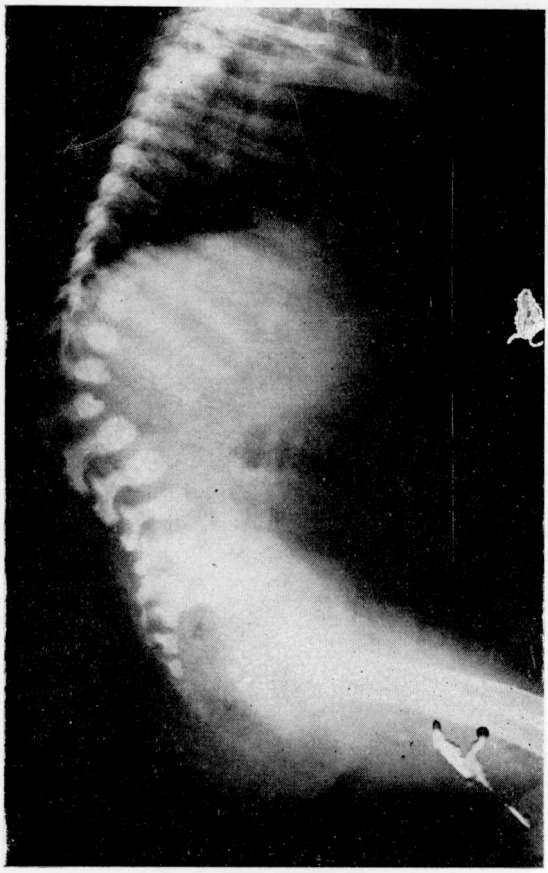

Fig. 7, Case 2—Lumbar spine, showing typical deformity.

Diffuse infiltration into parenchymatous tissues leads to enlargement of the liver and spleen, mental defect, corneal clouding and cardiomegaly. It is involvement of the myocardium which is frequently responsible for the cardiac failure, but occlusive disease of the coronary arteries caused the death of at least one case (Craig, 1954), and valvular involvement is also, in all probability, an important factor.

Other features which go to make up the protean clinical picture are deafness, abdominal distension with umbilical and other herniae, hirsutism, claw-like hands and infantilism.

An unusual feature in our cases was the remarkably early development of the disease. If the pigeon chest deformity of Case 1 is to be regarded as a manifestation of the morbid process, then there is evidence that the disorder was present at birth. Certainly it was well established at three months, when the gibbus was noted. In Case 2 the syndrome was well developed at five months. While Lindsay *et al.* (1948) state that signs may be present at birth, it is more usual for these to become obvious later, when material accumulates in large enough quantities to alter the normal growth of the skeleton and other structures.

Jackson (1951) stresses that pigeon chest deformity does not occur in gargoylism, but is a feature of Morquio's disease. The deformity of the sternum in our cases—pigeon chest in Case 1 and "pigeon-funnel chest" in Case 2—would seem to contradict this view. One of McKusick's cases and one of Hurler's original cases had funnel chests.

Jackson found deficiency of the lateral part of the clavicles in his cases and suggested that this appearance, though not previously commented upon, was also depicted in the radiographs of other authors. This appearance was not evident in our cases.

The separated skull sutures present in both our cases are indicative of increased intracranial pressure. This is a not uncommon manifestation in severely affected cases.

"Adler bodies," though sought on several occasions, were not seen in the polymorphonuclear leucocytes in either case. Originally observed by Reilly (1911), these large granules are present in many cases of Hurler's syndrome. There is histochemical evidence to suggest identity with the material deposited in cells elsewhere in the body (Lindsay *et al.*, 1948).

The sporadic occurrence of these two cases, children of normal parents, concords with the commoner mode of transmission of inheritance, namely, monomeric recessivity. However, it is noteworthy that there were no known cousin marriages in this family (Jervis, 1950).

There is a close similarity between Hurler's syndrome and Morquio's disease. First described independently in 1929 by Brailsford and by Morquio, the latter condition in its typical form would seem to be a distinct entity. There is thoraco-lumbar kyphosis with failure of the trunk to grow in length. The extremities are relatively normal. The vertebrae exhibit platyspondyly and the epiphyses of the long bones

are enlarged. There are deformities of the chest, but the ribbon-like ribs of Hurler's syndrome are not present. The skull, mentality, corneae, liver and spleen are normal. The joints are hypermotile and the joint spaces widened. The disorder is hereditary, but the inheritance would seem to be variable.

However much confusion exists in the literature with regard to these two disorders, McKusick, Jackson and others are of the opinion that they are two distinct entities, while the opposite view is held by Eichenberger, Ruggles and de Rudder (quoted by Jervis, 1950). The question is complicated on the one hand by the undoubted occurrence of "formes frustes" of Hurler's syndrome in which, for example, corneal clouding and mental defect may be absent, and, on the other hand, by certain inconsistencies in nomenclature whereby undoubted cases of gargoylism have been reported as Morquio's disease. It has even been claimed that the two syndromes occurred in different members of the same family (Bocker—quoted by McKusick, 1956).

The erroneous diagnosis of cretinism is often made in Hurler's syndrome. Stunting, mental retardation, hideous features, protruding tongue and protuberant abdomen are features common to both disorders. However, the normal bone age, characteristic bony changes, normal serum cholesterol, normal tests for thyroid function and lack of response to thyroid therapy differentiate the two conditions without undue difficulty.

Several other unusual disorders such as acrocephaly, cleidocranial dysostosis, Crouzon's craniofacial dysostosis, amyoplasia congenita, share one or two common features with Hurler's syndrome, but they are seldom serious sources of confusion.

The pathological features in the brain bear a close resemblance to those of Tay-Sachs' disease, a heritable disorder of lipoid metabolism.

Summary

Two sisters with Hurler's syndrome are described. The clinical aspects of this disorder are briefly reviewed.

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Addendum

Since going to print, these children have both died within two weeks of each other. The mode of death was idential—bronchopneumonia and congestive cardiac failure. Permission for autopsy in the elder was refused, but later agreed upon in the younger child. Pathological changes throughout the body were typical.