THE CLINICAL FEATURES, DIAGNOSIS, AND OSSEOUS LESIONS OF GARGOYLISM EXEMPLIFIED IN THREE SIBLINGS

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Gargoylism (Ellis, Sheldon and Capon, 1936), lipochondrodystrophy (Washington, 1940), dysostosis multiplex or chondro-osteodystrophy, of the type described by Hurler (1917) and Hurler (1919), is a remarkable symptom-complex consisting in the main of two basic components.

The first is a defect in cartilage maturation which involves most of the bones of the body and accounts for dwarfishness, kyphosis, restriction of joint movement, crouching posture, and claw-like hands. Depression of the nasal bridge, hypertelorism, prominent supra-orbital ridges, and prognathism partly explain the ugliness.

Secondly, the storage of an abnormal macromolecular substance of uncertain type occurs not only in reticulo-endothelial cells, but in parenchymatous and connective tissues all over the body. This produces hepato-splenomegaly, cardiac enlargement and failure, mental deficiency (Reilly and Lindsay, 1948) corneal clouding (Rochat, 1942), pyramidal tract involvement (Jervis, 1950), and deafness. Thickened, coarse, pasty skin, thick lips, large ears, and a large protruding tongue complete the gargoylistic appearance.

The hypertrichosis and frequent severe chronic nasal infection (Lindsay, 1950) are not obviously explicable.

The condition is an inherited one, starting in early childhood. It appears to be caused by a monomeric autosomal recessive gene and, like the Laurence-Moon-Biedl syndrome, the Ellis-van Creveld syndrome, and a few others, provides an excellent example of the potentiality of a single gene to produce multiple effects which are not necessarily morphologically connected.

Not every gargoyl shows all the features mentioned above and any one or more of the various outstanding peculiarities may be missing in individual cases (Jervis, 1950). On the other hand, it seems reasonable to say that the diagnosis cannot be made unless there is clinical evidence of both the fundamental defects, chondro-osseous 'storage,' or either with a family history.

By far the most important cause of death is cardiac failure. Lindsay found that out of 19 fatal reported cases, 14 died in this way. The present family came under our observation when the elder affected sister entered Groote Schuur Hospital with severe congestive cardiac failure.

Case Reports

Case 1. In Daphne (Fig. 1), a white girl aged 20, deformities had been observed when she was 3 years old. The neck seemed short, the trunk small, the fingers stiff

![Fig. 1.—Daphne and Patricia. Note facies, abdominal protrusion, hirsutes, genu valgum, short trunk.](image-url)
The wrists and spine were short, dark and the forearms slowing weeks. The apex, trophic (Fig. 4).

Heart slowed the mid-clavicular maxima rhythm gallop rumbling systolic accentuation oedema. Normal blood pressure 120/90. Tachycardia (regular, present sinus rhythm, 144) showed enlargement of the heart and congestion in the lungs (Fig. 4). An electrocardiogram employing 17 leads showed (Fig. 4a) a tall biphase P in lead 1, 2, V1 and V2 (left auricular hypertrophy), right ventricular hypertrophy and clockwise rotation. Any effects due to myocardial damage were masked by digitalis.

The heart responded well to digitalis and bed rest with a slowing of the pulse, diuresis, lessening of cyanosis and of breathlessness. She was able to walk out of hospital three weeks after admission.

As far as other features of the case were concerned, the girl was mentally normal and was a trained shorthand typist. She was under 5 ft. in height. The head was normal in size and shape and her face, except for the cyanosis, not unpleasing. The hair was dark and abundant, the eyebrows were thick, and the forearms covered with long black hair. The neck and trunk were short, and the muscular development poor. The wrists were large, and all movements of the limbs and spine were limited. There was spindle swelling at the phalangeal joints, and the fingers could not be extended, so that the hands were grotesque and claw-like (Fig. 3). The abdomen was protuberant with an umbilical hernia.

Both liver and spleen were enlarged down to the navel and were smooth and firm. There was palmar erythema. Further evidence of defective liver function after the cardiac failure had subsided was the plasma protein ratio (albumin 3:2, globulin 3:8) the abnormal glucose tolerance curve, and poor hippuric acid excretion after an intravenous injection of sodium benzoate. The flocculation tests were normal. Renal function was satisfactory as judged by urine concentration, blood urea (31 mg. per 100 ml.), uric acid clearance, and the phenol red test.

The corneae were diffusely hazy but the condition was so far mild, and no discrete opacities could be seen with a slit lamp.

The central nervous system was normal.

Case 2. Dudley, aged 22, a brother of Daphne, was a trained accountant. A haziness of the eyes was noticed when he was 3 years old. He had complained of aching pain in the lower back in recent months.

He was certainly ugly, but without the typical facies of gargoyleism (Fig. 2). He had a worried looking, young-old face with dry, pesty skin, gross myopia, peaked nose, receding chin, and prominent ears. His eyebrows and hair were thick, but there was no facial hair (he shaved once a month as a token), no axillary hair, and the pubic hair was scanty and flat-topped. The corneae were very cloudy.

He had palmar erythema, cyanosed hands and feet, mottled forearms, and superficial telangiectases on the feet. His teeth were good, but the lower incisors bit outside the top ones.

The upper abdomen was protuberant, with an umbilical hernia, and firmly enlarged liver but no splenomegaly.
Fig. 3.—Hand from each sibling showing maximum extension of fingers and enlargement of phalangeal joints.

Fig. 4.—Daphne. Enlarged heart with straightened left border. Congested lung fields. Wide horizontal lower ribs and short clavicles.

Fig. 4a.—The electrocardiogram after the administration of digitalis, shows evidence of left auricular hypertrophy, right ventricular hypertrophy, and clockwise rotation. It is impossible to say whether actual myocardial damage is present owing to the effect of digitalis.
Figs. 5a, b, c.—Shoulder girdles to show short, deformed clavicles, expanded medially and deficient laterally; irregular and enlarged humeral epiphyses; poorly formed glenoid fossae.

Fig. 9.—Knee joint in Morquio's disease showing, as distinct from gargoylism, wide joint spaces and metaphyseal expansion.
Fig. 6.—Radiograph of Patricia's chest to show wide, horizontal ribs with narrow necks.

Figs. 7a, b, c.—Radiographs of hips and pelvis showing enlarged femoral heads, flattened in b and c, and grossly deformed brim in c.
He was 5 ft. tall with a short trunk and bony, thin legs, the thighs leaving a gap inside his pants (Fig. 2). He had thoracic kyphosis, slight scoliosis, winged scapulae, sharply angulated clavicles, genu valgum, irregular enlargement of the knee joints, the malleoli and the calcanea, flat feet, and overlapping calloused toes. Movement of the spine, hips, knees, shoulders, elbows, and wrists was limited. In particular, abduction at the shoulder was absent (Fig. 2a). The elbows were large, pointed, and permanently flexed (Fig. 2b), the fingers knobbly and claw-like (Fig. 3).

There was a rumbling systolic murmur all over the precordium but no other signs in the heart.

The testicles seemed normal.

Gait was waddling.

**Case 3. Patricia, aged 18, a sister of Daphne and Dudley, is at a special school for the mentally backward. She gets frequent nasal catarrh.**

Her appearance was more typically gargoylistic than that of her siblings (Fig. 1). The face was ugly and round, the mouth open and the large fissured tongue visible, the chin flabby and very receding, the skin thick, coarse and pale, the ear lobes large. She was very short-sighted, and the corneae were severely clouded. The bridge of the nose was flat, the supraorbital ridges heavy and topped by a receding forehead. The hair of the head was normal, of the axillae and pubis absent, of the forearms excessive and black. There was no breast development and no neck. The feet were cold and a little cyanotic. The liver was enlarged in to the pelvis, the spleen one hand’s breadth below the costal margin. The abdomen protruded, and a hernia had been repaired. There was a softish systolic murmur all over the precordium and the pulmonary second sound was accentuated.

The skeletal system was similar to that of Dudley, without such great limitation of movement.

**Heredity**

There are three affected siblings of both sexes in the family, with three normals (one died at an early age), and no other member is said to suffer from the condition. The parents are not related. Autosomal recessive inheritance would explain this familial incidence, as in other reported families, despite the high proportion of affected members in the present generation.

**Radiological Features**

The radiological findings in these three patients are so similar that they may be considered together. The skulls are virtually normal, except that the maxillae protrude and the chin recedes. Dolichocephaly, syncephaly, frontal bossing, and elongated sella are not seen. The vertebrae show only mild changes; irregularity in the anterior, superior, and inferior surfaces, slight flattening and diminution of disc space, but no wedging or lipping. These changes are mainly in the thoracic region.

The clavicles are irregular and short with a sharp central backward angulation. They are expanded at the sternal end, but deficient laterally so that they do not reach the acromion process (Figs. 4 and 5). This lateral clavicular deficiency has not been previously commented upon in gargoylism, although it is depicted in the radiographs of other authors, for example Jervis (1950). Such a finding is reminiscent of cleidocranial dysostosis, osteodental dysplasia (Jackson, 1951a), with which condition gargoylism has no further points of comparison.

The scapulae seem short and thick and the superior portions abnormally shaped (Fig. 5).
ribs run horizontally and their posterior parts are wide (Fig. 6). The lower ones are lanceolate, their necks thin. The pelves are ill-formed and asymmetrical; the pubic rami do not properly connect; there is acetabular irregularity and protrusion (Fig. 7).

The long bones in general show almost normal shafts, but a variable degree of irregularity of epiphyseal ossification with flattening and enlargement of bone ends (Figs. 5 and 7). The joint spaces are not widened as is the case in Morquio's disease. A thick shaft tapering towards its ends is described by Reilly and Lindsay (1948) as typical of gargoylism. This is seen in a minor degree in our cases, in which terminal bony enlargement is due mainly to the epiphyseal irregularity (Fig. 5) in contradistinction to the metaphyseal expansion in Morquio's disease (Fig. 9). The articular surfaces of the lower end of the radii face inwards. The terminal phalanges show as remarkable thin pointed talons (Fig. 8).

There is some general osteoporosis.

**The Bony Defects in Gargoyleism Distinguished from Morquio's Disease**

From the point of view of bone structure gargoylism is classed as a general defect in cartilage maturation, epiphysis and diaphysis, affecting the whole bone (Jackson, 1951b). However, the frequent occurrence of acrocephaly, irregular skull vault, deformed mandible (hyperobtuse angle) and clavicle indicate defects in membrane bone also.

It is said that Morquio's chondro-osteodystrophy is so similar to the osseous syndrome of gargoylism that both may represent the same condition (Reilly and Lindsay, 1948; Jervis, 1950). Despite the similarities in epiphyseal and vertebral defects there are so many constant distinctions between the two diseases, apart from all the systemic effects of gargoylism, that they must be kept separate. The membrane bone abnormalities do not occur in Morquio's disease, in which the spine is always the most severely affected part of the skeletal system, and may even be the only part. Anterior central prolongation of the thoracic and lumbar vertebrae with marked platyspondyly is characteristic of severe Morquio’s affection, but is not seen in gargoylism. Beyond some depression of the nasal bridge, the skull is normal in Morquio’s disease. In mild cases the spine alone, or spine and hips with or without the knees and shoulders, are affected (Brailsford, 1945). The accent may be quite different in gargoylism, as in the present family. In more severe cases there is gross pigeon-chest deformity which is not exhibited by gargoyles. The wide, horizontal, ribbon-like lower ribs are typical of gargoylism, but may appear in lesser degree in Morquio’s syndrome. As regards the long bones, there are several apparently inviolate distinctions. Most striking is the increased joint space in Morquio’s disease (Fig. 9) without restriction of movement. The epiphyses are more irregular, fragmented, enlarged, and fuzzy in severe cases of Morquio’s disease, but not flattened as in some gargoyles (Fig. 7). Reilly and Lindsay point out that the enlargement and flaring out at the ends of long bones are solely epiphyseal in gargoylism, but largely metaphyseal in Morquio’s syndrome.

These distinctions, sufficient to separate skeletal gargoylism from Morquio’s disease, do not necessarily mean that the two conditions are entirely unconnected. Gates (1946) has suggested a genetic connexion between the various osseous dystrophies which would explain the appearance of irregular and intermediate forms (Ruggles, 1931; Snake, 1933; Jackson, 1951b).

**The Liver and the ‘Storage Substance’**

Hepatic function tests are nearly always normal in gargoylism, but Daphne had a reversed albumin: globulin ratio (3.2:3.8). The blood sugar figures after the administration of 50 g. glucose were:

- **Fasting** . . . 97 mg. per 100 ml. (Hagedorn and Jensen, 1923)
- ½ hour 114 " " " blood
- 1 hour 159 " " " capillary
- 1½ hours 186 " " " blood
- 2 hours 152 " " "
- 2½ hours 152 " " "

The intravenous hippuric acid test was also defective, an amount equivalent to 0.38 g. Na benzoate being found in the urine, which is about half the lowest permissible normal.

A liver biopsy (Fig. 10) was performed after the congestive cardiac failure cleared up. Prof. J. G. Thomson reported:

- ‘Histologically the liver cells are swollen, mainly due to a high glycogen content, but partly due to small droplets of fat, which show no double refraction with the polarizing microscope. The two constituents adequately explain the size of the cells; the glycogen is in excess for an ordinary liver, but not abnormal in distribution or staining reactions.’

Staining methods used were Best’s glycogen stain with alcohol fixation, Sudan III with a frozen section, and haematoxylin and eosin on a paraffin section.

**The ‘Incomplete Syndromes’**

Few, if any, gargoyles show all the reported characteristic signs of the disease, so that a definition of the ‘complete syndrome’ is largely conventional and dependent upon those features which were described first and those which are most outstanding.
conditions are quite described, disease is siblings are three case is cause of history. The elder sister had been taken and a errors hip, 'above, and with chondro-osteodystrophy, diagnosis seems only essential criterion for the above or with Perthe's disease of Jervis and with gargoylism, and it has been denied that the storage such as mental defect, corneal clouding, or hepatospleno-megaly.

Summary

Three siblings suffering from gargoylism are described. The elder sister was admitted to hospital with congestive cardiac failure, the most important cause of death in this condition. This girl did not have the typical facies, so that 'gargoylism' in her case is strictly a misnomer. The findings in the three siblings are summarized in Table 1.

The radiological features of these cases are described, and the differentiation from Morquio's disease is discussed. It is concluded that the two conditions are quite distinct.

Finally the 'incomplete' pictures or formes frustes of gargoylism are considered, and it is suggested that all that is needed for the diagnosis of gargoylism is the co-existence of specific osseous lesions with evidence of abnormal storage such as mental defect, corneal clouding, or hepatospleno-megaly.

Despite the fact that the term 'gargoylism' is not a good title for the disease, picking out as it does one particular feature which is not necessarily present, no better one can at present be suggested, except possibly the eponymous Hunter-Furler's disease. Since it has now been denied that the storage substance is lipoid in nature the term 'lipochondrodystrophy' must be held in abeyance.

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REFERENCES

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Addendum

Since this article was submitted for publication the first patient (Daphne) has died from congestive cardiac failure. She developed a diastolic murmur suggestive of mitral disease before death, which did not occur in hospital. Necropsy was refused.

The other sister (Patricia) has been ill with cardiac failure, but has not been in hospital.

Another case of gargoylism (unrelated to this family) has been discovered in Cape Town and reported in the South African Medical Journal by McDonald and Opie (1951), S. Afr. med. J., 25, 725.