THE PATHOLOGY OF GARGOYLISM

REPORT OF A CASE AND REVIEW OF THE LITERATURE *

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A syndrome of chondrodystrophic changes in the skeleton, corneal opacities, hepatosplenomegaly, and mental deficiency was reported by Hunter [1] in 1917 and by Hurler [2] in 1919. This is now well known as a clinical entity for which the term gargoylism was introduced by Ellis, Sheldon, and Capon [3] in 1936. More than 100 cases have been reported in the literature, and the clinical and radiographic features are well established. The syndrome is known to be familial; its genetic aspects have been discussed by Halperin and Curtis,[4] de Rudder,[5] and Böcker.[6]

The anatomic findings in gargoylism are still fragmentary and their interpretation is controversial. Most of the reports on autopsy findings have been incomplete, with main emphasis upon the examination of the cerebrospinal system. The lesions in the brain were reported to be identical with those in juvenile amaurotic idiocy.[7,8] This led to the assumption that gargoylism is a lipid storage disease. Kressler and Aegerter [9] found vacuolated cells in many internal organs. Even though no lipid substances were demonstrated by histologic methods, Washington [10] defined the condition as "a disease of congenital origin characterized by chondrodystrophiac changes in the skeleton and by a tendency toward the deposition of a lipid substance in the tissues, particularly in the brain," and coined the term lipochondrodystrophy. Schmidt [11] described severe disturbances of endochondral ossification and demonstrated lipid granules in the cartilage cells. He considered the chondrodystrophic changes as an integral part of a disturbance of lipid metabolism.

In view of the small number of complete autopsy reports on record, the case of a 3-year-old girl with the characteristic history and clinical picture of gargoylism will be described.

REPORT OF CASE

E. L., a 3-year-old white girl of Polish extraction, was admitted to the Pediatric Service of the Mount Sinai Hospital on March 17, 1945. The patient's parents were fourth cousins. The patient had an older normal sister. The child was born by

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spontaneous delivery after a normal full-term pregnancy. The birth weight was 4150 gm. She appeared to develop like a normal infant until the age of 6 months; however, she was unable to hold up her head. She did not sit up until she was 1 year old. The first tooth appeared at 1 year. When the child was about 6 months old the parents noted that she had a depressed nasal bridge and a chronic nasal discharge. When she was 1 year old a deformity of the head was noticed which progressed during the following 2 years. In addition there was flexion deformity of the fingers and limitation of motion of the extremities, as well as enlargement of the abdomen. Up to the age of 2 years mental and physical development were progressive though somewhat retarded. She was able to walk and talk, but from that time on development regressed, and at the time of admission she could not stand up, walk, or talk more than a few short words. There was progressive mental dullness. Her eyesight was poor. On the other hand, height and weight progressed normally. At the age of 3 years she weighed 15 kg.

Physical Examination. The patient was an obese, dull, irritable child with a large, deformed head and a purulent nasal discharge. She appeared mentally retarded and in poor contact with her environment. She did not raise her head or follow light. The skull was scaphocephalic; the fontanelles were closed. There were marked frontal and occipital protuberances. In the center of the frontal area there appeared to be an extra bone which was diamond-shaped and prominent. The eyes were widely spaced. Fundi could not be visualized because of bilateral, diffuse, punctate, corneal opacities. The nasal bridge was flat and the nostrils wide. The mouth was large, with thick lips (Fig. 1). The teeth were widely spaced and poorly developed, the lower teeth not yet fully erupted. The palate was high; the tongue appeared thick. The large head rested upon a short neck. Examination of the chest revealed rhonchi throughout both lungs. Respirations were 34 per minute. The heart appeared normal to percussion and auscultation. Pulse rate was 120; blood pressure, 120/80 mm. Hg. The abdomen was protuberant, and there was a small umbilical hernia. The liver and spleen were palpable 3 to 4 finger-breadths below the costal margins. The skin revealed abundant lanugo, especially over the back, forehead, and upper lids.

Fingers and toes were flexed and could not be fully extended; there also was limitation of extension of the knees and elbows. The arms could not be abducted above the head. The extremities appeared somewhat shorter than is normal. There was lumbar kyphosis. The neurologic status was normal.

A clinical diagnosis of lipochondrodystrophy (Hurler's disease) was made. Laboratory findings: Hemoglobin, 88 per cent; white blood cell count, 13,000, with 69 per cent polymorphonuclear cells, 27 per cent lymphocytes, 3 per cent monocytes, and 1 per cent eosinophils. The urine showed 3 plus albumin and one to three white cells in the sediment. Wassermann test of the blood was negative. Tuberculin patch test was negative. Serum phosphorus was 4.8 mg. per 100 cc.; serum calcium, 10.8 mg. per 100 cc.; blood cholesterol, 220 mg. per 100 cc. Electroencephalogram (Dr. H. Strauss) showed "severe diffuse cerebral dysfunction."

Roentgenologic Findings (Dr. W. H. Merrit). Examination of the skull showed the presence of a scaphocephalic deformity (Fig. 2). The frontal area bulged anteriorly. The frontal sinuses were absent. A small metopic suture was evident. There was also considerable enlargement of the posterior cranial fossa. The sella turcica was not well outlined, but appeared to be widened. The dorsum sellae appeared thinner than usual, and there was some pointing of the posterior clinoids. The tuberculum sellae and the anterior clinoids were obscured. There was an increase in the convolutional impressions in the parietal region. The dorsolumbar spine showed kyphosis in the lower dorsal and upper lumbar region. The body of the second lumbar vertebra showed a defect at its anterosuperior aspect with prominence or beaking of its antero-inferior aspect. This change was present, but to a lesser degree, in the subjacent vertebral body. The ribs showed a general increase

in breadth throughout the thorax. There was bilateral coxa valga. Both acetabular roofs were shallow. There were broadening and deformity in the proximal and distal metaphysis of the humerus, radius, and ulna bilaterally. The metacarpals appeared deformed at both ends and the proximal phalanges at their distal ends. "The changes described are consistent with the diagnosis of gargoylism, but present no features which would distinguish this condition roentgenologically from the usual type of osteochondrodystrophy."

Course. On the third day of hospitalization the patient's temperature, which had been 37° C. on admission, rose to 40° C., believed to be due to sinusitis. Sulfadiazine was given for 3 days, with no effect on the fever. The child at no time appeared dangerously ill, but at the end of 3 days of this febrile course she suddenly died. Death was believed to be due to sudden heart failure. Post-mortem examination (no. 13098) was performed by Dr. P. Gruenwald 11 hours after death.

Gross Examination

The body measured 84 cm. in length (normal average, 88 cm.*). Its external appearance conformed to that found on physical examination. Description of the internal organs will be restricted to the pertinent findings.

The heart weighed 82 gm. (normal average, 59 gm.). There was a slight, diffuse, whitish thickening of the epicardium, most marked on the anterior surface. The tricuspid and mitral valves showed nodules up to 3 mm. in size, with a smooth surface and fibrous consistency, at the insertion of the chordae. The chordae themselves were thick and short, and the usual web-like insertion was almost absent (Fig. 3). The left ventricle was markedly hypertrophied (Figs. 3 and 4); the myocardium, pale red and firm. There was slight thickening of the endocardium in the left ventricle. Marked bulging of the septum was present in the aortic outflow tract. The aortic and pulmonary valves appeared edematous and fleshy (Fig. 4). The aorta and its large branches were thickened. The intima was white with yellow plaques, and coarsely wrinkled (Fig. 4). The openings of the coronary arteries were slit-like, the arteries themselves being wide and grossly normal.

The combined weight of the lungs was 168 gm. (normal average, 168 gm.). The large bronchi on the right contained much viscid, yellow, mucopurulent exudate. The large branches of the pulmonary artery showed slight thickening of their walls. The hilar lymph nodes were swollen and reddened. The larynx was grossly normal.

The liver weighed 580 gm. (normal average, 418 gm.). Its surface was smooth and reddish yellow, and its consistency soft. On the cut surfaces the lobular markings were poorly defined. The gallbladder mucosa showed some yellow stippling.

The spleen weighed 78 gm. (normal average, 37 gm.). Except for its enlargement, it showed nothing unusual.

* The normal weights and measurements are taken from Coppoletta and Wolbach.[12]

Each kidney weighed 40 gm. (normal average, 48 gm.) and had a smooth, yellowish surface. There were petechiae in the right renal pelvis.

The tongue showed prominent, pale papillae. Its surface was dry and gray. There were no gross abnormalities of the esophagus, stomach, and intestine. The mesenteric lymph nodes were moderately firm and had a strikingly yellow color. There were no gross abnormalities of the thymus, pancreas, adrenals, peripheral lymph nodes, bladder, and internal genital organs.

On sagittal section the thoracic spine showed widening of the disks posteriorly. In the lumbar spine there were abnormally wide remnants of cartilage ventrally (Fig. 5). The ribs were broad and flat. The costochondral junctions were regular and not widened. The marrow of the left femur showed, on longitudinal section, a mottled appearance, due to alternating hematopoietic and fatty areas. The femur was slightly curved with the convexity directed laterally. The sagittal and lambdoid sutures of the skull had disappeared. The coronal suture was partly open. The fontanelles were closed. Traces of the frontal suture were seen externally. The base of the skull showed several irregular gyrus-like protrusions on the floor of the middle fossa, and marked protuberance of the petrous bone. The floor of the posterior fossa also showed protrusions, one of them at the posterior aspect of the foramen magnum, thus narrowing the foramen. There was marked flattening of the sphenoid bone.

Large portions of the liver, spleen, and brain were ground and preserved in cold acetone to await chemical examination.

Microscopic Examination

Heart. (Section was made through the posterior wall of the left ventricle, left atrium, and mitral valve.) The myocardium was hypertrophied. There were no vacuoles in the cytoplasm of the muscle fibers. Small foci were present where the muscle fibers were atrophied and encroached upon by delicate connective tissue septa. These were infiltrated by accumulations of large cells which were polygonal or oval; the cell body was vacuolated; the cytoplasm stained only very faintly with eosin and was finely granular or fibrillar. There was a small, dark, eccentric nucleus (Fig. 6). The cells usually were accompanied by varying amounts of collagen fibers. The connective tissue surrounding the small myocardial blood vessels had a similar appearance. Anitschkow cells could be encountered in these foci; their cytoplasm was poorly visible and appeared not to be vacuolated. Some

of the medium-sized branches of the coronary artery showed segmental thickening of the media, due to the presence of large, vacuolated, spindle-shaped cells; where these were present the smooth muscle fibers of the media were atrophic and replaced by connective tissue fibers. Where the large cells were missing, the muscle fibers in the media were well preserved. The intima and the internal elastica were intact. Vacuolated cells were seen also in the adventitia.

The endocardium of the atrium was diffusely thickened (Fig. 7), and there was focal thickening of the ventricular endocardium due to the presence of swollen cells accompanied by an increase of collagen fibers. No change in the elastic fibers was seen. The endocardial thickening was most marked at the base of the ventricle, in the region of the mitral ring, and continued throughout the mitral valve, the thickness of which was increased to about three times the normal (Fig. 7). It was made up of large numbers of swollen, vacuolated cells (Fig. 8). The cell body varied from a plump spindle to polygonal shape, apparently determined by the environment of the individual cell. Often the cells were arranged in rows or columns of varying length, either pressing upon each other or isolated and completely surrounded by a ground substance. Their cytoplasm stained only very faintly; most of it remained unstained. With Mallory's phosphotungstic acid hematoxylin stain, extremely delicate granules could be visualized in the cytoplasm. Most of the cells had a small, dark, eccentrically located nucleus. A considerable number, however, possessed nuclei exhibiting the characteristic appearance of the nucleus of the Anitschkow cell. Here, these cells had abundant cytoplasm showing evidence of storage, and well defined cell borders. Wherever these large cells were present there was also a marked increase in collagen fibers (Fig. 8), forming wavy bands of varying thickness throughout the valve. The vacuolated cells failed to stain by Best's carmine method for glycogen or by the sudan III and Smith-Dietrich stains for lipoid.

Aorta. The aorta was markedly thickened (Fig. 9). This was due chiefly to the width of the intima which exceeded that of the media. The thickening was patchy and did not affect the entire circumference. The microscopic appearance of the intima resembled that of the mitral valve. It consisted of layers of swollen, spindle-shaped, vacuolated cells and fine wavy fibers which stained like collagen. (There was a scanty cement substance staining blue with Mallory's aniline blue method.) In the media there were multiple spindle-shaped, clear cells between the muscle and elastic fibers. They had a slightly eccentric nucleus and probably were cells of the same kind as seen in the intima.

Frozen sections of the aorta stained with sudan III, Nile blue sulfate, and by the Ciaccio and Smith-Dietrich methods gave negative results. There was no doubly refractile substance within the cells.

Carotid Artery. The intima and media of a carotid artery included many vacuolated cells separated by wavy fibers. The artery was markedly thickened.

Mesenteric Artery. Section through a branch of a mesenteric artery showed marked thickening of the intima and media due to the presence of foam cells (Fig. 10).

Lungs. The lungs showed edema, emphysema, focal atelectasis, and acute bronchitis with plugging of bronchi with mucus and epithelial cells. There was focal hemorrhage. The arteries showed thickening of the media and intimal patches due to the presence of vacuolated cells. No foam cells were present in the parenchyma proper. The bronchial cartilage was normal.

Trachea. The trachea showed acute inflammation. Vacuolated cells were present in the pericartilaginous tissue.

Liver. The liver cells were diffusely vacuolated and their cytoplasm had a finely foamy structure (Fig. 11). The nuclei were normal. Best's carmine stain for glycogen was negative. Frozen sections stained with sudan III showed a number of large globules taking the stain, while the fine vacuoles remained unstained. A similar result was obtained with Nile blue sulfate (the fat globules stained pink). The Smith-Dietrich stain for lipoid was negative. No doubly refractile substance could be demonstrated. The Kupffer cells were swollen and finely vacuolated like the liver cells. No foam cells were present in the periportal spaces. The liver architecture was normal. There was no increase in connective tissue.

Spleen. The cells lining the splenic sinusoids were enlarged and their cytoplasm was finely honeycombed (Fig. 12). The malpighian follicles were small and depleted. Under oil immersion they revealed multiple vacuoles. There were no foam cells in the intersinusoidal reticulum or in the lymphatic tissue. The arterioles were not remarkable while in the walls of larger arteries vacuolated cells were seen. Sudan and Smith-Dietrich stains for lipoid were negative.

Pancreas. In the connective tissue around the larger pancreatic ducts, and in the peripancreatic tissue and arteries, vacuolated cells were found occasionally.

Kidney. In the interstitial connective tissue of the kidney, especially about vessels, there were scattered vacuolated cells. A large artery showed focal intimal thickening.

Alimentary Tract. In the esophagus there were hyperemia and focal

round-cell infiltration in the submucosa. The ganglion cells in the muscularis appeared vacuolated. In sections of the pylorus and of the small and large intestine, the cells of the myenteric plexus appeared enlarged and vacuolated. The submucous plexus of the intestine showed less conspicuous changes. In the muscularis propria of the small intestine there were many scattered, large, vacuolated cells. There was no increase in connective tissue.

Lymphatic Tissue. Section of a tonsil showed subacute inflammation. In the peritonsillar connective tissue there was a small accumulation of large, clear, vacuolated cells. The mesenteric and peripancreatic lymph nodes showed considerable post-mortem change. There were dilatation of the sinusoids and depletion of the lymphoid tissue. No vacuoles were seen in lymphocytes and reticulum cells.

Thymus. Large polygonal cells with vacuolated cytoplasm, having the appearance of histiocytes, were scattered through the thymic tissue.

Endocrine Organs. The adrenal cortex was considerably depleted of lipoid. In the connective tissue occasional foam cells were noted. The ovary showed primordial and growing follicles. An occasional small group of foam cells was present in the stroma. One ovary showed a nodule of heterotopic adrenal cortex. The thyroid and pituitary glands showed no abnormalities.

Cornea. Immediately beneath the corneal epithelium there were elongated cells with their long axes parallel to the surface of the cornea (Fig. 13). These were larger than the basal cells of the corneal epithelium, and separated from it by a fine basement membrane. They appeared swollen, and in places produced a bulge in the lower surface of the corneal epithelium. Their cytoplasm stained very faintly with eosin which left irregular unstained portions, particularly near the nucleus, which was small, poor in chromatin, and somewhat eccentric. These cells did not form a continuous layer, but occurred in small islands. Where they were present, Bowman's layer could not be recognized. They appeared to derive from the fibroblasts of the substantia propria of the cornea. The latter was otherwise normal. There were no changes in Descemet's membrane or in the corneal endothelium.

Rib. The resting cartilage of the epiphysis of the rib was normal. The zone of proliferating cartilage was shortened and the cartilage columns were plump, and in places missing. No lipoid substance could be demonstrated in the cartilage cells by sudan III or Smith-Dietrich stains. Where the proliferating cartilage cells were absent, there was an area of vascular connective tissue containing many large, swollen, vacuolated cells similar to those seen elsewhere in the connective tissues (Fig. 14). This area lay approximately in the center of the

epiphyseal zone, close to the costochondral junction. At its base there was a thin, transversely disposed layer of newly formed bone which lacked a calcified cartilage ground substance, in contrast to bony trabeculae normally formed from the cartilage. In places where short cartilage columns were present, the newly formed bony trabeculae were likewise short; however, they disposed themselves in the long axis of the bone and formed about a calcified cartilage matrix. The cancellous portion of the rib showed normal trabeculae. In the periosteum and perichondrium the collagen fibers appeared separated by large numbers of vacuolated, spindle-shaped cells having small eccentric nuclei. The periosteum was markedly thickened by the presence of the large cells and a conspicuous increase in the number of collagen fibers (Fig. 15). The infiltration with vacuolated cells was most striking in the cambium layer of the periosteum. The infiltrated periosteal tissue appeared to be engaged in the resorption and reconstruction of cortical bone which, along the surface of contact, showed many shallow and deep lacunae filled with the swollen cells (Fig. 15). Occasionally, small fragments of newly formed bone were completely embedded in the infiltrated periosteal tissue, and the osteocytes still resembled the swollen periosteal cells. It thus appears that bone may be formed directly within this tissue. The cortex itself was thick. The endosteum was thin and delicate, and there were very few osteoblasts and osteoclasts. The perichondrium also showed infiltration with large cells. These appeared to become incorporated in the cartilage, which was more cellular in its peripheral portions than in its depth. Also, the cartilage cells there appeared somewhat larger, but otherwise were not remarkable. One of the ribs showed a circular periosteal band ("Perioststreifen") interposed between the epiphyseal cartilage and the metaphysis, thus producing a marked constriction of the epiphyseal zone. The peripheral parts of the shaft were formed directly from the periosteal band instead of from cartilage. The same foam cells present elsewhere in the periosteum were scattered throughout the periosteal wedge, which otherwise was formed by dense collagen fibers.

Lumbar Vertebra. Sagittal section of the lumbar vertebra showed the structure of the spongiosa to be normal. The marrow was cellular and there were few fat cells. Proliferating cartilage was very scanty; columns of cartilage either were missing (Fig. 16) or very short (Fig. 17). Thus, much of the cartilage which would normally proliferate had remained in the resting stage (Fig. 16). Penetration of marrow cavities into the cartilage was very slight and occurred only where the short columns were present (in the center of the epiphyseal line). The zone of provisional calcification was almost absent, and bone was laid

down directly at the border of the epiphyseal cartilage, as a transverse layer (Fig. 17). Accordingly, ossification was mainly perichondral. The longitudinally directed trabeculae seen in normal bone were rare.

Along the anterior border of the vertebra there was a rather deep groove producing a concave outline of the vertebral body. This groove was filled with thick collagen fibers forming interlacing bundles. Adjacent to the cortex there was a layer of vacuolated cells which appeared to penetrate into the cortical bone, giving it an arroded border. Very few osteoclasts were seen, but the vacuolated cells appeared to exert osteoclastic activity. Small fragments of bone were laid down in the infiltrated zone of the periosteum.

Another lumbar vertebra showed a marked overgrowth of cartilage along its anterior border. Apparently this was the result of the poor endochondral bone formation from the epiphyseal cartilage. Thus the spongiosa of the vertebra became disproportionately small and its outline deformed. The anterior border of the vertebra became shorter than the posterior border and much more concave. The concavity was filled with periosteal and perichondral tissue consisting of interlacing fibers which blended with the overhanging cartilage, and of numerous vacuolated cells which appeared to become incorporated in the cartilage.

Head of the Femur and Sternum. The changes seen in the head of the femur and sternum were comparable to those seen in the ribs and vertebral bodies.

Skull. The skull was thick and compact. There was no diploe. The haversian systems were well developed. The periosteum showed infiltration by vacuolated cells in the cambium layer.

Central Nervous System. The gross and microscopic findings in the brain and spinal cord will be reported in detail elsewhere.[13] There was a marked internal hydrocephalus. On microscopic examination generalized degeneration of ganglion cells with ballooning and loss of Nissl substance was found. This change was most marked in the cerebral cortex and in the anterior horns in the spinal cord. There was a moderate increase in glial elements in the cortex. The swollen ganglion cells stained deeply with sudan III.

Discussion and Review of the Literature

Ellis, Sheldon, and Capon [3] introduced the term gargoylism because the large head and inhuman facies common to the majority of patients affected with this condition reminded them of the gargoyles seen on some Gothic cathedrals. Although the syndrome seems to have been recognized as a condition *sui generis* as early as 1908 (Henderson [14]),

it did not appear in the literature until 1917 when Hunter [1] described the disease in two brothers. The syndrome then returned to the literature under various names, among which Hurler's disease, dysostosis multiplex, gargoylism, chondro-osteo-dystrophy, and lipochondrodystrophy are the most common.

The multiplicity of names and the variety of forms have made it very difficult to evaluate accurately the number of cases so far reported, and different figures are given by the reviewers. Henderson [14]

TABLE I

Reported Cases of Gargoylism in Addition to Those Listed by Henderson [14] and Ellis [15]

Year	Author	No. of cases
1935	Reilly[16]	3
1939	Berliner[17]	3
1939	Nissler[18]	1
1939	Höra[19]	1
1940	Waardenburg[20]	2
1941	Stoeckel[21]	2
1941	Ross, Hawke, and Brown[22]	4
1941	Veasey[23]	1
1942	Kny[24]	1
1942	Schmidt[11]	1
1942	Wolff[25]	1
1942	De Lange [26]	1
1942	Halperin and Curtis[4]	1
1942	Harvey[27]	1
1942	Cordes and Hogan[28]	5
1943	Larson and Lichty[29]	3
1943	Lahdensuu[30]	4
1943	Rojas Dominguez[31]	1
1943	Expósito Martinez and de Feria[32]	2
1943	Boldt[33]	1
1943	Böcker[6]	1
1944	Lurie and Levy[34]	2
1945	Sear and Maddox[35]	1
1946	Debré, Marie, and Thieffry[36]	3
1946	Brouwer-Frommann[37]	1
1937	Bouman*	1
1940	Westrienen*	1
1946	Njå[38]	6

* Cited by Brouwer-Frommann.[37]

collected 57 cases from the literature, and he and Ellis [15] added 6 more. Since then, additional case reports have been published in various countries, and some previously reported cases have come to my attention which are not included in Henderson's paper. They are enumerated briefly in Table I.

This brings the total of known cases, including the one here presented, to 119. The case reports have illustrated amply the clinical features of the condition, which return with striking regularity in the majority of cases. The typical roentgenologic changes of the skeleton have been reviewed by Gillespie and Siegling,[39] Harvey,[27] and by Lar-

son and Lichty.[29] The occurrence of Sprengel's deformity has been stressed by Engel.[40]

The familial nature of the condition has long been recognized. It has been encountered repeatedly in two or more siblings.[4, 6] Consanguinity of the parents or grandparents of affected children has been found occasionally. The parents usually are healthy. However, in some reports deformities of the head, chest, or hands of one of the parents have been mentioned. An uncle of the patient reported by Jewesbury and Spence [41] had a similar disease leading to early death. Slot and Burgess [42] reported that a maternal aunt of their patient died in childhood as a deaf-and-dumb cripple. A suggestive history of mental deficiency in the mother's family was given by Lahdensuu.[30] Njå [38] studied the pedigree of a family in which 5 cases of gargoylism occurred. He observed that the afflicted members of the family were all males in whom the trait must have been transmitted from an unaffected mother. On this basis inheritance of a sex-linked type was suggested.

The few reports in the literature of autopsy findings in cases of gargoylism are gathered in Table II. Several of these cases were studied only incompletely, and in some the diagnosis of gargoylism must be considered as questionable.

Stoeckel's case [21] was clinically a typical case of gargoylism. Unfortunately, the autopsy report is limited to a macroscopic description of only a part of the viscera. The case of "typus E" described by de Lange and co-workers [46] is included in Table II notwithstanding the negative findings in the brain. Its relation to gargoylism will be discussed below.

Cerebral changes similar to those seen in the juvenile form of amaurotic idiocy were confirmed by the reports of Ashby, Stewart, and Watkin,[8] Kressler and Aegerter,[9] Kny,[24] and de Lange.[26] Such changes in the the nervous system were found in the present case; they will be reported in a separate publication by Green.[13] As a result of this similarity, cases of gargoylism may have been interpreted erroneously as instances of amaurotic idiocy. This occurred in the report of Zierl [43] who described Hurler's case along with 2 cases of amaurotic idiocy, stressing the presence of bone changes in all 3.

The interpretation of the changes in the central nervous system is of great importance for the understanding of gargoylism. Changes similar to those in juvenile amaurotic idiocy are not limited to a small group of closely related diseases, but constitute a more widely occurring type of nerve cell alteration than is commonly thought. This view was expressed by Jervis [47] when he described a familial syndrome which had clinical features in common with both gargoylism and

TABLE II

Reported Autopsy Findings in Cases of Gargoylism

Author	Sex, age	Clinical course	Heart, aorta	Spleen	Liver	Skeleton	Brain	Cornea	Other organs
Zierl,[48] Tuthill[7]	M 7 yrs.	Mental deficiency, deafness	Heart dilated	Enlarged	Enlarged	Chondrodystrophy; osteophytes at base of skull	Hydrocephalus; lipid granules in swollen nerve cells	Cloudy†	*
Reilly[16]	M 10 yrs.	Normal mentality, deafness, speech defect; sudden death	Mitral stenosis, dilated right heart	590 gm.; dilated sinusoids	Enlarged; mild interlobular fibrosis	Sella small, shallow; dolichocephaly	Post-mortem changes	*	Focal degeneration and necrosis in pituitary body, interlobular fibrosis in thyroid
Ashby, Stewart, and Watkin[8] (case 1)	M 19 yrs.	Mental deficiency; dwarfism; sudden death	Heart small†	100 gm.†	960 gm.; slight fatty change†	Thick skull; no diploe, wide sella†	1046 gm.; unilateral hydrocephalus; nerve cells as in juvenile amaurotic idiocy	Cloudy†	Pituitary body and thymus large; thyroid of fetal structure; other organs normal
Ashby, Stewart, and Watkin[8] (case 2)	F 9 yrs.	Large head; death in heartfailure; sibling similar	Mitral stenosis, hypertrophic left ventricle	Normal	567 gm.; small, firm, congested; mild fatty change; no foam cells	Brachycephaly; frontal and temporal bossing; sella enlarged†	1077gm.; similar to preceding case; changes most marked in thalamus; focal gliosis	*	Thyroid large, with fibrosis and atrophy; kidneys normal; other organs*
Kressler and Aegerter[9]	M 8 yrs.	Mental retardation; dyspnea, cyanosis; death in heart failure	Heart, 220 gm.; thick mitral, tricuspid valves; vacuoles in myocardial fibers; aorta streaked	140 gm.; vacuoles in some lymphocytes and reticulum cells; walls of small vessels infiltrated	1190 gm.; liver cells, cells in portal areas vacuolated	Sella shallow; clavicle short; acetabulum shallow; microscopically normal	1200 gm.; nerve cells large, lipid granules; degeneration of Nissl bodies	Cloudy; microscopically normal	Vacuolated cells in lungs, lymph nodes, testes; pituitary body enlarged, chromophobes "invaded;" thyroid, thymus normal

Berliner[17]‡	M 6 yrs.	Died after operation for umbilical hernia	*	*	*	*	*	Cloudy; vacuolated cells	*
Höra[19]	Newborn		*	*	*	Acrocephaly; hypoplastic chondrodystrophy; radio-ulnar synostosis	*	Cloudy†	*
Stoeckel[21] (case 2)	F 4 yrs.	Large liver; death from bronchitis	"Chronic endocarditis"†	Hyperplasia, large follicles†	*	Scaphocephaly; wide sella; elevations at base of skull†	Internal hydrocephalus	Cloudy†	Coloboma of iris
Kny[24]	F 6 yrs.	Typical syndrome	Fat in myocardium	Slightly enlarged; microscopically normal	Enlarged; early cirrhosis; liver cells vacuolated; Kupffer cells negative	Skull thin; osteophytes at base; sella wide; hypoplastic chondrodystrophy	Hydrocephalus; sudanophil granules in ganglion cells	*	Pituitary body slightly enlarged; nests of large, clear cells in thymus; fat in convoluted tubules in kidneys
Schmidt[11]	4 yrs.	*	*	*	*	Chondrodystrophy; lipid granules in cartilage cells	*	*	*
Rochat[44]	F 6 yrs.	Typical syndrome	*	*	*	*	*	Vacuolated cells	*
Wolff[25]	M 28 yrs.	Deafness; death in heart failure	"Chronic endocarditis of mitral, tricuspid and aortic valves"	Splenectomy at 10 years	Liver cells large, variable in shape	Calvarium thick; sella wide; external auditory canals narrow; mastoid antra small	Normal	*	Persistent thymus (7 gm.); exhaustion of lymph nodes

TABLE II (cont'd.)

Author	Sex, age	Clinical course	Heart, aorta	Spleen	Liver	Skeleton	Brain	Cornea	Other organs
De Lange,[26] Zeeman[45]	F 6 yrs.	Typical syndrome; unexpected death	Heart (80 gm.) and large vessels normal	78 gm.; normal	560 gm.; liver cells vacuolated; Kupffer cells swollen; focal fibrosis	Thin skull; lumbar kyphosis†	Internal hydrocephalus; changes as in amaurotic idiocy	Vacuolated cells	Lymph nodes swollen; degenerative changes in pituitary body; other endocrine organs normal; bronchitis
De Lange, Gerlings, de Kleyn, and Lettinga[46]	M 19 yrs.	Hearing defect; systolic murmur; stridor; sudden death	Thick valves, "chondroid change"; acute myocarditis	405 gm.; slight fibroadenia	1720 gm.; slight cirrhosis; liver cells foamy, contained much glycogen	Scaphocephaly; flexion deformity; "chondroid change" in perichondrium; retarded bone growth; poor pneumatization of mastoid	Normal	Not cloudy†	Larynx narrow; "chondroid change" in perichondrium of larynx, trachea, bronchi; increase of connective tissue in pituitary body
Nja[38]	M 11 yrs.	Typical syndrome; chronic bronchitis; death in cyanosis and dyspnea	Heart, 140 gm.; hypertrophy of left ventricle; thick aortic and mitral valves; plaques in aorta	215 gm.†	1280 gm.†	Thick skull; protrusions at base of skull; narrow marrow cavities; long bones short, thick†	Internal hydrocephalus; thick leptomeninges†	Not cloudy†	Thymus, 41 gm.; bronchitis; massive lymphocytic infiltration of digestive and respiratory tracts
Present case	F 3 yrs.	Mentally retarded; death in sudden heart failure	Heart, 82 gm.; vacuolated cells in valves, endocardium, connective tissue, vessels of heart, and in aorta	78 gm.; vacuolated cells lining sinusoids	580 gm.; vacuolated liver cells and Kupffer cells	Scaphocephaly; protrusions at base of skull; chondrodystrophy; vacuolated cells in periosteum, perichondrium	Hydrocephalus; ballooning, degeneration of ganglion cells with sudanophil granules	Cloudy; vacuolated cells	Vacuolated cells in blood vessels; bronchitis; fat in convoluted tubules of kidneys; other organs normal

* Not examined or not reported.
† Not examined histologically.
‡ The other organs of this case were examined by Dr. Eugene Opie, who found microscopic changes almost identical with those described in the case here reported.

juvenile amaurotic idiocy (early onset of mental retardation, dwarfism, characteristic "gargoyle" facies, and thickening of the skull); however, other stigmata of gargoylism such as hepatosplenomegaly and corneal clouding were not present. At autopsy, examination of the liver and spleen revealed normal organs while the changes in the brain were found to be identical with those in well authenticated cases of gargoylism as well as in amaurotic family idiocy. Chemical examination of the brain disclosed the presence of neuramic acid which thus far has been found only in Tay-Sachs' disease (Klenk [48,49]). On the basis of chemical differentiation, this case is to be grouped with the neuramic acid lipidoses while it is hard to classify it on the basis of clinical or morphologic characteristics. Tropp [50] offered an explanation for the degenerative changes in the brain in the infantile form of Gaucher's disease which, modified, might be applied to gargoylism. He assumed that the degenerative changes in the central nervous system are secondary to the general metabolic disorder rather than an essential part of it in the sense of Spielmeyer.[51] The finding of almost identical nerve cell changes in a variety of apparently nonrelated conditions (infantile morbus Gaucher, Niemann-Pick's disease, amaurotic idiocy, gargoylism) raises the question to what extent the lesions of the central nervous system are specific, and whether we are justified in placing such diverse diseases in a common group merely because of the morphologically similar changes in the brain. One may rather assume that swelling of nerve cells and the appearance in them of fat-like substances indicate a local disturbance of cellular metabolism resulting either from a deficiency of the necessary building materials (this deficiency being the direct result of a systemic metabolic disorder) or from an inherent inability of the nerve cells to utilize the substances necessary for their growth and preservation. This viewpoint was expressed by Globus [52] when he discussed the relationship of the lesions of the central nervous system in the various forms of amaurotic idiocy and Niemann-Pick's disease. The histologic findings in gargoylism seem to justify this assumption. In this disease only the swollen ganglion cells contain granules stainable with sudan while the storing cells elsewhere in the body cannot be stained with fat stains.

Internal hydrocephalus was found in the present case as well as in 5 other cases listed in Table II. In the case here presented, bony elevations were observed at the base of the skull which compressed the hindbrain and may have interfered with the drainage of liquor. In 4 of the other 5 cases in which hydrocephalus was found at autopsy, elevations or osteophytes at the base of the skull also were mentioned. This suggests that hydrocephalus, when it occurs in gargoyles, is due

to a skeletal abnormality which compresses the brain stem. A similar mechanism has been described by Grüneberg [53] in a mutation in mice which produces skeletal abnormalities and hydrocephalus by preventing drainage of cerebrospinal fluid from the fourth ventricle.

Among the well recognized anatomic changes are those found in the cornea in those cases in which corneal clouding existed. Although Kressler and Aegerter were able to demonstrate only artifacts in the cornea of their case,[9] Berliner,[17] Rochat,[44] and Zeeman [45] have described defects in Bowman's membrane, which contained vacuolated cells with granules in their cytoplasm. Berliner considered these as lipid granules. Rochat mentioned that the granules were soluble in ether and alcohol, not doubly refractile, and that they gave a pale yellow-brown stain with sudan III. In the case here reported the corneal changes were identical with those described by Berliner, Rochat, and Zeeman. No attempt was made to determine the chemical nature of the cytoplasmic granules. The ocular findings in gargoylism have been reviewed most recently by Cordes and Hogan.[28]

Comparatively little attention has been paid thus far to the anatomic changes of the internal organs. Cardiac failure is often given as the apparent cause of death in gargoyles. The presence of hepatomegaly and splenomegaly has long been stressed as a part of the characteristic clinical picture. Splenectomy and a biopsy of the liver in a 2-year-old boy showing the classical picture of gargoylism (Ellis [54]) revealed an enlarged spleen with hyperplasia of the pulp. The liver cells were described as "well filled with glycogen." A search for abnormal lipids was negative. A biopsy of the liver in the first case of Debré, Marie, and Thieffry [36] showed no histologic or histochemical abnormality.

Kressler and Aegerter [9] were the first to stress the widespread visceral changes characterized by the presence of vacuolated cells in many organs, particularly the liver, spleen, lymph nodes, and myocardium. In the case presented here, the visceral changes were outstanding and so obvious that it seems strange that they should have escaped recognition for such a long time, unless there is a comparatively wide variability in their degree and extent, possibly related to age, or determined by modifying genetic factors. There are certain differences between the lesions described by Kressler and Aegerter and those in the present case. In the liver, involvement of the Kupffer cells was found in addition to extensive vacuolization of liver cells. On the other hand, the vacuolated cells in the portal areas mentioned by Kressler and Aegerter were not present.

The striking enlargement and vacuolation of the sinusoidal endo-

thelium in the spleen were not observed by Kressler and Aegerter [9]; they reported vacuoles in lymphocytes and reticulum cells not seen in the present case. Kny [24] found no microscopic changes in the spleen while the liver was described as showing early cirrhosis and vacuolation of the liver cells. The Kupffer cells, however, appeared free of changes.

Thus it seems that involvement of the reticulo-endothelial system is not a prominent or constant feature of gargoylism. Even in the present case, it is overshadowed by the striking alterations in the connective tissues of various organs. The extensive involvement of mesenchymal structures, such as the endocardium, the myocardial connective tissue, and the intima and media of large and medium-sized arteries, with an increase of collagen fibers apparently has not been observed by other writers. Kressler and Aegerter [9] mentioned only infiltration of small vessels in the spleen, and although there was thickening of the mitral and tricuspid valves and streaking of the ascending aorta in their case, apparently the microscopic appearance did not correspond to what was seen in the case here reported. However, an increase of areolar connective tissue in the myocardium and vacuoles in the pericardium was mentioned by these authors.

Stoeckel,[21] in his gross report, described chronic endocarditis with fibrous thickening of the valves and a glassy sclerosis of the aorta. Chronic endocarditis was mentioned also by Reilly [16] and Wolff.[25] Njå [38] described thickening of the aortic and mitral valves, the latter showing knotty borders, as well as shortening and thickening of the chordae. The left ventricle was hypertrophied. There was no microscopic examination of these tissues. Yellow intimal plaques were observed in the aorta.

Although the gross appearance of the heart valves might have suggested chronic valvulitis, histologic investigation rules out this interpretation. The thickening of the valves is produced entirely by the accumulation of vacuolated connective tissue cells, together with an increase of collagen fibers and ground substance. The identity of the ballooned cells is not unequivocally established except for those which show the typical nucleus of the Anitschkow cell. Their localization and close association with newly formed collagen fibers support the view that for the most part they are fibroblasts rather than histiocytes. Attempts to demonstrate lipid substance in these cells have been unsuccessful. The same is true of the vacuolated cells in the spleen and liver, except that a small percentage of the vacuoles in the liver cells proved to be neutral fat.

Stains with mucicarmine, thionin, and basic fuchsin for mucin, car-

ried out on liver tissue fixed in absolute alcohol, as well as the toluidine blue stain on formalin-fixed tissue (mitral valve, aorta) also have been negative.

Reilly [55] found, in the cytoplasm of polymorphonuclear leukocytes in the peripheral blood, sternal marrow, and spleen, coarse granules which stained dark lilac with Giemsa's stain and which sometimes were eosinophilic. He observed these in 4 of 8 cases examined. Such granules were not observed in the present case.

Lesions of endocrine organs have been looked for by many writers, in an attempt to find an explanation for the pathogenesis of gargoylism. Reilly [16] reported 3 cases of "an atypical familial endocrinopathy," which he later on included in the syndrome of gargoylism.[56] In one of these, autopsy had revealed changes in the thyroid and anterior lobe of the pituitary gland, as well as an enlarged thymus. Ashby and co-workers [8] mentioned changes in the thyroid gland and a large thymus in their 2 cases, and enlargement and hyperplasia of chromophobe cells of the pituitary body in one. Kressler and Aegerter [9] described the pituitary gland as enlarged and showing "infiltration" of chromophobe cells. In de Lange's case,[26] the pituitary gland showed degenerative changes and loss of chromophobe cells. These findings are not consistent, and no noteworthy changes have been found in the endocrine organs by other authors. In the present case the thyroid, pituitary body, thymus, adrenals, and ovaries were essentially normal.

The bone changes form a prominent part in the disease complex of gargoylism. Their rôle in the pathogenetic mechanism of this condition has been the subject of much thought and controversy. De Rudder [5] felt that the dysostosis is not necessarily related to what he calls "Phosphatiddiathese" (corneal changes, changes in the central nervous system, hepatosplenomegaly), but that each is transmitted through a recessive gene, and that the complex of Hurler's dysostosis results only when the two genes combine. In other words, he believed that the skeletal changes in gargoylism are unrelated to a general metabolic disorder.

It seems that only with a better knowledge of the genetic, anatomic, and chemical substrate may the rôle of the chondrodystrophic changes within this disease complex be elucidated.

The chondrodystrophic nature of the skeletal deformities has been apparent ever since the syndrome was first recognized, and the skeletal changes are the most constant clinical feature of this disease. In analogy with other known chondrodystrophies, this was thought to be a genetically determined anomaly. The first post-mortem studies of gargoylism did not concentrate on the histologic features of the bone

changes. At the most, the bone marrow was examined for lipid-storing cells which were never found. Kressler and Aegerter [9] reported that microscopic examination of bone revealed "normal ossification and healthy bone growth." Among the first to call attention to the histologic bone changes were Washington,[10] Kny,[24] and Schmidt.[11] Washington summarized the changes in the epiphyses as follows: Shortness of the zone of proliferating cartilage indicating slowness of cartilage growth, and formation of trabeculae disposed horizontally along the under surface of the epiphyseal cartilage as a result of the slowness of the process of endochondral ossification. The bony trabeculae lack calcified cartilage ground substance as a basis for the osteoblasts to build on. Washington mentioned storage in endosteal cells and osteoblasts, without elaborating on this finding.

Kny [24] also stressed that, while ossification was essentially normal, the growth process was markedly slow, particularly in the region of endochondral ossification. According to the classification of Kaufmann,[57] this is characteristic of chondrodystrophy of the hypoplastic type. Schmidt [11] found what he considered lipoid storage in cartilage cells in the epiphyses, being able to stain some of the granules in their cytoplasm with the Smith-Dietrich method for lipoids. This storage was found mainly where normal proliferation of epiphyseal cartilage had failed to take place. He thought that the lipoid storage interfered in some way with normal endochondral ossification. Thus he was the first to attempt an explanation of the chondrodystrophy as an integral part of the disease complex of gargoylism, rather than as an independent phenomenon as had been suggested previously (de Rudder [5]). Schmidt's findings as to lipoid storage in cartilage cells could not be confirmed by Kny, nor could I do so.

As for the periosteum and perichondrium, Schmidt's findings [11] differ markedly from those in the present case. In the vertebra he described the periosteum as thickened, but no mention was made of the vacuolated cells observed by me. In the neck of the radius Schmidt found thickening of the cambium layer under the fibrous periosteum, but no abnormal cells. Since no membranous bones were examined by Schmidt, he did not elaborate on the pathogenesis of their deformity. Washington [10] felt that the deformity of membranous bone in the skull could not be explained along with the chondrodystrophy, and he attributed it to a deficit in the "blastemal capsule" of the top of the skull. Sections through portions of the cranial vault in the present case showed vacuolated cells in the periosteum, and it is thought, therefore, that the disturbance of the function of the perichondrium and periosteum leads to the skeletal deformities. By what

mechanism this takes place is still open to question, especially since we do not know the nature of the severe changes in the bone-forming and other connective tissues.

An interesting histologic observation is that of the periosteal band [Perioststreifen] in a rib, which is a common finding in chondrodystrophy (Landauer [58]).

The similarities and differences of gargoylism, chondrodystrophy, pléonostéose (Léri), Morquio's disease, and other hereditary diseases of the skeletal system have recently been discussed by Nöller [59] and Debré and co-workers.[36] A case of chondrodystrophy combined with mental retardation and bilateral corneal clouding was reported by Tröster,[60] who discussed its relation to gargoylism. Autopsy failed to reveal the typical changes of amaurotic idiocy in the brain and the characteristic visceral involvement of gargoylism. The nature of the corneal clouding was not investigated.

It appears that although the syndrome of gargoylism generally is very uniform, there are cases which do not present the fully developed clinical picture. These are so-called intermediate forms, or formes frustes, which share features both with gargoylism and with other known diseases having apparently a similar anatomic and genetic substrate. For example, the group of cases reported by Jervis,[47] which have been discussed above, belongs in this intermediate class. Cases with normal or almost normal mentality have been reported by Hunter,[1] Reilly,[16] Lahdensuu,[30] Nonne,[61] Liebenam,[62] Cockayne,[63] and others. One has to assume that the central nervous system in these cases lacked the severe changes described in some post-mortem studies. Nevertheless, the other stigmata of gargoylism were present in the majority of these patients, except for the absence of corneal clouding in some. Absence of corneal changes is mentioned also in the case reports of Ross, Hawke, and Brown,[22] Lurie and Levy,[34] Debré and co-workers,[36] Njå,[38] and de Lange and Woltring.[64] In all reported instances of gargoylism with normal corneae the patients were males, and usually the disease was present in siblings or, as in Njå's report, in 5 male members of one family. Njå's postulation of gargoylism of a special sex-linked type with normal corneae is of interest in this connection.

De Lange and Woltring [64] were hesitant to consider their 2 cases as examples of gargoylism because of the absence of corneal clouding, kyphosis, and widening of the sella; also, because mental retardation was not very marked. They designated them as "typus E" after the initial of the patient's family name. The photographs of the patients,

showing the typical facies and dwarfism, the presence of hepatosplenomegaly and skeletal deformities, seem to justify the inclusion of these cases in the group of gargoylism. In the meantime, one of the 2 brothers has been autopsied at the age of 19 years [46] (See Table II). The lack of cerebral changes is difficult to explain in view of manifest mental retardation at the time of the patient's death. It appears that in the case of typus E, lesions were most striking in mesenchymal structures such as the perichondral tissues of the larynx, trachea, bronchi, and elbow joint, and in the heart valves and aorta. What is described as a "chondroid" appearance of the heart valves and of the perichondrium may very well be identical with the changes described in the present case of gargoylism. It is not quite clear what the writers meant by mucoid degeneration of the connective tissue; possibly it corresponds to the peculiar swelling of the ground substance described in the heart valves of the case here reported. It is possible, but not proved, that in the case of typus E, vacuolation of the liver cells was due entirely to deposition of glycogen. Mild cirrhosis of the liver has been observed by others in typical cases of gargoylism. The lack of storage in the spleen apparently does not speak against gargoylism. Discrepancy in the skeletal findings may be accounted for by the difference in age at the time of death of the case of typus E and of this case. It appears that typus E constitutes a most interesting link between the formerly described classical cases of gargoylism and the case reported here. Several genetic mechanisms may account for the variability in the expression of gargoylism and other hereditary disorders. One of these is the existence of genetic or environmental modifiers similar to those which have been demonstrated in genetic studies in laboratory animals, for instance, taillessness in the rat.[65] Another possibility is that the severity and the time of onset vary with the mode of inheritance (dominant, recessive, or sex-linked) as has been demonstrated for retinitis pigmentosa [66] and peroneal atrophy.[67]

It has been suggested that histologically or biochemically detectable storage of substances may be due to a genetically determined enzyme deficiency.[68-70] In some of the human storage diseases the accumulated substance has been chemically identified. It is glycogen in von Gierke's disease, sphingomyelin in Niemann-Pick's disease, kerasin in Gaucher's disease, neuramic acid in Tay-Sach's disease. In gargoylism chemical identification has not been possible until now.* However, the morphologic similarity of the histologic changes with those in other storage diseases suggests that here too the basic abnormality

* Chemical investigation of organs in the case here reported is being carried out.

is a hereditary disturbance of metabolism. Thannhauser and Schmidt [71] have stressed that the stored substance accumulates not only in the reticulo-endothelial system, but in many tissue cells as well. They therefore assumed that intracellular metabolism is disturbed in these diseases. The involvement of a variety of tissue cells, and particularly of the connective tissues, in gargoylism seems worth mentioning in this connection.

It seems premature to conclude that gargoylism is a lipid storage disease, as long as the stored substance is unknown. The presence of cells with a foamy cytoplasm is not necessarily the result of storage of fat or fat-like substances. It occurs in glycogen storage disease, and has been produced in experimental animals after the administration of nonlipid substances of high molecular weight.[72]

Summary

A case of gargoylism in a 3-year-old girl, with gross and microscopic post-mortem examination, provided an opportunity for comparing the reported findings with those in the present example.

The previously described lesions in the central nervous system, eyes, skeleton, and visceral organs are for the most part confirmed. Emphasis is placed on striking alterations in the connective tissues of the viscera, cardiovascular system, and skeleton, which hitherto had not been observed. These are characterized by the presence of large vacuolated cells, probably fibroblasts for the most part, in association with a proliferation of collagenous fibers and sometimes with an increase of ground substance.

These alterations have a rôle in producing some of the characteristic clinical manifestations of gargoylism (hydrocephalus, skeletal deformities, cardiac symptoms).

The nature of gargoylism must be considered in its relation to the known diseases of lipid metabolism (amaurotic idiocy, Niemann-Pick's disease, Gaucher's disease). The inclusion of gargoylism in the group of storage diseases is suggested because of the evidence of storage in many cells of the body, and because of the similarity of the changes in the central nervous system with those in amaurotic idiocy; but the chemical nature of the stored substance thus far has not been identified. It appears that there is a widespread disturbance of intracellular metabolism resulting in the accumulation of an abnormal substance in many cells of the body. However, the question whether gargoylism is a form of lipidosis must remain open.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 138

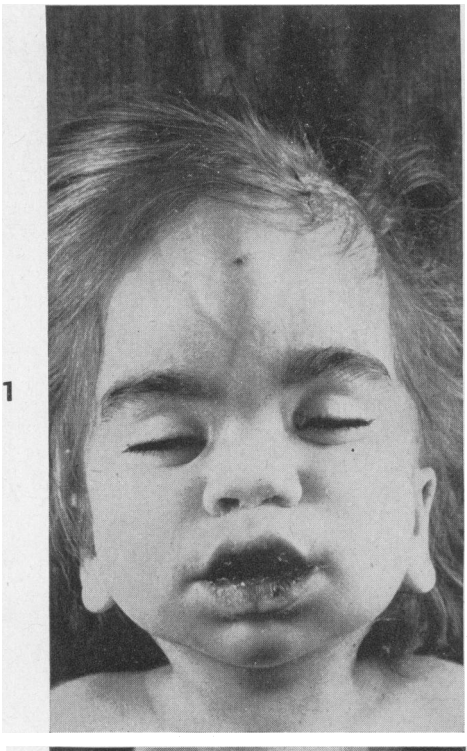
FIG. 1. Typical gargoyle facies of patient (post-mortem photograph).

FIG. 2. Roentgenogram of skull showing the marked scaphocephalic deformity.

FIG. 3. Heart. Hypertrophy of the left ventricle. Nodular, fleshy thickening of the mitral valve. Shortening and thickening of the chordae tendineae.

FIG. 4. Heart. Concentric hypertrophy of the left ventricle. Thickening of the parietal endocardium in the aortic outflow tract. Thickening of the aortic valve leaflets. Intimal plaques in the ascending aorta.

FIG. 5. Lumbar spine. Sagittal section through vertebral bodies showing deformity with "beaking" of the antero-inferior portions. (The anterior border of the vertebrae corresponds to the upper border of the figure.)



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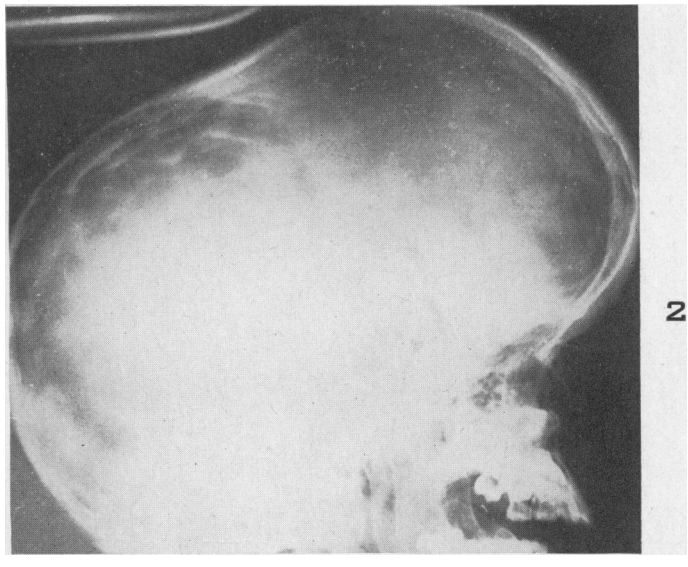

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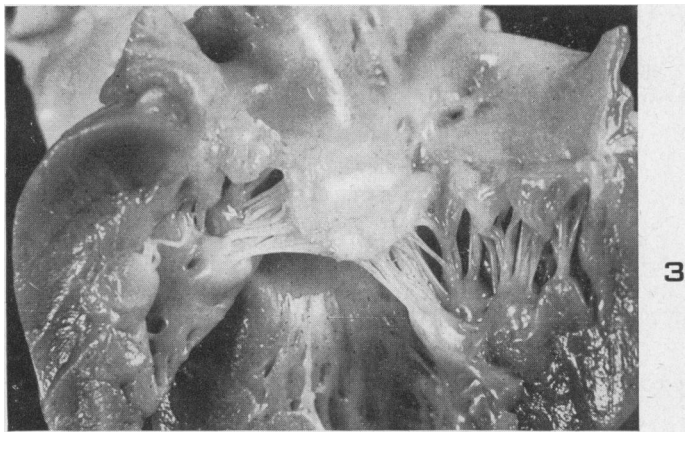

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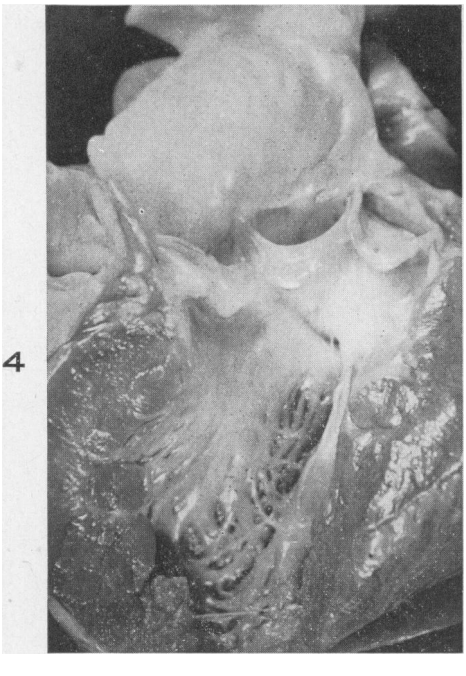

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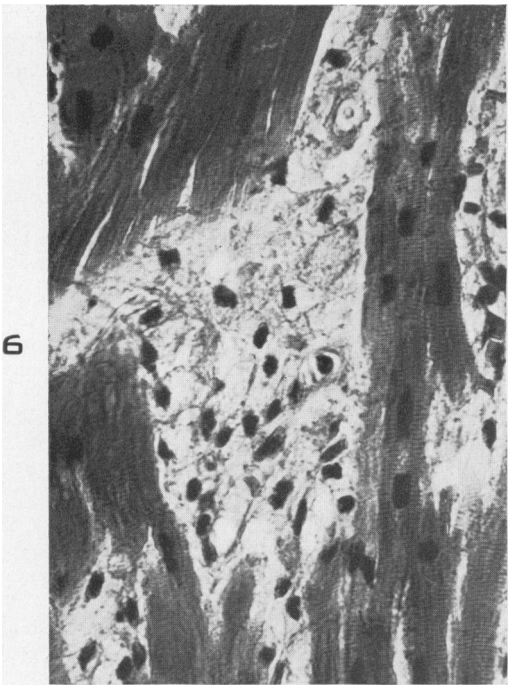
PLATE 139

FIG. 6. Myocardium. Patch of interstitial fibrosis containing vacuolated cells. Hematoxylin and eosin stain. × 475.

FIG. 7. Mitral valve and left atrium. There is striking thickening of the atrial endocardium and the mitral valve. Hematoxylin and eosin stain. × 10.

FIG. 8. Mitral valve. The valve is made up of large vacuolated cells associated with thick bands of collagen fibers and a homogeneous ground substance. Some of the cells are arranged in rows. Hematoxylin and eosin stain. × 475.

FIG. 9. Aorta containing a large intimal plaque. Weigert's elastica and van Gieson's stain. × 10.



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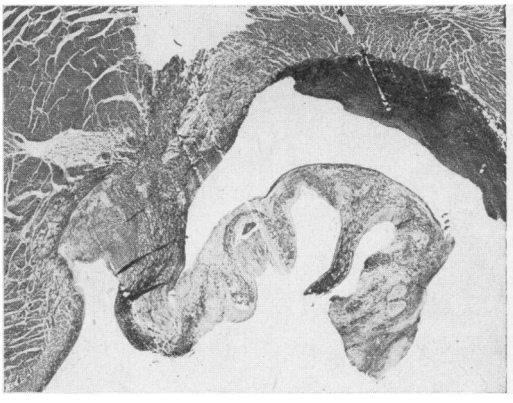

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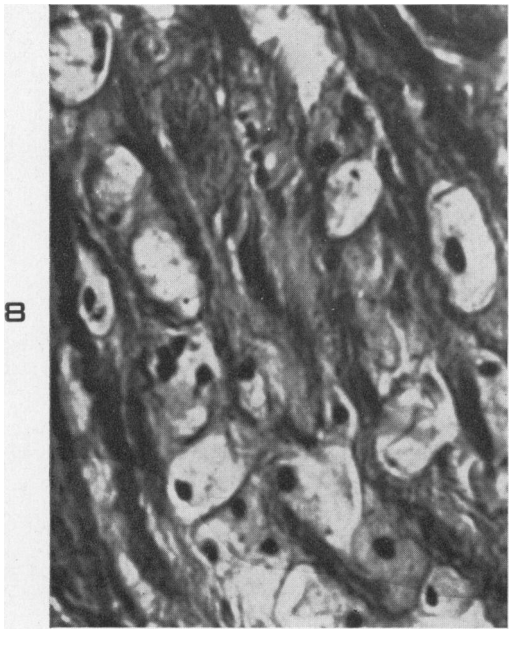

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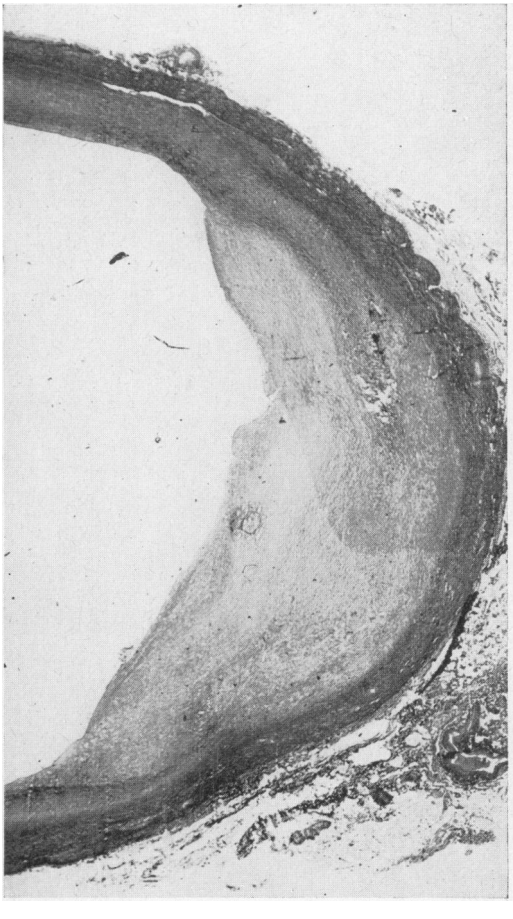

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PLATE 140

FIG. 10. Intimal plaque in a branch of the superior mesenteric artery. Hematoxylin and eosin stain. × 75.

FIG. 11. Liver. The liver cells are enlarged and have a honeycombed appearance due to diffuse vacuolization. There is no fibrosis. Mallory's aniline blue-orange G stain. × 380.

FIG. 12. Spleen. The endothelial cells lining the sinusoids are enlarged and vacuolated. The sinusoids are empty. The follicles are depleted of lymphocytes. There is no infiltration of the intersinusoidal reticulum. Mallory's aniline blue-orange G stain. × 300.

FIG. 13. Cornea. There are large vacuolated cells interposed between the corneal epithelium and the substantia propria, replacing Bowman's membrane. Hematoxylin and eosin stain. × 475.

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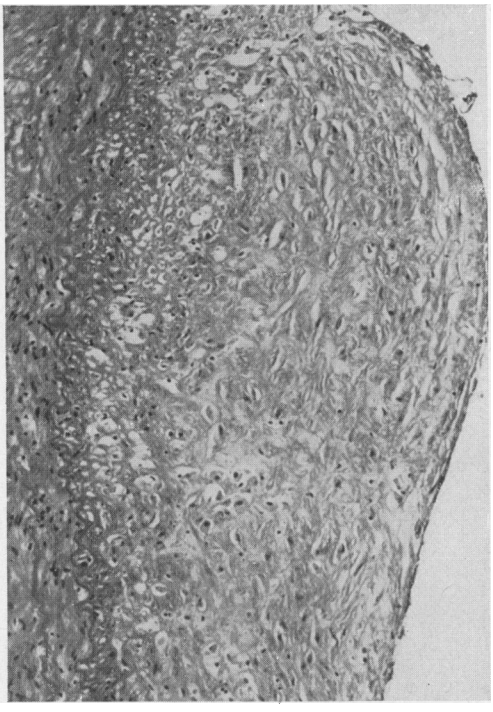

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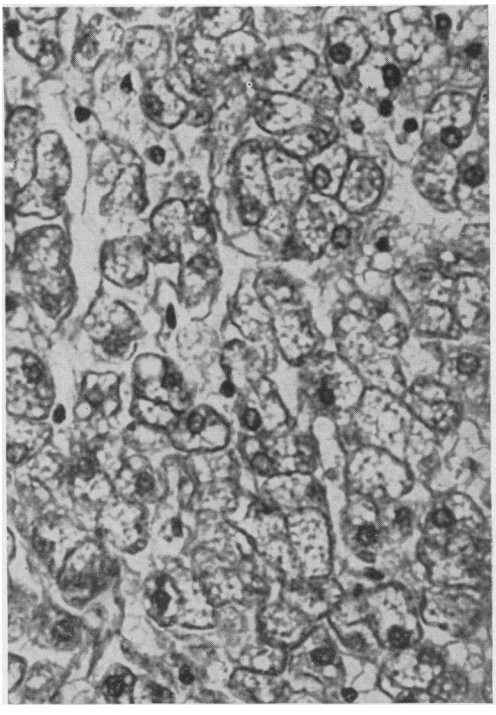

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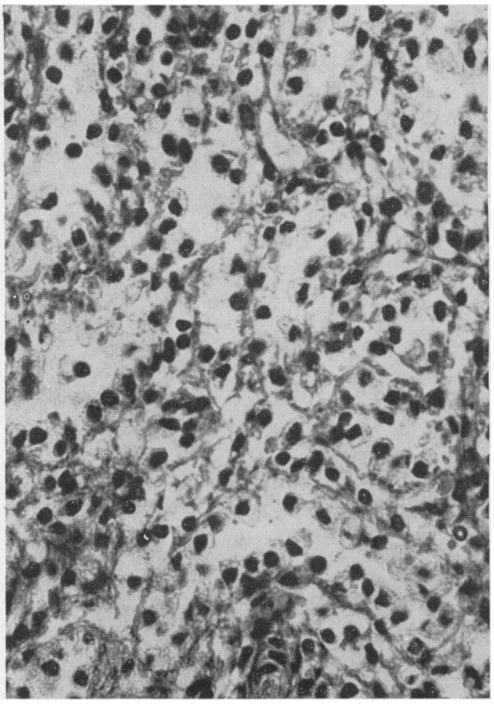

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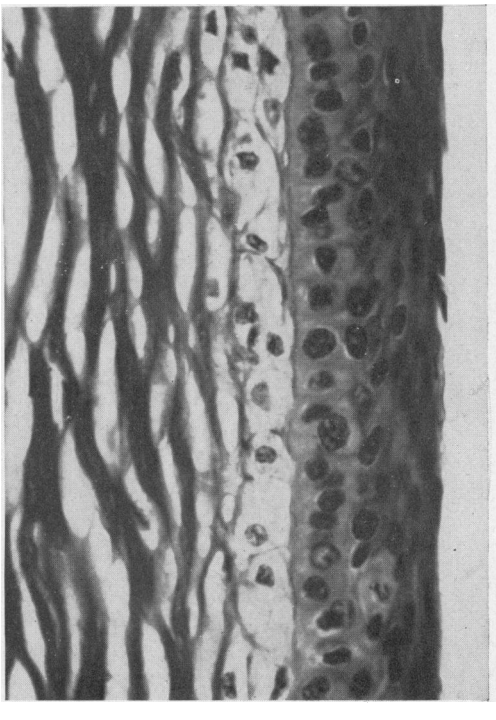

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PLATE 141

FIG. 14. Rib. The center of the epiphyseal zone shows replacement of the proliferating cartilage by a vascular connective tissue containing vacuolated cells. A transverse plate of bone is laid down along the epiphyseal line. Hematoxylin and eosin stain. × 200.

FIG. 15. Rib. Cortex with adjacent periosteum which is thickened and diffusely infiltrated with vacuolated, spindle-shaped cells. The vacuolated cells penetrate into lacunae in the cortex. Hematoxylin and eosin stain. × 300.

FIG. 16. Vertebra. The epiphyseal zone shows the cartilage in the resting stage. There is no evidence of proliferation or arrangement of cartilage cells in columns. Ossification is of the perichondral type. Hematoxylin and eosin stain. × 200.

FIG. 17. Vertebra. Epiphyseal zone shows fair proliferating activity of the cartilage and endochondral type of ossification (for comparison with Fig. 16). Hematoxylin and eosin stain. × 200.

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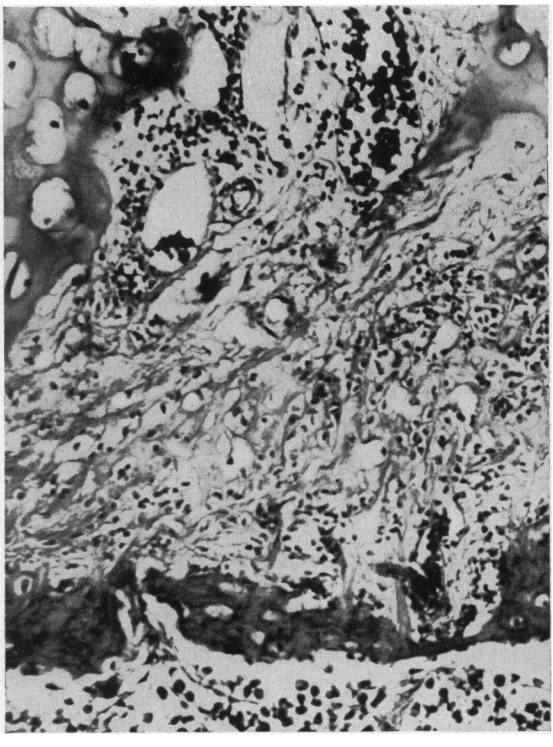

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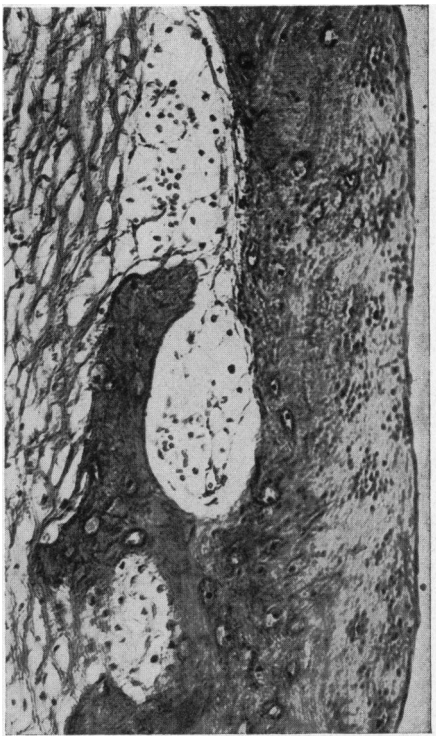

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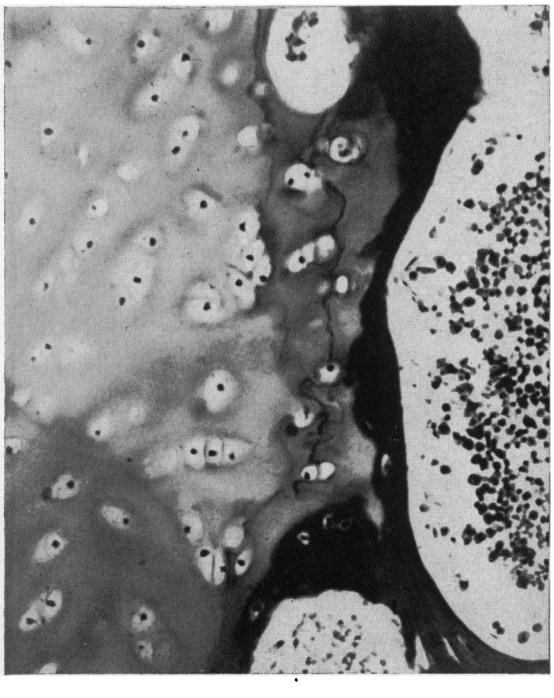

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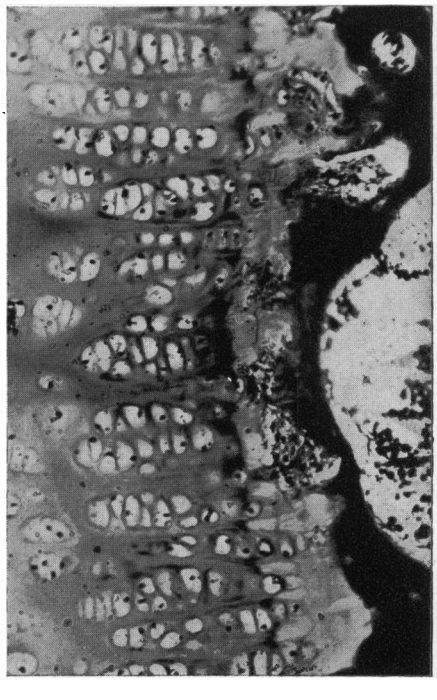

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