DYSTROPHIA MYOTONICA ASSOCIATED WITH FAMILIAL PAGET'S DISEASE (OSTEITIS DEFORMANS) WITH SARCOMATA

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The skull in dystrophia myotonica—In a previous study of dystrophia myotonica Caughey and Brown (1950) suggested that the endocrine lesion was primarily a failure of the androgenic function of the adrenals and the gonads. In the same paper the authors reported the radiographic abnormalities in the skull in some patients with dystrophia myotonica. In subsequent papers Caughey (1952a and 1952b) reported further cases of dystrophia myotonica with radiological changes in the skull, and it was suggested that such changes should come to be accepted as some of the variable features of the disorder. The changes described were a thickened calvarium, a small pituitary fossa, extensive pneumatisation of the air sinuses, and hyperostosis

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internas (Fig. 1). Walton and Warrick (1954) reported the changes found in seventeen cases of dystrophia myotonica and confirmed the presence of a thickened calvarium and the small sella turcica. They could not confirm the presence of hyperostosis interna or of excessive pneumatisation of the air sinuses. Further investigation however has confirmed our previous findings. The incidence of some or all of these skull changes is uncertain, but out of thirty-six cases we have found changes in eighteen. There is no evidence yet reported to suggest that, in dystrophia myotonica, radiological changes occur in other parts of the skeleton.

The skull in Paget’s disease—Paget’s disease of bone is one of the commonest diseases of bone after the age of thirty years. The lesions have a “spotty” haphazard distribution. In Gutman and Kasabach’s (1936) series of 105 cases eighty-two had involvement of the skull (sixty-five with advanced changes and seventeen with early changes).

The usual findings in the skull are early “cotton wool” changes in the frontal and parietal regions, or later a thickened “coarsely moth-eaten” appearance. Osteoporosis circumscripita may occur in association with the “cotton wool” appearance of the calvarium, or it may appear as the only skull change in Paget’s disease elsewhere. As the calvarium becomes thickened the distinction between the inner and outer tables and the diploe is obliterated. The base of the skull tends to sink and platybasia may result.

Familial Paget’s disease—Paget (1877), in his original publication, found no evidence of an inherited tendency in the disease; but soon after the original paper it came to be recognised that Paget’s disease of bone may occur in families, although uncommonly. Roberts and Cohen (1926) found thirteen instances with an inherited tendency. Since then several authors have referred to the familial incidence of the disease. Hanke (1935) reported a family in which four brothers, their mother and a maternal uncle had the disease. Koller (1946) reviewed the world’s literature and found twenty-eight instances of familial Paget’s disease of bone.

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In a previous publication Caughey (1952b) stated that in a patient with skull changes and dystrophia myotonica a differential diagnosis had to be made from Paget's disease and secondary carcinomatosis. Dystrophia myotonica and Paget's disease affecting the skull have in common thickening of the calvarium, but apart from this the diagnosis would be quite apparent to one familiar with the appearance in both disorders.

In view of the feature in common, and the comparative rarity of familial Paget's disease of bone, it is considered worth while to report details of some members of a family which exhibit familial Paget's disease of bone and dystrophia myotonica (Fig. 2).

In this family two members of the second generation have definite dystrophia myotonica and Paget's disease. A third member of the same generation had dystrophia myotonica. In the third generation one member has myotonia with marked psuedohypertrophy, and there is one child who is mentally defective. In the fourth generation there were two children who died at birth, one with gross physical defects, and there is one other child who is mentally defective. Physical and mental defects have previously been shown to occur in families with dystrophia myotonica (Caughey and Barclay 1954). So far as could be ascertained there was no case of consanguineous marriage in the family. The family has been investigated as fully as possible and details of our findings are apparent from the accompanying family tree (Fig. 2).

**CASE REPORTS**

**Case 1**—Man aged sixty-six (11, 4 in Fig. 2). In 1951 he fell and fractured his right femur at the site of a lesion of Paget's disease. He made an uneventful recovery. Three years later he was readmitted to hospital and stated that three weeks previously he had developed pains in the mid-thoracic region of the spine radiating round the abdomen at the level of the umbilicus. These pains persisted, and five days before admission he developed numbness of the toes and weakness of both legs. For three weeks he had had difficulty in passing urine.

On later direct questioning he stated that he had begun to go bald when he was seventeen or eighteen, and that he had had difficulty in relaxing his grasp for as long as he could recall. He had noticed that his leg muscles were "stiff," and in cold weather he was inclined to fall. From youth until middle life his limb muscles had been very large, although he realised he was not abnormally strong. He had never complained of weakness apart from the disability occasioned by the "stiff" muscles. There had been no impairment of his sex function and his vision had deteriorated very little.

*Examination*—He was a well developed man, partly bald (Fig. 3). He had bilateral cataract. The temporal muscles were wasted. He had mechanical myotonia of the tongue. The anterior cervical muscles were wasted, and neck flexion was weak; the neck extensors were strong. There was hypertrophy of the biceps group and of the forearm muscles. There was moderate myotonia of the grip on both sides, and mechanical myotonia of the thenar and hypothenar muscles. The power was average, but less than would have been expected with such large muscles.

The abdominal muscles were very weak. He was unable to sit up with arms folded across his chest. There was loss of sweating and loss of appreciation of pain, heat and cold, light touch.

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**FIG. 3**

Case 1—Wasting of temporal and anterior cervical muscles. Frontal baldness.
and vibration up to a level of the tenth thoracic segment. The upper abdominal reflexes were present; the lower were absent.

In the lower extremities the muscles of the calves and thighs were large. There was mechanical myotonia of the calf muscles. All muscle groups were weak, especially the gastrocnemii muscles. The deep reflexes in the arms were all present, but in the lower extremities all deep reflexes were increased and the plantar responses were extensor. The prostate gland and testes were normal to palpation.

*Investigations*—Radiography of the lumbar spine and pelvis revealed Paget's disease involving most of the vertebrae and the pelvis. The skull showed thickening of the calvarium, Paget's disease of the frontal bones with sarcomatous changes, and extensive pneumatisation of the frontal sinuses (Fig. 4). There had been some enlargement and compression of the lumbar and thoracic vertebrae, causing some encroachment upon the neural canal. This was most marked in the upper lumbar region. The left clavicle and both femora had manifest evidence of Paget's disease. The serum alkaline phosphatase was 68 units.

*Operation*—Two days after admission his legs became progressively weaker and the sensory impairment more complete. In view of the clinical findings and the radiological changes myelography was considered unnecessary, and Mr R. G. Robinson carried out a laminectomy at the level of T.8-11. When the upper two laminae were removed there was found a large extradural mass arising from the laminae and enveloping the dura. This was most marked.

**FIG. 4**
Case 1—Skull showing thickening of the calvarium, Paget's disease of frontal bone with sarcomatous change, and extensive pneumatisation of frontal sinuses.
on the left side and the pedicles and body were involved. It seemed apparent that there was sarcomatous change at the site of the Paget's lesion.

*Progress*—After operation the muscle power slowly returned, but he became incontinent of urine and an indwelling catheter became necessary. He continued to make good progress with his walking, but two months after the operation he slipped and fell in hospital and fractured his right femur. Radiography revealed a pathological fracture at the site of a Paget's lesion. The leg was splinted with traction, but in the course of the next two months his general condition deteriorated. He developed three large soft swellings over the vertex. He died in April 1955.

*Necropsy*—The forearm and calf muscles were very well developed. The skull was thickened, soft and brittle. Three separate expanding lesions were observed in the vault, varying from four to eight centimetres in diameter. Histological examination revealed in all sections the irregular thick trabeculae of Paget's disease. In the neoplastic areas the marrow spaces were filled with solid sheets of spindle-shaped and round cells characteristic of an osteosarcoma. There was some formation of tumour bone; and osteosarcomatous deposits were seen in the dura in relation to the skull lesions (Fig. 5).

Muscular system: The sternomastoid muscles showed marked atrophy, and the gastrocnemii, quadriceps and vertebral muscles showed severe changes. The fibres varied considerably in size and were separated by broad strands of collagen. Degenerative change was seen in the fibre cytoplasm, with loss of striation, vacuolation and uneven staining reaction. Islands of adipose tissue were seen in many sections (Fig. 6). The gastrocnemii showed marked fibrous replacement in some of the sections. A few atrophied fibres only remained
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**FIG. 6**
Case 1—Section of right sternomastoid muscle. Marked variation in fibre size, atrophy and replacement by adipose tissue.

**FIG. 7**
Case 1—Sagittal section and radiograph through lumbar vertebrae with Paget’s disease and osteosarcoma with encroachment on the spinal canal.
and these were separated by dense collagen. The quadriceps muscles showed negligible scarring and there was great variation in the fibre size. The arm flexors showed variation in fibre size with varying degrees of sarcoplasmic degeneration. A striking appearance was the presence of a number of fibres which were represented by a peripheral zone of homogeneous cytoplasm, the centre of the fibre being empty.

Skeletal system: The vertebral column was removed, deep frozen, and sectioned sagittally through the spinal canal. The lower thoracic and upper lumbar vertebrae were irregularly expanded and there was infiltration of the vertebral muscles by tumour. The cut surfaces of the vertebrae were pale and mottled, and of soft texture. The neoplastic process had invaded and encroached upon the spinal canal with compression of the cord in the lumbar region (Fig. 7). The inner two-thirds of the left clavicle were diffusely expanded, measuring four centimetres in diameter. The right femur was expanded, and the cortex irregularly destroyed with infiltration of the muscles by tumour; there was extensive neoplastic change at the site of a healed fracture near the middle of the shaft.

Histologically in all the bones described the features of Paget's disease could be recognised. Thick irregular bony trabeculae showing the characteristic, haphazard mosaic pattern, were prominent. The marrow spaces were filled by neoplastic spindle cells and round cells with occasional tumour giant cells. Tumour bone was also prominent in some of the sections. Similar sarcomatous deposits were seen in the vertebral and thigh muscles.

The testes were of normal size, and histological sections revealed a diffuse fine scarring, although seminiferous tubules showed only minor atrophy.

Case 2—Man aged sixty-seven years (II, 3 in Fig. 2). In 1951 when getting off a tram he was struck by a car and dislocated his right hip. He was admitted to hospital, where the dislocation was reduced. While in hospital he complained of pain in the left hip, and radiographs revealed Paget's disease of the left femur with associated osteoarthritis. The lumbar vertebrae and pelvis were also affected with Paget's disease. Radiographs of the skull showed a normal pituitary fossa and normal pneumatisation of the sinuses. There was, however, generalised thickening of the calvarium. No definite evidence of Paget's disease was seen in the skull.

When interviewed in 1955 during the investigation of the family, he stated that he had noted difficulty in relaxing his grasp for as long as he could remember. He noticed some difficulty getting up from a chair on account of "stiffness," and when playing bowls he sometimes had difficulty in relaxing his grasp of the wood.

On examination he had frontal baldness and marked leucoderma of the face and limbs. There were bilateral lenticular opacities with cuneiform clefts and streaks; there were also numerous grey punctate opacities throughout the anterior lens cortex, and there were a few in the posterior cortex. No angioid streaks were seen in the retina. There was mechanical myotonia of the tongue and of the small muscles of the hands in the thenar and hypothenar eminences. There was voluntary myotonia on gripping which disappeared after repetitive grasping. The facial muscles were normal. There was weakness of the neck flexors and of the abdominal muscles. He had difficulty in sitting up from the lying position. There was little wasting of the forearms. The deep reflexes were all present. There was no obvious gonadal atrophy.

Case 3—Man aged thirty-five years (III, 5 in Fig. 2). This patient was interviewed during the investigation of the family. At the age of nine years he noticed difficulty with "stiff" muscles and once when starting to run in a race he fell because of tightening of his leg muscles. He had noticed difficulty relaxing his grasp all his life, but this had caused little inconvenience. He was aware that this myotonia was relieved after taking alcohol. He began to go bald at twenty. As a younger man he did a great deal of wrestling. He always had large muscles but, although fairly strong, was aware that his strength was not in proportion to the size of his muscles.

On examination he had frontal baldness and was very muscular. The lenses were normal
Discussion

It is necessary first to attempt to establish the diagnosis of the disorders affecting this family. The development of Paget's disease of bone in two brothers could be coincidental, but we take it to be an example of familial Paget's disease.

The nature of the muscular dystrophy too, is open to discussion. The patient in Case 1 had myotonia and hypertrophy for many years and at the age of sixty-six made no actual complaint of muscle weakness. On examination he had obvious weakness of the neck flexors and the abdominal muscles. The marked histological changes in the sternomastoid muscles and in the gastrocnemius muscles strongly support the diagnosis of dystrophia myotonica. This was further supported by the presence of cataracts. In Case 2 myotonia had been apparent for years, but no obvious hypertrophy. There were well marked myotonia, weakness of neck flexors and abdominal muscles and bilateral lenticular opacities, which is very comparable with Case 1. Although no muscle biopsy has been obtained to support the diagnosis, it is felt that there is adequate evidence to support the diagnosis of dystrophia myotonica of very slow development. In Case 3 the clinical picture at thirty-five was that of myotonia congenita (Thomsen's disease) but the natural history of this familial disorder, as seen in this patient's father and uncle, suggests that other dystrophic features will develop later in life. The diagnosis will be discussed in greater detail elsewhere, but it is our opinion that this family has dystrophia myotonica.

The signs and symptoms of dystrophia myotonica are usually obvious, and seldom could there be any confusion in diagnosis from Paget's disease. The occurrence of familial Paget's disease in a family with dystrophia myotonica does, however, raise some points of interest on account of the radiological changes in the skull in both disorders.

The level of serum alkaline phosphatase, as in other conditions in which bone matrix is being laid down in excess, is high in Paget's disease—in fact, higher than in any other condition. In Case 1 it was 68 units. In dystrophia myotonica, on the other hand, Caughey and Brown (1950) found no change in the alkaline phosphatase in five fully developed cases. In one other case two estimations were 17–22 (King Armstrong units). Thus it seems that the level of serum alkaline phosphatase may be a useful biochemical aid in the differential diagnosis.

In Table 1 the radiological changes in the skull in both disorders have been tabulated. It will be noticed that the ages differ, but that general thickening of the calvarium may be common to both. On occasions this may be the only abnormal radiographic feature (as in our Case 2) and we are unable to state in this case whether it was due to Paget's disease or to dystrophia myotonica. However, it is most unusual that the diagnosis cannot be made with confidence on account of other signs and symptoms of either disorder.

The sarcomatous changes—Finally, there are some points of interest in the bony lesions. A relationship between Paget's disease and the development of osteosarcoma was noticed by Paget himself (1877). Frequent reports of such an association have appeared since. Willis (1953) estimated that osteosarcomata may be expected to occur in 5–10 per cent of cases of Paget's disease. Assessment is difficult because of the large number of symptomless cases of...
Paget's disease that are not diagnosed. Willis (1953) considered that most patients over sixty years of age with osteosarcoma have Paget's disease. Coley and Sharp (1931) found Paget's disease in only 28 per cent of seventy-two cases of osteosarcoma occurring in patients over the age of fifty. Moore (1944) found Paget's disease in 25 per cent of a similar group. Knaggs (1925), Speiser (1928) and Sear (1936) considered the relationship to have been exaggerated. From a review of the literature Summey and Pressly (1946) confirmed the general opinion that Paget's disease is a presarcomatous condition. They found a reported incidence of sarcoma varying from 2–14 per cent of cases of Paget's disease. The observations of Jaffe (1933) were similar, and Bird (1927) found seven cases in sixty-four patients with Paget's disease.

It has been observed that only those bones showing the changes in Paget's disease develop osteosarcoma. This was pointed out by Coley and Sharp (1931) and by Albertini (1928). Jaffe (1933) considered that the great proliferative capacity of the tissue in the marrow spaces in the disease is the basis of tumour formation. Albertini (1928) described a pre-invasive neoplastic change in the marrow tissues which he believed to be intermediate in nature between Paget's disease and sarcoma. We observed concurrence of undisturbed Paget's disease architecture with definite osteosarcoma in the same sections in some of our material.

The stimulus to neoplastic change has been discussed by Summey and Pressly (1946). Injury to bone has been incriminated by some, but this relationship is not well substantiated. It is unusual for sarcoma to develop at the site of a pathological fracture complicating Paget's disease. Summey and Pressly (1946) referred to a paper by Störhr (1929) who reported twelve cases, none of which led to sarcoma. However, occasional cases of sarcoma at the site of fracture have been recorded, and it seems that fracture does not increase the likelihood of malignant change, nor does it preclude it.

The occurrence of multiple growths arising simultaneously in many bones affected by Paget's disease has often been reported. The simultaneous appearance of the lesions only in bones showing osteitis deformans, and the absence of lesions in the lungs and other sites, seem to preclude the possibility that these multiple tumours might be metastatic deposits

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Dystrophia myotonica</th>
<th>Paget's disease</th>
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</thead>
<tbody>
<tr>
<td><strong>Thickness of calvarium</strong></td>
<td>Increased—moderately—usually begins in the frontal region</td>
<td>Increased—grossly—variable—often greatest in the frontal region—usually diffuse but may be localised</td>
</tr>
<tr>
<td><strong>Shape of vault</strong></td>
<td>Retained unchanged</td>
<td>Changed</td>
</tr>
<tr>
<td><strong>Skull tables</strong></td>
<td>Easily identified</td>
<td>Outer table affected</td>
</tr>
<tr>
<td><strong>Hyperostosis interna</strong></td>
<td>Common (frontal and/or parietal)</td>
<td>Nil</td>
</tr>
<tr>
<td><strong>Pituitary fossa</strong></td>
<td>Normal to very small (occasional ossification of diaphragma sellae)</td>
<td>Normal unless partly effaced by involvement of the skull base</td>
</tr>
<tr>
<td><strong>Pneumatisation of sinuses</strong></td>
<td>Usually extensive with large frontals—and back to posterior clinoid processes</td>
<td>Usually normal</td>
</tr>
<tr>
<td><strong>Lower jaw</strong></td>
<td>May be prognathic</td>
<td>Normal unless involved with Paget's disease</td>
</tr>
<tr>
<td><strong>Osteosarcomatous change</strong></td>
<td>Not reported</td>
<td>Relatively common</td>
</tr>
<tr>
<td><strong>Skull base</strong></td>
<td>Not involved</td>
<td>Involved in late stages—platybasia</td>
</tr>
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(Coley and Sharp 1931, Davie and Cooke 1937). The evidence in our case is strongly in favour of the view that the lesions are multiple primary tumours. Sarcomatous change occurred in a vertebral column lesion. We can find no record of such a change.

**Summary**

1. A report is given of a family suffering from dystrophia myotonica and familial Paget's disease of bone.
2. Radiological changes in the skull occur in both disorders, which are quite dissimilar. Thickening of the calvarium, however, may be common to both.
3. The serum alkaline phosphatase is high in Paget's disease and normal in dystrophia myotonica.
4. In one patient the Paget's disease was complicated by the development of multiple sarcomata. Sarcomatous involvement of the vertebral column, observed in one of the cases, has not been recorded before.

It is a pleasure to thank physicians and surgeons who have given us access to their cases, and also Dr A. Veale for advice in the genetic aspects of this paper. We are indebted to the members of the Photographic and Artistry Departments of the Otago Medical School for the photographs and the family tree, and to Miss J. Smith for secretarial assistance.

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