STUDIES OF PAGET'S DISEASE (OSTEITIS DEFORMANS)*

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In this paper are recorded the results of studies into two of the complications of Paget's disease—sarcoma and fracture.

1. SARCOMA COMPLICATING PAGET'S DISEASE

Sarcoma is an invariably fatal complication of Paget's disease of bone. Solution of the problems it presents may aid the understanding of all sarcomas of bone, and certain facts have emerged from a study of the present series and from cases recorded in the literature. In Paget's second commentary (1882) on osteitis deformans he recorded several examples of malignant tumour in his small series, of which at least two were bone sarcomas. The association of sarcoma with Paget's disease is now unquestioned, although there is no agreement on its incidence. Recorded cases are probably only a small fraction of the total.

Schajowicz collected all the published cases of Paget's sarcoma up to 1942 and this registry was enlarged by Sumney and Pressly (1946). Since then nineteen more sarcomas have been recorded (Dickson et al. 1945, Platt 1946, Russell 1949, Sear 1949) to which seven are added now (Appendix I). The significant features of this collected series (total, 102 cases) are reviewed in this paper.

Incidence

The incidence of sarcoma in osteitis deformans has been calculated variously between 2 and 15 per cent (Bird 1927, Breslich 1931, Coley and Sharp 1931, and others). Sear (1949), who had seen twenty-three cases, considered that less than 2 per cent of patients with Paget's disease develop sarcoma. The present writer is in agreement with this view, for it must be borne in mind that Paget's disease is commoner than might be expected: many cases are discovered accidentally during routine pyelography, barium meals and other radiographic studies. However, of patients in hospital with Paget's disease at the Brisbane Hospital between 1943 and 1949, 5 per cent developed sarcoma of bone.

Age—The age incidence was similar in a series of 140 cases of Paget’s disease and in 102 collected cases of sarcoma complicating this disease (Fig. 1). Figures from the Registry of Bone Sarcoma in 1931 showed that 27-4 per cent of bone sarcomas in patients over fifty years of age occurred as complications of Paget's disease (Coley and Sharp 1931). However, bone sarcoma at this age without Paget's disease is now much less common than these figures indicate.

Sex—Four-fifths of the collected cases occurred in males, whereas uncomplicated Paget's disease shows little if any male predominance.

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Trauma—The incidence of trauma, and its evaluation as an etiological factor in Paget’s sarcoma (and in all bone sarcoma) must await accurate statistical analysis, as Coley (1949) and others have pointed out. Furthermore, there may be difficulty in excluding “traumatic determinism”—Ewing’s term for local injury providing the first notice of a pre-existing lesion. The following notes are therefore limited by these provisos. In Case 2 (Appendix I) there were three fractures during the two years preceding development of Paget’s sarcoma. In Case 5 a sarcoma developed behind the patella, which had been fractured ten years before. In Case 6 the patient attributed her sarcoma to a fall fourteen months previously. There is a previous history of trauma in many other recorded cases. From the three cases mentioned it is difficult to escape the impression that injury, either general or local, is an important—perhaps a precipitating—factor in the genesis of many Paget’s sarcomas. Sarcoma after fracture is uncommon, but not unknown. Willis (1948) has emphasized that injury to a carcinogenically prepared area, perhaps of long standing, may precipitate tumour formation.

Pathology

Paget’s sarcoma is highly malignant; the average survival period is shorter than for “ordinary” bone sarcoma. Sarcoma is said to arise more commonly in the vascular phase of osteitis deformans. Its origin is frequently subperiosteal (Jaffe 1933) and often multicentric (32 per cent in the collected cases). Metastasis is by dissemination through blood vessels or lymphatics (Gruner et al. 1912), but the abdominal cavity often seems to escape. The duration of pre-existing osteitis deformans varies, and may be up to thirty-five years.

Histologically, in some cases there is a gradual transition from the apparently simple process of Paget’s disease to a state of diffuse malignancy, but in others there may be an abrupt change to neoplastic cells. If the incidence of Paget’s sarcoma and of “ordinary” bone sarcoma is compared with that of uncomplicated Paget’s disease, several significant points emerge (Fig. 2; Table I). There is no certain relationship between the sites of maximal incidence of uncomplicated Paget’s disease and of Paget’s sarcoma. Where sarcoma is common, as in the humerus, uncomplicated Paget’s disease is not. Where sarcoma is less frequent, as in the vertebrae, sternum and clavicle, Paget’s disease is common. Some local factor may determine the development of Paget’s bone into sarcoma, and trauma immediately suggests itself. In the skull, where ordinary bone sarcoma is rare, Paget’s sarcoma is not uncommon.

Cell type—Cell anaplasia in bone sarcoma complicating Paget’s disease is frequent. The cell types were unrecollected in nineteen of the collected series. In the remainder the relatively high frequency of anaplastic spindle- and round-cell type is interesting (Table II). Fibrosarcoma in Paget’s disease and “ordinary” fibrosarcoma are about equally common in the affected age group as shown by comparison of the present series of Paget’s sarcoma and a series that included all types of fibrosarcoma (Meyerding
et al. 1936). This focuses attention on the conjecture that osteogenic sarcoma is merely fibrosarcoma ossified by virtue of its environment (Leriche and Policard 1926). The fibrosarcomas seen by the writer have been very well differentiated histologically.

The variety of cells in these sarcomas suggests that all cell types found in Paget’s bone are able to respond to the neoplastic stimulus. No report of a Ewing’s tumour in osteitis deformans is known.

**TABLE I**

Comparative Incidence of Sarcoma Complicating Paget’s Disease, Sarcoma of Bone in General and Uncomplicated Paget’s Disease in the Bones that are Infrequently Affected

<table>
<thead>
<tr>
<th>Site</th>
<th>Paget’s sarcoma (per cent of all cases)</th>
<th>All bone sarcoma (per cent of all cases)</th>
<th>Uncomplicated Paget’s disease (per cent of all cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scapula</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Ribs</td>
<td>5</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Radius</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Ulna</td>
<td>3</td>
<td>0·3</td>
<td></td>
</tr>
<tr>
<td>Clavicle</td>
<td>3</td>
<td>0·6</td>
<td>13</td>
</tr>
<tr>
<td>Maxilla</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Mandible</td>
<td>1</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Sternum</td>
<td>1</td>
<td>1</td>
<td>23</td>
</tr>
</tbody>
</table>

**TABLE II**

Cell Type in 102 Cases of Sarcoma Complicating Paget’s Disease

(After Willis)

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteosarcoma (all types)</td>
<td>87</td>
</tr>
<tr>
<td>osteogenic</td>
<td>33</td>
</tr>
<tr>
<td>polymorphic-cell</td>
<td>10</td>
</tr>
<tr>
<td>spindle- and round-cell</td>
<td>21</td>
</tr>
<tr>
<td>chondrosarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>4</td>
</tr>
<tr>
<td>Giant-cell sarcoma</td>
<td>7</td>
</tr>
<tr>
<td>Ewing’s tumour</td>
<td>-</td>
</tr>
<tr>
<td>Unrecorded</td>
<td>19</td>
</tr>
</tbody>
</table>

Total: 102

**Biochemical Features**

Alkaline phosphatase—The usually elevated phosphatase of Paget’s disease often rises further when sarcoma supervenes, falling to lower levels after amputation, except in the presence of metastases or multicentric origin of the tumour (Fig. 3). The malignant osteoblast produces phosphatase even when morphologically indistinguishable from a fibroblast (Franseen and McLean 1935), so that a rise in phosphatase after amputation denotes a very poor prognosis. There may be a terminal fall in phosphatase level if much central necrosis of the growth occurs (Franseen and McLean 1935).

Magnesium—Several facts about the metabolism of magnesium suggest a new line of investigation in Paget’s sarcoma and bone sarcoma in general. Magnesium increases the solubility of bone calcium and phosphorus (Gill and Stein 1936). Paget’s bone contains considerably more magnesium than ordinary bone (Newton 1939). Haury (1942) found that
increased magnesium in the culture medium of a tumour caused increased growth, and that after injection magnesium is stored in tumours. Lastly, there is a higher magnesium concentration in neoplastic than in normal tissues (Haury and Cantarow 1941).

**Discussion**

It is worthy of emphasis that the two peaks of incidence of bone sarcoma are related to maximal epiphysial growth (adolescence) and to active Paget's bone (" menopause " and later). This study has also brought out the much higher incidence of Paget's sarcoma in males than females. The obvious common factors of importance are: 1) actively growing vascular bone; and 2) changes in hormonal balance occurring at the extremes of gonadal activity.

It follows that attempts to suppress androgens and their effects are rationally based. Yet although in some cases of bone sarcoma radiological evidence of lung metastases has disappeared after administration of oestrogen, the final course was in no way altered, so that some other carcinogenic factor continues to operate. Further investigation of the significance of the relatively high incidence in males may still be valuable.
Trauma, possibly the third etiological factor, may act as an osteoblastic stimulus and thus precipitate neoplasia in a previously prepared bone. To borrow Osler’s parable, the Paget’s soil seems to provide ideal conditions for the transition to malignancy, and the progress of leukoplasia to carcinoma is in many ways analogous to the development of sarcoma in bones affected by osteitis deformans.

**Prognosis**—Fewer than five of the patients in this collected series survived two years. One of Platt’s (1850) patients survived five years after amputation, the longest period recorded. Serial phosphatase estimations are a relative guide to the patient’s progress.

**Treatment. Prophylaxis**—A patient with Paget’s disease who has pain, swelling or known injury should be subjected to the closest scrutiny—clinical, radiological and biochemical (phosphatase) examinations, to be repeated within one month, and again if there is still doubt. There should be no hesitation in performing biopsy when doubt persists. Fractures slow to heal call for similar precautions, especially when there is radiographic evidence of marked proliferation or rarefaction.

**Treatment of established sarcoma**—The available methods of treatment are ineffective, and most patients die within two years of diagnosis. No discussion of methods will be attempted. The patients in this series were all subjected to amputation when feasible, with or without pre- or post-operative radiation (Table III). Oestrogen and adrenal cortical extracts, although not of immediate therapeutic value, hold experimental promise.

**Summary and Conclusions**

Sarcoma complicating Paget’s disease is uncommon; ninety-five cases have been collected and seven further cases are now reported. Sarcoma probably complicates less than 2 per cent of all cases of Paget’s disease. There is a relatively high incidence in males, especially in the sixth decade, whereas bone sarcoma over the age of fifty years without osteitis deformans is rare. Injury is prominent in the history of many cases.

Comparison of Paget’s sarcoma, “ordinary” bone sarcoma and the bones affected by uncomplicated osteitis deformans reveals some important differences. As to the type of tumour, osteogenic sarcoma is the commonest, but fibrosarcoma and round-cell sarcoma are also frequent.

The serum phosphatase is a most useful prognostic guide in a disease with a generally poor prognosis. Magnesium metabolism in relation to bone sarcoma requires further study.

Prophylaxis is based on a clinical suspicion of this complication in Paget’s disease, and measures are outlined which may be of assistance.

Sarcoma in Paget’s bone is highly lethal, but Nature in striking down these old people may have provided us with facts which will ultimately solve problems common to all sarcomas of bone.

**APPENDIX I**

**Seven Cases of Sarcoma Complicating Paget’s Disease**

**Case 1**—F. C., male aged forty-two years. Sarcoma of left ilium. Complained of pain left hip and knee, and fever, for five weeks. Previously in good health. On examination he appeared very ill. Left hip held in flexion; much pain in thigh. Mass felt in left iliac fossa. No obvious signs of Paget’s disease. W.B.C. 18,000 per cubic millimetre. Radiographs showed irregular sclerosis of the left ilium and ischium, with central erosion suggestive of sarcoma. Skull showed Paget’s disease. 

**Biopsy**—Centre of mass almost pure blood, with fragments of bone. Histological examination (Dr J. V. Duhig)—Highly vascular connective tissue and membranous bone production with changes typical of Paget’s disease. Cultures were sterile. Progress—Palliative radiation therapy failed to slow the sarcoma. Death occurred three months later. No autopsy.

**Comment**—Diagnosis mainly on radiological grounds. Sarcoma probably anaplastic.
Case 2—B. B., male aged fifty years. Multicentric sarcoma of right ulna and left ilium. Complained of swelling and pain in right wrist for one month during after-treatment of a slowly healing fracture of left femur. Known to have Paget's disease for twenty years. Previous fractures neck and shaft of right femur. Radiographs showed osteosarcoma of right ulna (Fig. 4). Biopsy—Gelatinous cystic tumour. Histological examination (Dr J. V. Duhig) Osteitis deformans. Much young fibroblastic tissue, abundant osteoclasts. Some of the tissue well differentiated and fibrous. Fibrosarcoma. Progress—Lung metastases developed. Death occurred three months later. Autopsy—Typical Paget's disease. Tumour of right sternum, tibiae, forearms, calvarium and pelvis. Thoracic viscera extensively seeded with secondaries. Sarcoma of left iliac crest.

Comment—Previous Paget's disease for twenty years not unusual. Sarcoma diagnosed by clinical observation during convalescence after fracture.

Case 3—E. T., female aged seventy-six years. Multicentric sarcoma of left femur, right femur, sternum and left maxilla. Complained of persistent pain in thighs for one month. Radiographs at that time showed a suspicious area in the right upper femur, with Paget's disease. She refused biopsy and was discharged after course of radiation therapy. Two months later returned with more pain in knees. Known to have Paget's disease for eight years; admissions for congestive cardiac failure, diabetes mellitus, and basilar invagination. Examination revealed a mass in the left upper thigh, manubrium sterni, and later in left maxilla. Breasts and thyroid normal. Radiographic examination—Evidence of sarcoma in Paget's disease left femur. No evidence of pulmonary metastases. Progress—Became rapidly worse; died from bronchopneumonia six and a half months later. No autopsy.

Comment—Diagnosis principally radiological. This patient also had diabetes, a frequent association.

Case 4—C. K., male aged sixty-three years. Sarcoma right femur. Complained of pain in right lower thigh of several months duration, and a popliteal swelling for one month. Known to have Paget's disease for two years. On examination—Paget's disease of skull and limbs. Warm, hard swelling at apex of popliteal fossa, attached to femur. Overlying skin mottled. Radiographs showed sarcoma complicating Paget's disease (Fig. 5). Progress—Amputation of femur. Subsequent course not traced, presumably died. Histological examination of amputated specimen (Dr J. V. Duhig).—General structure of spindle-cell sarcoma, with great variety of polygonal multi-nucleated forms.

Case 5—J. H., male aged fifty-six years. Sarcoma right femur. Complained of pain and swelling of right knee for seven months; fractured right patella ten years previously, sutured with kangaroo tendon. On examination—Clinical changes of Paget's disease. Large bluish tumour right knee which was cool and not tender. Radiographic examination—Sarcoma right femur. Progress—Subtrochanteric amputation right femur. Femoral glands enlarged (no deposits microscopically). Serial phosphatase estimations are shown in Figure 3 (Case A). Patient died some months later with obvious metastases in frontal bones. No autopsy. Histological examination of amputated specimen—Fibrosarcoma in Paget's disease of bone.

Comment—Injury prominent in history.

Case 6—M. W., female aged fifty-nine years. Sarcoma left femur. Complained of painful, swollen, stiff left knee for eight months, attributed to fall fourteen months previously. Relief by rest. Loss of weight (2 stones 28 lb. in twelve months). Examination—Hot, red, tender, swollen left thigh; mass lower end of left femur. Joint effusion. Radiographic examination—Sarcoma of left femur with soft-tissue spread and destruction of lateral condyle (Fig. 6). Paget's disease in skull. Progress—Pre-operative radiation therapy; subtrochanteric...
amputation. Patient alive and well fifteen months after operation. *Histological examination* of amputated specimen—osteogenic sarcoma.

*Comment*—Injury to knee six months before clinical evidence of sarcoma is suspicious.

![Fig. 6](image1)

**Fig. 6**
Case 6—Sarcoma of left femur complicating Paget’s disease.

![Fig. 7](image2) ![Fig. 8](image3)

**Fig. 7**
Case 7—Initial radiograph (Fig. 7) showed marked Paget changes with degenerative arthritis of the elbow joint but no definite evidence of sarcoma. Radiograph six months later (Fig. 8) showed a large area of bone erosion in the lower end of the humerus.

joint, fixed to posterior aspect humerus. Radiographic examination—Early radiographs, at onset of symptoms, showed arthritis of the right elbow joint, and Paget's disease (Fig. 7). Further radiographs taken after admission to hospital six months later showed evidence of sarcoma of right humerus (Fig. 8). Progress—Subcapital amputation right humerus. Alive and well five months after operation. Serial phosphatase estimations are shown in Figure 3 (Case B). Histological examination of amputated specimen (Professor Canny)—Tissue appears sarcomatous; major differentiation towards fibrous tissue. No differentiation towards osteogenic sarcoma seen. Comment—This case reveals the danger of relying solely on ancillary methods. The early radiographs did not give definite evidence of sarcoma, but history of progressive pain was suggestive. Strong family history of Paget’s disease.

APPENDIX II

TWENTY-FIVE CASES OF SARCOMA COMPLICATING PAGET’s DISEASE REPORTED IN THE LITERATURE SINCE 1945. SUPPLEMENT TO THE TABLE PREPARED BY SUMNEY AND PRESSLY (1946) WHICH INCLUDED SEVENTY-SIX COLLECTED CASES

<table>
<thead>
<tr>
<th>Collected case number</th>
<th>Author</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Location and histological type of sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dickson, Camp, Ghormley</td>
<td>77</td>
<td></td>
<td>52</td>
<td>F</td>
<td>Osteogenic sarcoma tibia</td>
</tr>
<tr>
<td></td>
<td>78</td>
<td></td>
<td>47</td>
<td>F</td>
<td>Osteogenic sarcoma ilium</td>
</tr>
<tr>
<td></td>
<td>79</td>
<td>1945</td>
<td>70</td>
<td>M</td>
<td>Fibrosarcoma thigh</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td></td>
<td>45</td>
<td>M</td>
<td>Giant-cell tumour ilium</td>
</tr>
<tr>
<td>Platt</td>
<td>81</td>
<td></td>
<td>63</td>
<td>M</td>
<td>Spindle-cell sarcoma lower femur</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td></td>
<td>60</td>
<td>F</td>
<td>Spindle-cell sarcoma lower femur</td>
</tr>
<tr>
<td></td>
<td>83</td>
<td>1946</td>
<td>53</td>
<td>M</td>
<td>Sarcoma pubis, body L.3, chest</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td></td>
<td>61</td>
<td>M</td>
<td>Spindle-cell sarcoma upper humerus</td>
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<tr>
<td></td>
<td>85</td>
<td></td>
<td>67</td>
<td>M</td>
<td>Polymorphic-cell sarcoma upper humerus</td>
</tr>
<tr>
<td></td>
<td>86</td>
<td></td>
<td>62</td>
<td>M</td>
<td>Spindle-cell sarcoma upper humerus</td>
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<tr>
<td>Russell</td>
<td>87</td>
<td></td>
<td>70</td>
<td>M</td>
<td>Malignant osteoclastoma upper femur</td>
</tr>
<tr>
<td></td>
<td>88</td>
<td>1949</td>
<td>49</td>
<td>M</td>
<td>Malignant osteoclastoma parietal</td>
</tr>
<tr>
<td></td>
<td>89</td>
<td></td>
<td>59</td>
<td>F</td>
<td>Malignant osteoclastoma tibia</td>
</tr>
<tr>
<td>Sear</td>
<td>90</td>
<td></td>
<td>80</td>
<td>M</td>
<td>Sarcoma ilium</td>
</tr>
<tr>
<td></td>
<td>91</td>
<td></td>
<td>70</td>
<td>M</td>
<td>Sarcoma femur</td>
</tr>
<tr>
<td></td>
<td>92</td>
<td>1949</td>
<td>64</td>
<td>F</td>
<td>Spindle-cell sarcoma femur</td>
</tr>
<tr>
<td></td>
<td>93</td>
<td></td>
<td>47</td>
<td>M</td>
<td>Osteogenic sarcoma tibia, ribs and vertebrae</td>
</tr>
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<td></td>
<td>94</td>
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<td>M</td>
<td>Fibrosarcoma ulna, ilium</td>
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<td></td>
<td>98</td>
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<td>76</td>
<td>F</td>
<td>Sarcoma femora, sternum, maxilla</td>
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<td></td>
<td>99</td>
<td>1950</td>
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<td>F</td>
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<td>56</td>
<td>M</td>
<td>Fibrosarcoma femur</td>
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<tr>
<td></td>
<td>101</td>
<td></td>
<td>63</td>
<td>M</td>
<td>Spindle-cell sarcoma femur</td>
</tr>
<tr>
<td></td>
<td>102</td>
<td></td>
<td>54</td>
<td>M</td>
<td>Fibrosarcoma humerus</td>
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</tbody>
</table>
2. FRACTURES COMPPLICATING PAGET'S DISEASE

Fracture is probably the commonest complication of Paget's disease. There is still justification for the statement that such fractures are "recognised, taken for granted and forgotten" (Ghormley et al. 1937). This survey has two aims: to review a series of fractures in Paget's disease, and to discuss biochemical advances applicable to their treatment.

Reifenstein and Albright (1944) studied the metabolism of two patients while immobilised with fractures complicating Paget's disease, and their views are presented below. Other authors have presented reviews of small numbers of cases, and most of the available series of Paget's disease briefly mention the number of fractures in the total, but no detailed review of Paget's fracture has been found in the literature of the last decade.

Clinical Material

Thirty-four patients were admitted for fracture, some more than once (a total of forty-five fractures) among 140 in-patients with Paget's disease at the Brisbane Hospital between 1943 and 1949. Four patients returned with a second fracture of the same bone, and a fifth with fracture in a different limb. One patient suffered three successive fractures, and ultimately developed a bone sarcoma.

Twenty-two fractures occurred in the femur—sixteen in the neck, intertrochanteric and subtrochanteric regions, the remainder in the shaft. Other bones affected were tibia (eight cases), pelvis (six cases), fibula (four cases), humerus (two cases), spine, jaw and tarsus (one case each).

In thirteen instances union occurred more rapidly than the average for such bones unaffected by Paget's disease. There was delayed or absent union in six fractures, and four patients died during the convalescent period. The remaining twenty-two showed union in normal time. The age incidence was similar to that of uncomplicated Paget's disease.

The fracturing injury was severe in at least six patients. In one no violence was known. Two patients not included in this series had Paget's disease in other bones, with no evidence of the disease in the broken limb.

Discussion

Incidence of fracture—No figures are available for the absolute incidence of fractures complicating Paget's disease, but 24 per cent of the patients in our series of Paget's disease were admitted for fracture. At the Mayo Clinic there were seventy-seven fractures in 367 admissions for Paget's disease (Dickson et al. 1945), and more than half of these fractures affected the vertebral column, compared to only one of our series. Early writers (Knaggs 1925, Packard et al. 1901) thought that fracture was rare in Paget's disease, doubtless for want of radiological facilities.

Repair—There are two separate phases in Paget's disease of bone. In the initial phase the bone is highly vascular, soft, and may sometimes be indented by digital pressure. Albright and Reifenstein (1948) believe that this change follows destruction of normal bone. In a later phase the bone is characteristically dense, sclerotic, and sometimes very brittle. Both processes may occur together. Fracture is commoner in the vascular phase (Dickson et al. 1945, O'Reilly and Race 1932, Schmorl 1932), when the usual long regular trabeculae of normal bone are replaced by short and very irregular processes which, with the softening, must lessen the tensile strength of the bone.

Callus formation appears to be normal or enhanced in these fractures (Rogers and Ulin 1936), but the impression has been gained from this study that in the vascular stage of Paget's disease union is rapid, while in the sclerotic phase union is slow or fibrous, even though the callus may have been abundant and immobilisation satisfactory. Therefore while ossification appears defective in fractures in the sclerotic stage, in the vascular phase an unknown factor acts to accelerate union.
The type of fracture most commonly seen is Codman's "rotten wood" or transverse fracture without comminution, and such fractures are not immune to the difficulties that transverse fractures of normal bone sometimes present (Urist and Johnson 1943). Refracture is not infrequent; it occurred in four cases of this series. Incomplete transverse fissures on the bowed side of bones affected by Paget's disease—the pseudofractures of Looser (Brailsford 1938)—usually heal but may extend to become complete breaks.

There is much periosteal proliferation in Paget's disease, and this is enhanced when fracture occurs. The healing bone takes part in the Paget's process (Jaffe 1933). Occasionally Paget's bone breaks at the site of a sarcoma, a fact to be remembered when examining a Paget's fracture. Rarely sarcoma may develop in a healing fracture.

**Physiological pathology.** Effects of immobilisation—Bone is a tissue in a constant state of flux. Absorption and deposition of matrix and bone salts proceed together, principally governed in health by demands imposed on the bone by local stresses. Activity is the principal stimulus to bone deposition, while inactivity favours bone absorption. With enforced immobilisation, absorption predominates and bone calcium is mobilised. This fact is easily confirmed by the Sulkowitch test (Barney and Jones 1941), by which increased urinary excretion of calcium can be demonstrated. Should there be any renal insufficiency, as is common in patients in the age group affected by Paget's disease, calcium may be retained in the blood, and metastatic calcification may occur. In Paget's disease, particularly when complicated by fracture, the effects of immobilisation are enhanced (Reifenstein and Albright 1944). Two cases of the series are of interest in this respect. One patient sustained a fractured tibia, and after immobilisation for some months passed a small renal calculus of calcium phosphate and oxalate. The second patient developed radio-opaque renal calculi (not present in the pre-operative radiograph) during four months' convalescence after prostatectomy. Although this patient had no fracture, and limitation of space forbids discussion of the many variables, both cases may be considered as examples of metastatic calcification consequent upon immobilisation in Paget's disease. There have been two other reports of
patients, both of whom died, with metastatic calcification in this disease (Seligman and Nathanson 1945, Wells and Holley 1942).

Magnesium metabolism—Haury's study (1942) of two ununited fractures led him to believe that there is an optimal magnesium level for ossification of the fracture site. Magnesium is a co-enzyme of bone phosphatase, and is increased in the bone of Paget's disease. These observations suggest that further study of the influence of magnesium in bone physiology is needed.

The adrenal cortex—The writer's experiments support the proposition that the adrenal cortex plays some role in Paget's disease, but just how important this may prove is difficult to determine in the light of present knowledge. The administration of adrenal cortical extracts to patients with Paget's disease has altered the serum phosphatase considerably (Fig. 9), and has increased a tendency to diabetes found in many of these patients.

Berman (1936) first suggested that the adrenal cortex played a part in Paget's disease, and he considered that an imbalance between the adrenal cortex and the parathyroids was directly responsible. While it is true that the adrenal cortex indirectly influences calcium storage in bone (for example, osteoporosis in Cushing's syndrome) there has not been any confirmation of his interesting hypothesis. Depression of adrenal cortical function by injury—Selye's (1946) adaptation syndrome—causes a general curtailment of tissue metabolism. Fracture, especially in Paget's disease, probably produces some modifying influence on the effects of the adaptation syndrome, because of the abundance of callus often seen around the bone ends.

Treatment—Many of the fractures that complicate Paget's disease unite quickly and without incident. On the other hand, at least 13 per cent in the present series presented difficulties and slow union. The vascularity of the bone may make open reduction a chastening procedure if a transfusion has not been anticipated. Some writers (Lennox 1949, Watson-Jones 1943) have advised against the use of retained metal (nails, pins or plates), but internal fixation may sometimes have a place especially if the bone is not excessively soft or hard. Bohler (1948), writing on the subject of intramedullary nailing, stated: "Some cases of bone disease, e.g., Paget's disease, cannot be nailed if the medullary cavity is not patent. As a rule, however, fractures in Paget's disease are transverse and therefore particularly suited for medullary nailing." He gave details of successful nailing of a mid-shaft of the humerus affected by Paget's disease. One femoral neck in this series was nailed, with moderate success. Another attempt failed because the bone was very sclerotic.

Early walking—"Chemical death"—Albright and Reifenstein's (1948) dramatic term for the sequelae of metastatic calcification in the aged—may follow prolonged immobilisation of Paget's fracture, as discussed above. The shortest period of immobilisation consistent with firm union should be the aim.

Diet—Diet, and more specifically, calcium and fluid intake, is important in the patient immobilised with Paget's disease. Increased calcium ingestion may be harmful to a system already overloaded by calcium released from bone by immobilisation, and may precipitate a chain of hypercalcaemic manifestations. Accordingly, high calcium foods should be restricted during the period of recumbency. Fluids must be copious because dehydration may affect the renal excretion of calcium. The average hospital diet, with free fluids, rarely culminates in hypercalcaemia, but the danger does exist, as emphasized by our two cases discussed above. It has been suggested that a high magnesium diet (Gill and Stein 1936) or magnesium carbonate given by mouth (Barney and Jones 1941) may be beneficial.

Adrenal cortical extract—There is no adequate treatment for Paget's disease. However, Berman (1936) found a lowering of serum phosphatase and subjective improvement with adrenal cortical extracts, and a trial of such treatment is in progress. The interim results are not hopeful.
Summary and Conclusions

Fracture is the commonest complication of Paget's disease, and one of the commonest types of pathological fracture. Thirty-four patients (with forty-five fractures) have been reviewed, and they constituted 24 per cent of the cases admitted to the Brisbane Hospital with Paget's disease from 1943 to 1949.

The vascular and sclerotic processes of Paget's disease affect the healing of the fracture. It appears from this study that callus is abundant in both, but firm union is normal or accelerated in onset in the vascular stage, and delayed, sometimes indefinitely, in the sclerotic stage. Refracture is common.

The usual decalcification consequent upon immobilisation is increased in Paget's disease, particularly if renal disease is present, and must be limited so far as possible by early movement and walking. Two cases are quoted where failure to appreciate this resulted in renal calculi.

High concentration of magnesium and phosphatase in the bone may be responsible for the rapid union so commonly seen. The adrenal cortex plays some role in Paget's disease, at present uncertain.

Open reduction and skeletal fixation are not always contraindicated.

A minority of fractures complicating Paget's disease do badly. After prolonged and careful supervision, either the patient dies or discouragement gains the upper hand. A modest wish is that this review may help to thin the ranks of such cases.

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