"OBSERVATIONS on OSTEITIS DEFORMANS"

T H E S I S

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by

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CONTENTS

OBSERVATIONS ON OSTEITIS DEFORMANS

INTRODUCTION

James Paget was born in 1814 in Great Yarmouth and spent his early life there. His father, Samuel Paget was an able and prosperous shipowner and ships' chandler and after The Battle of Camperdown his services to the Royal Navy were publicly commended by Lord Duncan. His mother, Sarah Elizabeth Tolner, a woman of tremendous domestic industry had artistic interests as well and was a painter of distinction - a pupil of John Crome. Samuel Paget became Mayor of Great Yarmouth, then a busy Royal Naval Base and flourishing mercantile centre. James Paget was reared in a community of great vitality and cosmopolitan complexion and in a domestic environment of comfort and elegance. Three elder brothers were educated at Charterhouse and Cambridge, one becoming a Fellow of Caius College. His father's business later encountered such adverse circumstances that, for lack of money, James was educated locally and in due course, after a brief longing for the Navy, was guided into an apprenticeship with Mr. Charles Costenor, a surgeon in Great Yarmouth. In later life he regretted only the duration of his apprenticeship but not the lack of his brother's more elaborate education.

His time with Mr. Costenor was largely spent collecting herbs and dispensing medicine. He was encouraged in the study of anatomy from amputation specimens, and attended an anatomy class for apprentices conducted in Acle by a Mr. Randall, and in later years remembered with pleasure his benefits from that teacher. After two and a half years he moved to London and enrolled as a hospital apprentice at St. Bartholomew's Hospital, and passed the examination for membership of The Royal College of Surgeons of England eighteen months later. For several years life in London was hard but Paget was not discouraged. He earned a little as sub-editor of *"The Medical Gazette"* and being a competent French and German scholar was much in demand for translation work. He became curator of the museum of St. Bartholomew's Hospital and was later engaged to write the catalogue for the museum of The Royal College of Surgeons including the Hunterian collection. By 1843 he had achieved such recognition that he was appointed lecturer in physiology at St. Bartholomew's Hospital. Subsequently, in the service of that school and of The Royal College of Surgeons he found ample fulfilment as surgeon, pathologist and teacher.

He was a man of culture and science. He travelled widely and was a close friend of Virchow and Pasteur. As a botanist he was esteemed by Hooker and Dawson Turner, both leading authorities in that science in his day. He was popular among the eminent of the literary and artistic world. Tennyson, Browning and Leigh Hunt were close friends and so were Gladstone and the Prince of Wales. He was Surgeon to The Queen. Happily during a long life of great variety and opportunity his allegiance to his clinical vocation never varied.

Osteitis deformans was a subject of special interest to him. Over a period of years, from the vast quantity of rheumatic and arthritic disease in his own practice he set aside a group of patients, finally numbering 23, clearly discerning the separate identity of their affliction. These and related matters were the subject of his now famous publications of 1876, 1882 and 1889. Paget knew and readily acknowledged the earlier single case reports by Czerny, Wrany and Wilks. Czerny in fact had used the name *'ostitis deformans'*. Wrany described his patient's illness as a *'spongy hypertrophy of the bones'* and Wilks wrote a very lucid description of the histological features of the disease.

In 1888 Sir Jonathan Hutchison, to pay tribute to his distinguished contemporary suggested that osteitis deformans might appropriately be known as Paget's disease and this is now a universal usage. Widespread and sustained interest followed Sir James Paget's discoveries. Problems of etiology and pathology have beckoned continuously and much distinguished work is recorded in these fields. Although its clinical expression is familiar the underlying pathological disturbance still eludes understanding and the etiology remains an enigma. Promising lines of theory and investigation seem often to lead in random rather than in converging directions.

In this thesis an attempt has been made to outline the present state of knowledge of osteitis deformans. Observations on a small personal series of 29 cases are recorded and appraised. The opportunity has been taken to examine the radiographs of patients with osteitis deformans who were encountered during the period 1955 - 1959 in the radiological departments of The Greenock Royal Infirmary and related hospitals and information so obtained, relating to 70 patients in all, has been incorporated in this study.

TABLE I

AUTHOR	*YEAR*	*FREQUENCY AMONG HOSPITAL ADMISSION*
Osler	*1912*	*1 in 10,000*
Hurwitz	*1913*	*1 in 10,000*
Da Costa	*1915*	*1 in 13,000*
Bird	*1927*	*1 in 3,000**
O'Reilly & Race	*1932*	*1 in 3,700 (Leeds General Hospital)* *1 in 1,400 (The London Hospital)*
Abel & Halgreen	*1938*	*1 in 1,400*
Sugarbaker	*1940*	*1 in 4,500*
Newman	*1946*	*1 in 1,548*
Rosenkrantz	*1952*	*1 in 850*

* *In this hospital 80% of admissions had Radiological investigation done.*

INCIDENCE

Osteitis deformans was thought by early authors to be a rare disease. For them diagnosis rested on the history and physical signs and no doubt many cases went unrecognised. Increasing interest and the advent of radiological methods of investigation revealed the ubiquity of the disease. Table I gives some published figures relating to the incidence of Paget's Disease among hospital admissions. These vary widely and reflect the differing interests of hospitals and the differing extent of radiological examination.

A more precise appreciation of the incidence of Paget's disease of bone was made possible by the post mortem studies carried out in Dresden by Schmorl (1932), and in this country by Collins, in Leeds and Sheffield (1936).

In 4,614 consecutive autopsies performed in subjects over 40 years of age and over a period of five years, Schmorl searched for evidence of osteitis deformans and found this on 138 occasions - an incidence of 3%. D.H. Collins in his survey modelled on Schmorl's, found 24 cases in 640 autopsies - an incidence of 3.7%. Hobson and Pemberton (1955) made an interesting and quite different approach to the same problem. In their study of *"The Health of the Elderly at Home"* they used

TABLE II.

Age Distribution	AUTHOR				
	1932 Schmorl	1936 Collins	1946 Newman	1955 Dickson Camp and Ghormley	Currie
Under 40	-	-	3.7%	8.2%	-
40 - 49	4.3%	4.2%	11.0%	19.1%	7.1%
50- 59	18.8%	33.3%	25.6%	36.5%	14.3%
60- 69	30.4%	16.7%	35.4%	26.4%	24.3%
70- 79	22.5%	29.2%	24.4% *	9.0%	30.0%
80- 89	21.0%	16.7%	-	0.8%	7.1%
90+	2.2%	-	-	-	1.4%
Un- known	0.7%	-	-	-	15.7%
TOTAL NUMBER OF CASES	138	24	82	367	70

* Newman includes all patients over 70 years in this group.

the serum alkaline phosphatase level as a screening test in a search for Paget's disease. One hundred and sixty two old age pensioners, chosen at random, were examined. Seven men and four women were found to have abnormally high levels. After further examination the diagnosis of osteitis deformans was established in six of the men and two of the women. Hobson and Pemberton concluded that if their sample truly represented all people of that age group in Sheffield then the incidence of Paget's disease there is 8.6% for men and 2.2% for women. It must be noted that all their patients were over 65 years of age.

The disease appears to occur in all social classes and in many races. It has been found in ancient remains Dickson et al (1955), Rosenkrantz et al (1952). A few reported instances of its occurrence in animals have been studied by Jaffe (1933) who doubts their authenticity. Brailsford (1938) and Mercer and Duthie (1955) also doubt if the disease occurs at all in animals.

DISTRIBUTION BY AGE.

The study of the age incidence of osteitis deformans is of considerable interest and may relate to the etiology. Many authors' findings closely correspond. Table II shows the age distribution in some published series and the figures clearly reveal a predilection for the middle-aged and elderly. Young patients however are not at all rare and in a study of the now

TABLE III

AUTHOR	*TOTAL NO. OF CASES*	*NUMBER WITH NO COMPLAINTS*	*%*
Gutman & Kasabach 1931	*116*	*27*	*23.2*
O'Reilly & Race 1932	*30*	*8*	*26.6*
Kay, Simpson & Riddoch 1934	*34*	*6*	*17.6*
Collins 1936	*24*	*7*	*29.1*
Newman 1946	*82*	*43*	*52.4*
Dickson Camp & Ghormley 1955	*367*	*75*	*20.4*
Hobson & Pemberton 1955	*8*	*5*	*62.5*
Currie	*29*	*22*	*75.9*

voluminous literature on Paget's disease the following instances were soon encountered.

Author.	Age of Patient.
Czerny.	22 years.
Paget.	28 years.
Newman.	21 years.
Irvine.	18 years. (two affected twin girls)
Brailsford.	27 years.
Collins.	30 years.
Stradford.	19 years.
Dickson Camp and Ghormley.	29 years.

Among the author's cases No.15 and No.27 appear to have begun at the ages of 30 and 26 years respectively. Dickson Camp and Ghormley, in a series of 367 patients included 30 who were under the age of 40 years.

SUBCLINICAL FORMS.

In assessing the importance of these figures it should be appreciated that many people with osteitis deformans have no complaints referable to their condition. Pagetic changes in bone are often revealed by investigations done in connection with another and perhaps unrelated disease. That such patients are a substantial proportion of most large published series is shown by Table III.

TABLE IV.

AUTHOR	TOTAL	MALE	FEMALE	MALE %	FEMALE %
1. Packard Steel & Kirkbride 1901	65	41	24	63	37
2. Roberts & Cohen 1926	16	8	8	50	50
3. Gutman & Kasabach 1931	116	58	58	50	50
4. Schmorl 1932	138	79	59	57.2	33.8
5. Kay, Simpson & Riddoch 1934	34	18	16	52.9	47.1
6. Collins 1936	24	13	11	54.1	45.8
7. Collins 1936	100	57	43	57	43
8. Brailsford 1938	154	82	72	55.4	44.6
9. Currie	70	41	29	58.6	41.4

The records of 7,964 patients cared for by the geriatric service of the Peter Bent Bingham Hospital were examined by Monroe (1951) and it emerged that only 85 of these had been found to have Paget's disease and of the 85 only 3 had related complaints. There is, unfortunately, in Monroe's publication no note of the extent to which these patients had been examined.

The present series of 29 cases contains a higher proportion of patients with related complaints - 22 out of 29 - and this is due to the number with fractures who were first encountered in the Casualty Department where the author works.

SEX DISTRIBUTION.

The sex distribution shows a preponderance of males. The findings are reflected in Table IV. Collins' first set of figures refers to his well-known autopsy series. The second set refers to a wider statistical investigation. The undoubted male preponderance is of special interest. Senile bone atrophy and osteoporosis, considered by some to have a possible etiological relationship to osteitis deformans have an even more definite female preponderance.

FAMILIAL INCIDENCE

In Paget's day and for some time after, the diagnosis of osteitis deformans was uncommon and few people had knowledge of any number of cases. It was difficult then to reach a reasoned opinion on the question of familial incidence. In 1889 Paget wrote: *"I have tried in vain to trace any hereditary tendency to the disease. I have not found it twice in the same family."* Now, detailed studies of large numbers of patients have been made on numerous occasions and many authorities are agreed that there is a familial factor.

Osteitis deformans is a common disease and it would be surprising if, from time to time and by chance alone, it did not occur in more than one member of a family. Those who doubt the existence of a familial factor seem to have this consideration in mind although McKusick (1960) who has studied this question deeply, considers that random occurrence in more than one member of a family is only a remote possibility. To offset his weighty and erudite opinion there is the disconcerting discovery by Sabatini (1948) of two instances of a husband and wife both with osteitis deformans and with no known blood relationship between them.

Certain difficulties immediately come in the way of any enquiry into the possible operation of a heritable

TABLE V.

AUTHOR	*INSTANCES OF FAMILIAL AGGREGATION*
Smith 1904	*Father and Son*
Kilner 1904	*Brother and Sister*
Stahl 1912	*Brother and Sister*
Rummert 1934	*7 Instances of 2 affected Generations* *1 Instance of 3 affected Generations* *14 Instances of affected siblings*
Lambert 1939	*3 Siblings* *1 Identical Twins*
Dickson Camp & Ghormley 1945	*1 Identical Twins*
Koller 1946	*1 Identical Twins*
Mozer 1946	*1 Identical Twins*
Martin 1947	*1 Identical Twins*
Schmorl 1948	*3 Brothers*
Murphy 1950	*Brother and Sister*
Irvine 1953	*Father and Twin Daughters*

factor in the causation of the disease. Often when a case is encountered the siblings are widely scattered. Death has depleted the ranks of the previous generation and the patient's own offspring have not yet reached the age groups in which the disease commonly occurs. Subclinical forms of the disease are common and relatives thus affected may escape suspicion.

Despite these difficulties however, some factual evidence has accumulated to support the widespread belief in the operation of a hereditary tendency.

Familial aggregations of two patients in the same or succeeding generations are recorded many times and in the present series of 29 patients Case No.3 had an affected sister and Case No.15 had an affected father.

Rummert (1934) has collected 14 instances of affected siblings and seven instances of two successively affected generations and one instance of three successively affected generations. McKusick knows one family in which he believes the disease to have affected four successive generations.

Concordance in identical twins has been observed several times.

Authors who have had the opportunity to examine large series and who have enquired into this question give figures which are shown in Tables V and VI.

TABLE VI

AUTHOR	NO. OF INSTANCES OF FAMILIAL OCCURENCE	TOTAL NO. OF CASES	PER CENTAGE
Elmslie 1908	7	90	7.8
Kay, Simpson & Riddoch 1934	2	34	5.9
Dickson, Camp & Ghormley 1945	16	367	4.4
Newman 1946	1	82	1.2
Currie	2	29	6.9

McKusick concluded that a heritable factor is of importance and he believed the evidence points to transmission by a simple autosomal Mendelian dominant. He offers the last viewpoint tentatively, and quotes the different opinion held by Ashley-Montague, that a sex-linked recessive gene carries the tendency to osteitis deformans.

CLINICAL FEATURES

The clinical manifestations of osteitis deformans are few. Pain and deformity are the principal ones. Headache is common - undue muscular weakness is less so. Pathological fractures occur frequently and sarcoma occasionally. This much is sure. Also it is established that in some cases there are alterations in cardiac output and in the blood flow in affected bones leading to deleterious effects and these are considered later.

Here, however, it is appropriate to note certain other abnormalities particularly relating to the vascular and nervous systems and to the joints. These are so frequently associated with osteitis deformans that their status as integral parts of the disease has been widely accepted. In the main, they are common attributes of middle and later life and in respect of them statistical comparison with random samples of similar age would seem desirable. I have found no

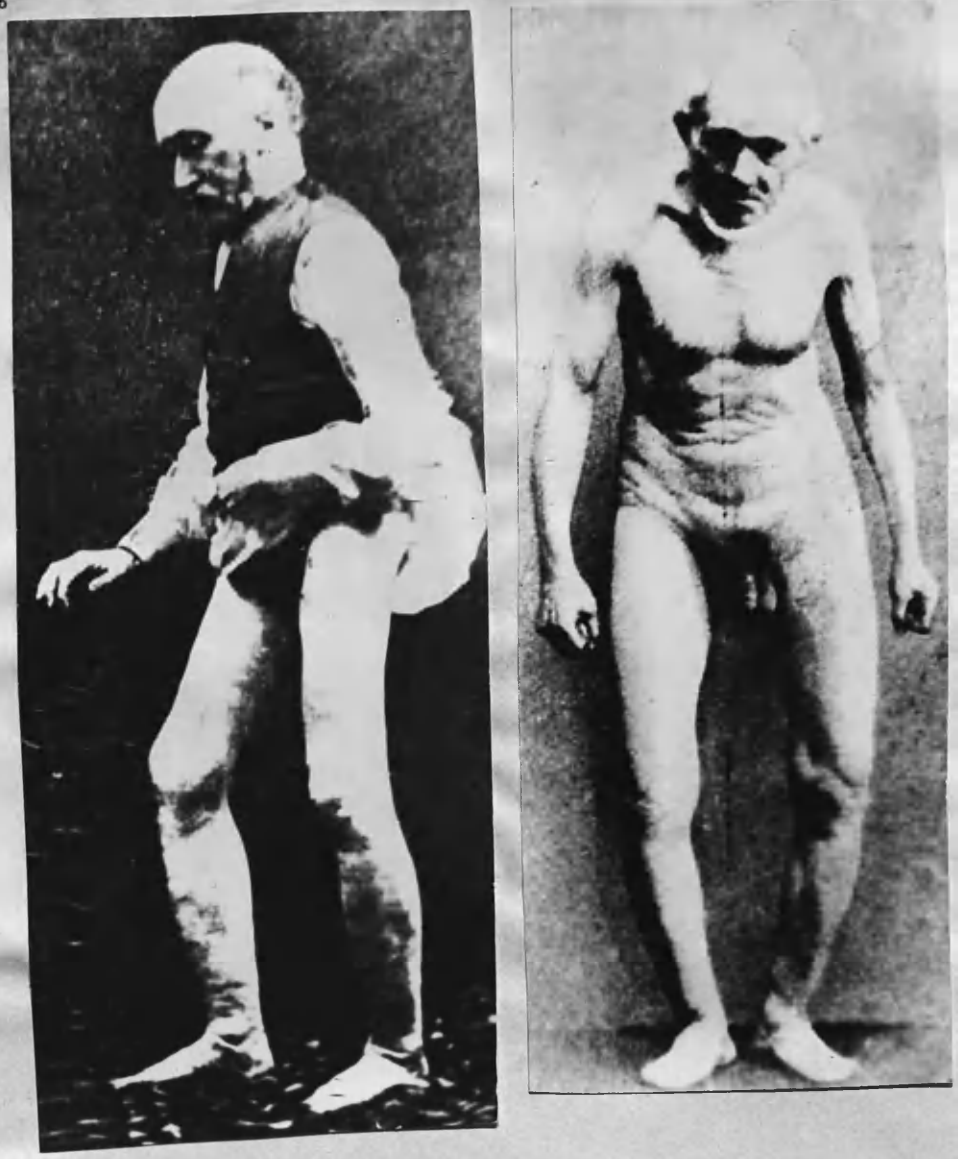

Fig. 1

Fig. 1. *While several of Sir James Paget's early illustrations have now a "classic" status and are well known these pictures are also of some historical interest. They are reproduced from a syn on osteitis deformans in 'The Illustrated Medical News' of 1884. 'A' is contributed by Sir James Paget himself and 'B' is by Mr. John R. Lunn who even at that early date had an active interest in and considerable experience of the disease.*

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9/3/61.

Alistair John Cameron.

record of any investigation of this type and views established before statistical study became popular lack the authority which such examination might confer.

PAIN.

Pain is the commonest complaint. It is generally constant, often severe, and there may be long remissions. Kay, Simpson and Riddoch (1934) and Gutman and Kasabach (1936) have drawn attention to a group of patients where pain is of a paroxysmal type and of extreme severity. Case No. 1 in the present series had such pain and was often close to fainting from the severity of the attacks. There is no constant relation to exercise or to changes in the weather.

DEFORMITY.*

Deformity is frequent and enlargement of the head is the most commonly encountered. This may be asymmetrical. There may be loss of stature from kyphosis and the head sinks in between the shoulders. The thighs bend forwards and outwards. In less severe cases the big head, kyphotic stoop and long reach of the arms may lend the patient a certain air of distinction. Elongation of the radius when the ulna is normal produces a pronation deformity, not often mentioned but remarked upon by Symmonds (1881) and Brailsford (1928). Paget observes (and it is quite noteworthy) that as the disease increases in severity

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* *See Fig. 1*

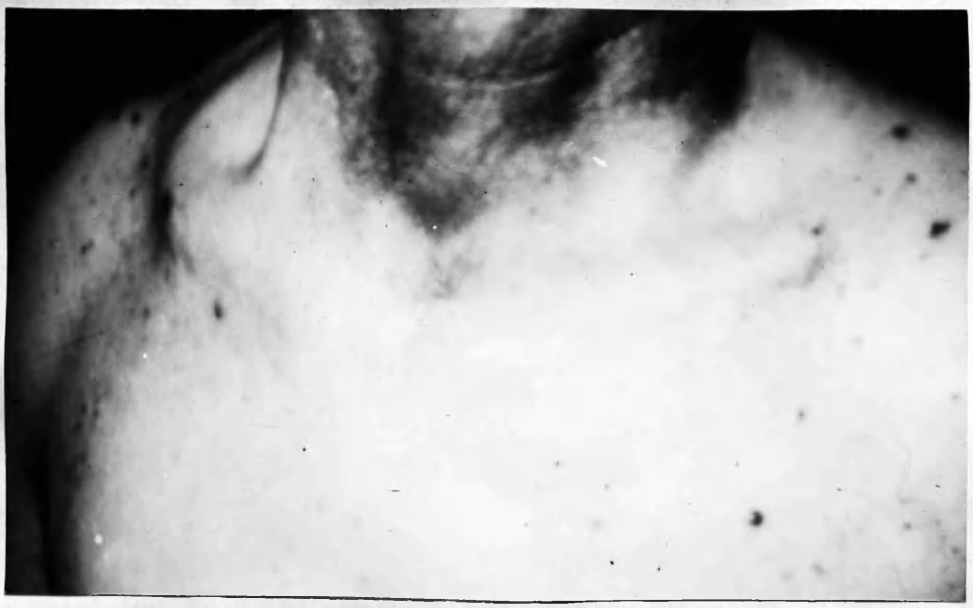

Fig. 2 A.

Fig. 2 'A'. Shows the marked hyperostosis of the clavicle to which the patient's attention was first drawn when he was 30 years old.

Fig. 2 'B'. Shows the deformed tibiae in the same patient.

Fig. 2 B.

the patients come to bear some resemblance to each other. Coxa vara results from involvement of the femoral neck. Deformity may either precede or follow the experience of pain and in many instances it is remarkable that severe and long standing deformities have never been painful.* Among the 116 patients studied by Gutman and Kasabach 48 had long bone deformities and in 22 instances the deformity preceded the pain.

Facial deformity with an underlying osteodystrophy is often diagnosed as leontiasis ossea. It has been disputed if such changes might also result from osteitis deformans and if, indeed, the two diseases may not be the same. The jaws do not seem to have been involved in any of Paget's cases and Schmorl makes no mention of this. Mercer (1950) believes the facial bones are never involved and Fairbanks (1951) says: *"The evidence that leontiasis ossea is not the same as Paget's disease is overwhelming."* Knaggs (1926) believed that minor degrees of facial bone involvement were common or probably usually overlooked. Muir (1958) accepted that the two diseases may not be distinct pathological entities and Jaffe (1933) though not inclining to a belief in their separate identity feels that the question is still undecided.

A difficulty is that leontiasis ossea generally is diagnosed in young adults and osteitis deformans at a

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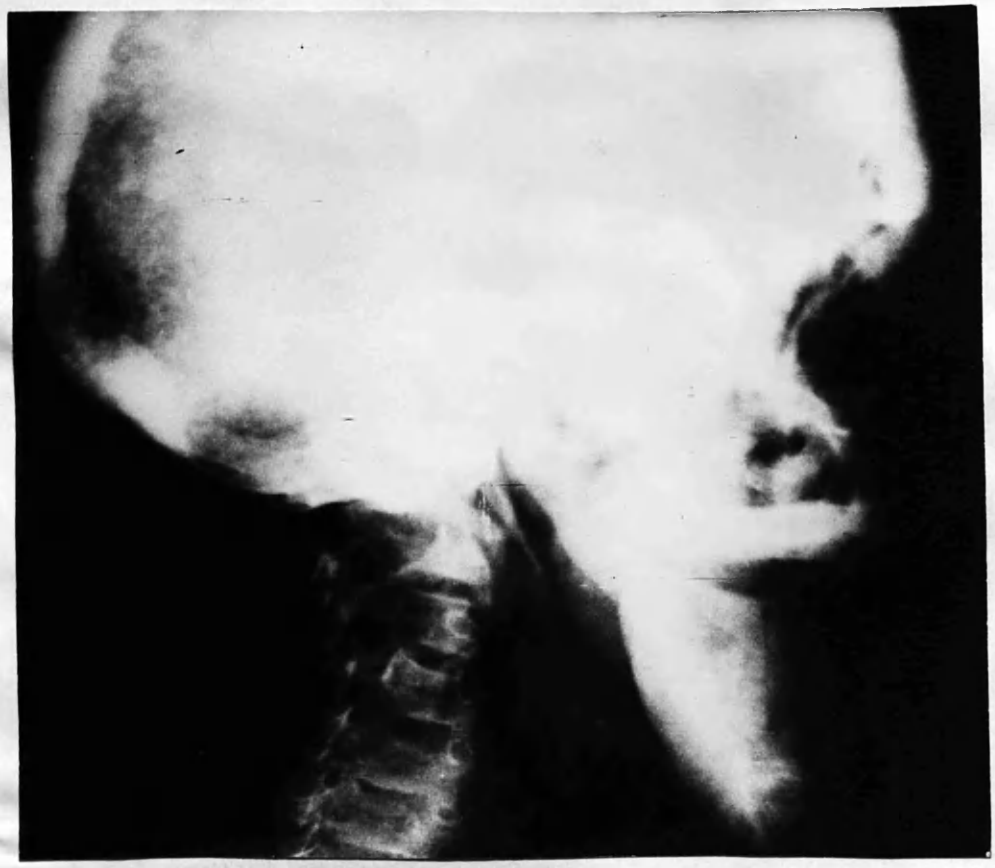
* *See Figs. 2A and 2B.*



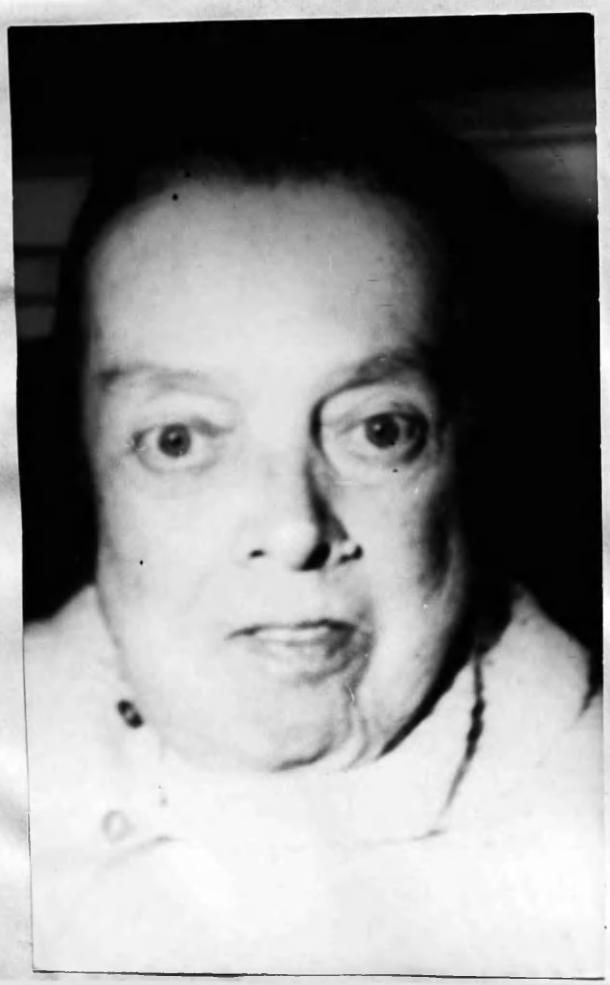


Fig. 3. 'A' *X-Ray reveals a densely sclerotic mandible. The head is severely affected and there are other lesions throughout the skeleton.*

Fig. 3. 'B' *Shows the marked facial deformity resulting from the jaw affection. Despite the exophthalmos there were no signs of hyperthyroidism*

much later age. In general, osteitis deformans has often been observed in the mandible in association with lesions of the skull cap, e.g., 23 out of 138 cases described by Stafne and Austin (1938). Cooke (1956) described 15 cases in which the maxilla was involved. Snapper (1943) and Davis (1956) declared that histologically the lesions of leontiasis ossea and osteitis deformans are indistinguishable. Weinman and Sicker (1955) believe that the two diseases are the same. Of 34 cases of osteitis deformans described by Kay, Simpson and Riddoch, two had also leontiasis ossea. Davis describes cases in which Pagetic changes in long bones were found in later life following an earlier diagnosis of leontiasis ossea. So does Snapper.

The position would seem to be that Virchow's term "*Leontiasis ossea*" should be used in a non-specific way or that cases so described will probably in some instances, if not in a majority, prove to be osteitis deformans.

HEADACHE.

Headache is common and severe. In the nine patients so affected in the present series it has accompanied involvement of the skull in seven, two of whom also had hypertension.

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* *See Figs. 3A and 3B.*

MUSCULAR WEAKNESS.

Muscular weakness of undue degree was noted in five patients of the present series. Roberts and Cohen (1926), Gutman and Kasabach (1936) Helfet (1940), and Dickson, Camp and Ghormley (1955) all made the same observation and Helfet regards its frequent occurrence as supporting evidence in his attempt to relate the disease to hyperparathyroidism.

UNDUE SKIN HEAT.

Undue heat in the skin overlying affected bones is sometimes observed and in Case No. 12 has been the only abnormality associated with long standing gross deformity of the femur. Case No. 15 had severe peroxysmal frontal headache associated with fairly gross deformity and during the attacks the skin on the frontal area became red, swollen and shiny. Kilner (1904) published the only record of similar changes that I have encountered. In this connection it is interesting to note Elting's (1901) description of the pain as 'congestive'.

DEAFNESS.

This is reported in a high proportion of cases. It is generally not due to any involvement of the ear or auditory nerve in the bone lesions of Paget's disease and Monroe declares that it is no commoner among Pagetic patients than among the generality of people of the same

age group. Hobson and Pemberton reached the same conclusion. Of Kay, Simpson and Riddoch's cases 10 were deaf but examination revealed that this was due to chronic inflammatory middle ear disease in nine patients, and to oto-sclerosis in the tenth. Hobson and Pemberton's four deaf cases all had chronic suppurative otitis media. In the present series there were four deaf patients and all had old-standing chronic inflammatory disease of the middle ears. Gutman and Kasabach found 26 deaf patients among their total of 116 but they gave no details as to the cause of the deafness. On the other hand, of 51 cases reported by Sugarbaker (1940) six had nerve deafness and only one had chronic suppurative otitis media. Snapper says deafness is more likely to result from osteitis deformans of the petrous temporal bones and destruction of the inner ears than from pressure on the auditory nerves and it has been argued that oto-sclerosis is a monostotic form of Paget's disease.

CARDIO-VASCULAR ABNORMALITIES.

Degenerative Changes.

Elmslie (1908) in an early review of 90 cases said then that *"arterio-sclerosis was more common than can be accounted for on the grounds of age alone"*. Many authors, including Sugarbaker, Roberts and Cohen and Snapper have supported this view. Cone says: *"Clinical observations coupled with the pathologidal findings in more than nine hundred autopsies convince me that Paget's disease is the result of chronic cardio-vascular disease"*. Knaggs says, *"Atheromatous arteries are almost a constant feature in these cases.."* and Locke (1921) that *"More or less generalised arterio-sclerosis may be regarded as an almost universal manifestation of the disease"*. Twenty-nine out of 34 cases reported by Kay et al were arterio-sclerotic. Among my own patients clinical examination of the radial artery revealed arterio-sclerosis in 16 instances. In 6 cases the radial artery was normal and in the other cases this point was not recorded. Vascular calcification was revealed in the X-Rays of 11 patients out of 69.

The lack of any record of soft tissue changes in the extremities due to ischaemia is a striking feature of the literature of Paget's disease of bone. None of the present series of cases showed any such change.

Harrison and Lennox (1948) say that although occlusive vascular disease is not unduly common in osteitis deformans, Monkeberg's sclerosis is, but I have found no cases of this type.

Calcification in the heart valves and chordae tendiniae is recorded by Stahl (1912) and Harrison and Lennox describe the same in 6 out of 13 cases of wide-spread osteitis deformans saying that this is five times the rate for non-Pagetic patients of the same age. The authors quoted here have on occasion attributed heart block to the presence of metastatic calcification in the interventricular septum of patients with osteitis deformans.

That heart failure occurs frequently is generally accepted, but here again statements are vague and unsupported or feebly supported. However, of Newman's 9 clinically manifest cases 6 had been admitted to hospital for cardiac disabilities.

Sornberger and Smedal (1952) suggest that the limited physical activity of these patients masks their cardio-vascular and respiratory insufficiency, causing inadequate alveolar exchange. Kyphotic chest deformity and chronic carbon dioxide retention may, by causing pulmonary vaso-constriction, lead to heart failure.

Increased cardiac output in patients with osteitis deformans has been described by Edholm, Howarth and

TABLE VIII

	Total No. of Cases	Arterio-Sclerotic	Hypertension	Low diastolic blood pressure	High pulse pressure	Heart Enlarged
Kay, Simpson & Riddoch (1934)	34	29	13	5	14	14
Rosenkrantz, Wolf and Kaicher (1952)	111	2	17	-	-	-
Edholm & Howarth (1953)	17	-	-	-	2	5 ou of 6 X-Ra
Currie	29	17	15	0	10	*

* 18 X ray records of heart size were available from the total of 70 patients; 6 of these showed cardiac enlargement.

McMichael (1945) in this country, and in France by Bricaud et al (1955), Rutishauser et al (1954), Léquime and Denolin (1955), Molimard and Lièvre (1958), and in America, Rappaport et al (1957), agree that this occurs generally in association with a widespread affection, involving one-third or more of the entire skeleton. There is usually an associated high pulse pressure and the inference generally made is that an arterio-venous shunt exists in the affected bones producing this effect by increased blood-flow there, and also producing enlargement of the heart and in some cases a high output type of heart failure. While this is a reasonable inference no such fistulous connection has ever been demonstrated.

HYPERTENSION.

Hypertension is also common and Table VIII gives the incidence of this in the present series and also the incidence of high pulse pressure, and radiographically demonstrated cardiac enlargement.

ABNORMALITIES OF THE CENTRAL NERVOUS SYSTEM.

Apart from the question of impaired sight and hearing there occurs the serious complication of spinal cord compression due to the collapse of affected vertebrae. In addition to minor degress of pressure on the cord and nerve roots complete paraplegia has been recorded many times (Kay et al and Dickson et al (1945)). Burrows (1950) has said that antero-lateral decompression of the cord may be necessary for this complication.

While it is generally agreed that the skull cap enlarges outwards, a relative protusion inwards of the basi-occiput and basi-sphenoid has been said to produce effects by stretching of the free edge of the tentorium cerebelli. While the theoretical possibility of cranial nerve and brain stem irritation arising in this way cannot be denied I have not recognised any instance of this and have not found any recorded. The term 'convexobasie' describing the radiological appearance of this deformity is often encountered in French writing but not elsewhere, though Snapper and Brailsford have both noted it.

DIFFICULTY IN WALKING.

Difficulty in walking has been noted by Gutman and Kasabach and Sugarbaker, and was present in two cases of this series. In respect of these two the associated deformities provided sufficient explanation without

invoking the existence of a nervous cause nor was any evidence of this found. Gutman and Kasabach and Sugarbaker simply record this point without elaboration or explanation.

MENTAL DISTURBANCES.

Many authors record occasional cases of associated mental abnormalities but Dickson et al and Hobson and Pemberton seem to give a true assessment when they say that mental disturbances are no commoner among patients with osteitis deformans than among the generality of people of the same age.

CALCULI.

Dickson, Camp and Ghormley found 22 patients with urinary stones among their total of 367 and it is often said that there is a high risk of stone formation in osteitis deformans. As urography will fortuitously tend to reveal bony abnormalities in those parts of the skeleton most liable to show Pagetic changes, it is to be expected that a disproportionate number of patients subjected to this examination will find their way into collected series. Newman discovered four cases of urinary calculi among 82 patients with osteitis deformans. There were stones in 10% of Snapper's material. There were none seen in the X-Rays of 70 patients examined by me.

A more striking observation is the occurrence of salivary calculi in 20 out of 111 cases reviewed by

TABLE VII

% INCIDENCE OF CLINICAL FEATURES	Gutman & Kasabach, 1931		Kay Simpson & Riddoch, 1934	Sugarbaker, 1940	Rosenkrantz Wolf & Kaicher, 1952	Dickson Camp & Ghormley, 1955	Currie
TOTAL NUMBER OF CASES IN SERIES	161		34	51	111	367	29
	1	2	3	4	5	6	7
Pain in limbs, back and hips	31.0	54.0	76.5	29.4	49.5	47.4	51.7
Muscular Weakness	-	-	-	3.9	-	13.4	17.2
Headache	5.1	26.1	23.5	3.9	12.6	17.4	65.5
Deformity including Big Head	25.3	65.5	-	52.9	49.5	-	58.6
Local Heat over lesion	-	-	-	3.9	-	-	6.9
Deafness	2.5	2.0	29.4	11.8	12.6	-	
Fractures	5.1	12.9	14.7	-	15.3	21.0	27.6
Vertigo	-	18.9	-	-	-	10.1	-
Difficulty in Walking	4.3	32.7	-	7.8	7.2	-	6.9
Paraplegia	-	-	5.9	-	0.9	-	-
Arthritis	-	-	8.8	-	34.2	-	34.5

In Columns 1 and 2 Gutman and Kasabach have shown the clinical features at the onset of the disease and at a later stage in development. The onset is insidious and many observers have found difficulty in recognising in retrospect the initial disturbances. This has been my own experience and I have been unable reliably to make a similar analysis.

Rosenkrantz who suggested that the salivary excretion of phosphatase might be the cause of this, a point which does not seem to have been followed up.

An attempt is made to tabulate information culled from several analyses and Table VIIIgives a partial account of the clinical presentation of osteitis deformans. Features particularly relating to the cardio-vascular system are shown in Table VII . The complications of pathological fracture and sarcoma are considered at greater length in the following two sections.

PATHOLOGICAL FRACTURES

Pathological fractures commonly complicate the course of osteitis deformans. The 29 patients who form the basis of the present study sustained the following fractures:-

Case No. 2 - fracture of neck of femur.

Case No. 4 - fracture of neck of femur (osteo-porosis).

Case No. 9 - fracture of mid-shaft of left femur (osteitis deformans) associated with fractures of right tibia and fibula (osteo-porosis but not osteitis deformans),

Case No. 24 - fracture of shaft of right humerus (osteitis deformans).

Case No. 25 - subtrochanteric fracture of left femur (osteitis deformans).

Case No. 27 - fracture of upper third of left femur (osteitis deformans).

Case No. 29 - fracture of patella (osteitis deformans).

When the further series of X-Rays were examined these were also found:-

Case (a) - fracture of humerus (osteitis deformans).

Case (b) - fracture of neck of femur.

Case (c) - two fractures of shaft of femur (osteitis deformans).

Case (d) - compression fracture of dorsal spine (osteitis deformans).

TABLE IX

AUTHOR	NUMBER OF FRACTURES	TOTAL NUMBER OF CASES	PERCENTAGE OF FRACTURES
Gutman & Kasabach 1931	14	116	12.0%
Kay, Simpson & Riddoch 1934	4	34	11.7%
Brailsford 1938	23	154	14.0%
Dickson et al 1945	62	367	16.8%
Newman 1946	15	82	18.3%
Rosenkrantz Wolf, Kaicher 1952	19	111	17.1%
Lake 1957	78	255	30.5%
Currie	13	70	18.6%

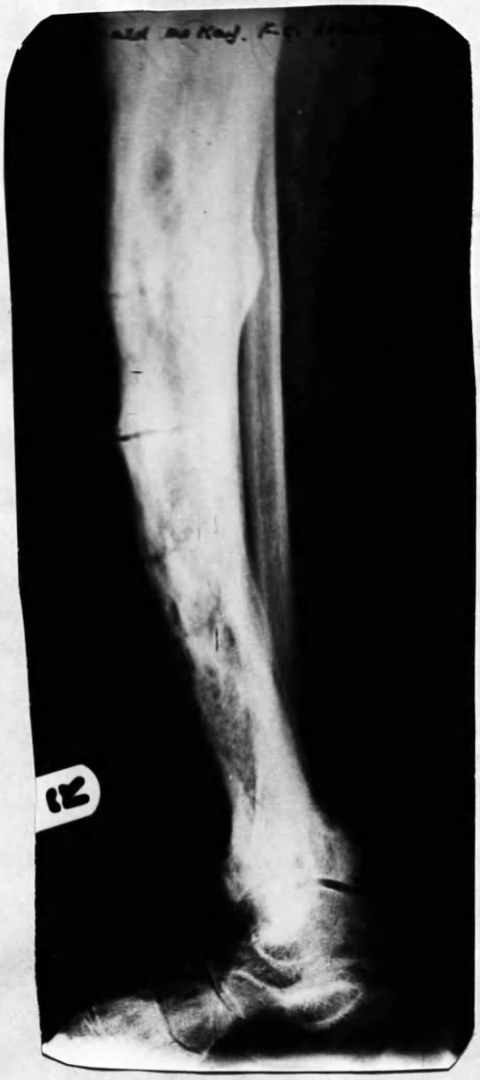

Fig. 4.

Fig. 4. Shows the typical appearance on X-Ray of multiple pseudo-fractures - incomplete, and all on the convexity of the bone.

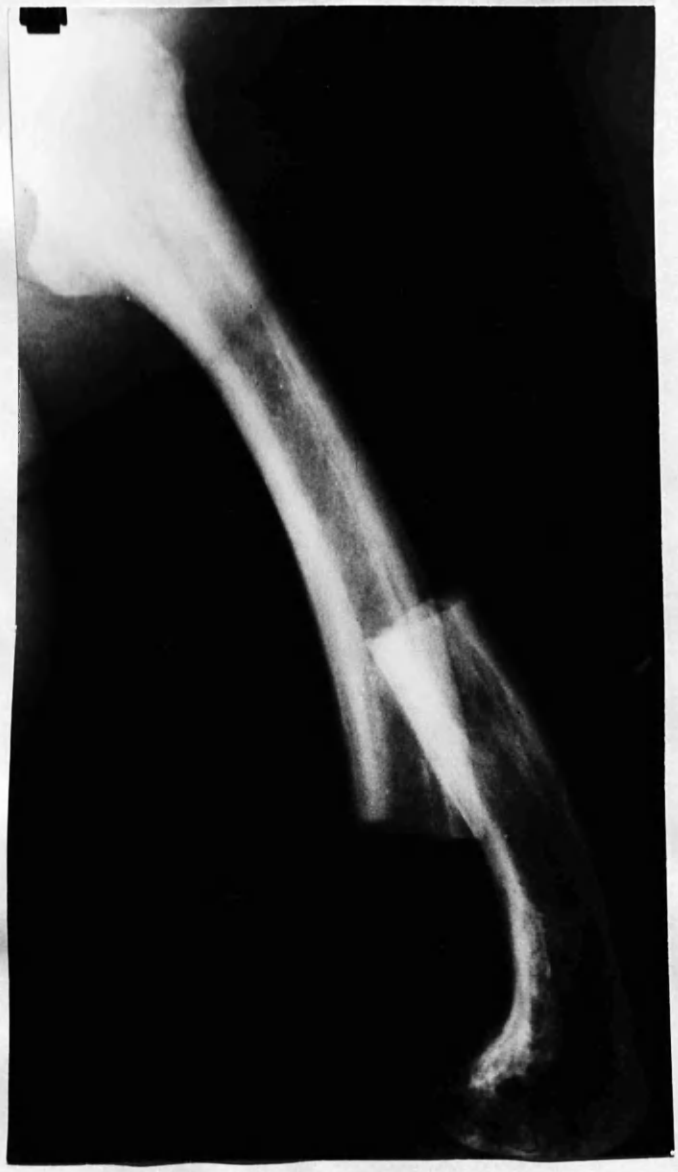

Fig. 5.

Fig. 5. *A typical pathological fracture in Osteitis Deformans. Case No. 9.*

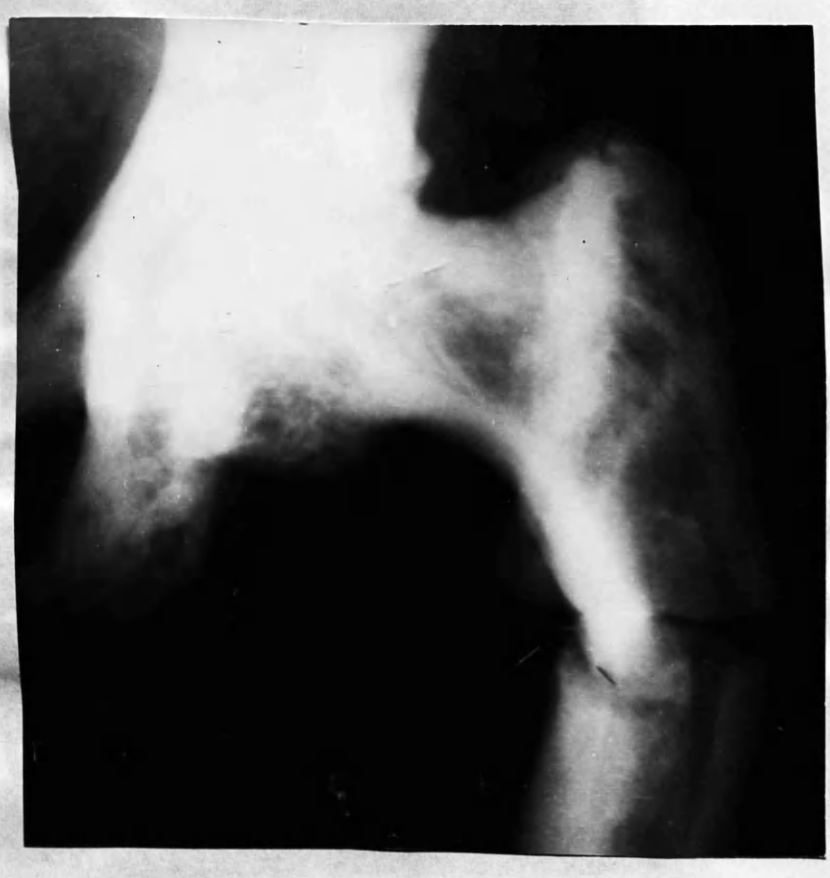

Fig. 6.

Fig. 6. A typical pathological fracture occurring in Osteitis Deformans. Case No. 28.

Case (e) - compression fracture of lumbar spine (osteitis deformans).

Case (f) - fracture of pelvis (osteitis deformans).

Case (g) - fracture of tibia (osteo porosis).

Case (h) - fracture of tibia (osteitis deformans).

The incidence of fractures in published series is shown in Table VIII and IX.

There are several arresting features of the pathological fracture occurring in this disease.* It is nearly always in a proliferative or absorptive rather than in a sclerotic area. The fractures generally unite rapidly. In the occasional instance of fracture in a sclerotic area Lake (1958) has noted a tendency to refracture at the same site. A commonly encountered radiographic appearance is the pseudo-fracture which is often multiple. This may be observed unchanged in serial X-Rays taken at intervals of several years. It appears as an incomplete fracture involving one cortex, always on a convexity. The significance of this X-Ray appearance is disputed and is discussed later but here it is worth noting that in long bones the pathological fracture of osteitis deformans is usually very regular - a transverse fracture exactly at right angles to the long axis of the bone and looking as if it had been cut by a razor. The appearance is what one might expect from a complete break occurring through one of these pseudo-fractures.

Pathological fractures were the subject of study in a wider concept by Ghormley, Sutherland & Pollock (1937)

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* *See Figs. 4, 5 and 6.*

and they noted that among 269 pathological fractures due to benign lesions, osteitis deformans accounted for 20 (8%).

In the eight patients cared for by me who sustained fractures, these occurred through Pagetic bone in five out of the eight. Of the 15 fractures occurring in Newman's series of 82 patients, nine only were in Pagetic bones. None of the other authors quoted in Table VII make it clear what proportion of the fractures were in Pagetic bones and what proportion were in osteoporotic or in normal bones, and it would seem desirable to make these distinctions. Of the 70 patients studied by X-Ray (and the above 29 are included) 18 fractures occurred, 11 being in areas of osteitis deformans, five in bones with osteo-porosis, and the remainder in bones which appeared normal in other aspects.

SARCOMA.

Packard Steele & Kirkbride (1901) were among the first to suspect a tendency to sarcoma. When the wide prevalence of the disease in the community was established by Schmorl and by Collins, doubts were expressed if there was any such tendency, and some authors Speiser (1927) and Moehling (1936) believed no such tendency existed. Coley and Sharp (1931) seem to have placed the question beyond doubt and a proclivity to form sarcomata must be admitted as a feature of osteitis deformans. Jaffe considers that

this feature helps to establish the separate identity of Paget's disease from the other bone dystrophies. Snapper states that the tumour never arises in a sclerolic area. There is usually a palpable and often visible tumour and associated bone destruction is extensive. Only the Pagetic bones in an affected patient seem to develop sarcomata and multiple primary tumours may occur without the simultaneous presence of demonstrable visceral metastases.

Albert von Albertini in 1927 reported in detail a case of sarcoma complicating Paget's disease, in which throughout the skeleton other Pagetic bones showed tremendous fibrous proliferative changes in the marrow, which he thought to be pre-sarcomatous. Collins noted the constant association of marrow fibrosis with tumour. And in the same vein Lassère (1950) perhaps slightly over-stating the case, declares "*Nous pensons plutot a un état prétumoral et susceptibles de terribles reveils*".

Collins asserts that the tumour is always a spindle-celled sarcoma but many grant the occasional occurrence of chondro-sarcoma, fibro-sarcoma and malignant osteo-clastoma (Willis (1950), Mercer & Duthie (1955), Ledoux & Lebard (1956).

Sumney and Pressley (1946) reviewed 77 cases of sarcoma found in the Mayo Clinic in patients of 40 years of age and upwards, and 28% were complications of Paget's disease.

Mercer in a similar survey found the incidence to be 25%. Of Sumney and Pressley's 77 cases, 26 were considered to have multiple primary tumours.

The work by Coley and Sharp is probably the most celebrated in this connection. They discovered the sarcoma in Paget's disease to be very rare under the age of 40 years, the average age being 57.7. The proportion of males to females was 5 : 1. It is on interest that the male preponderance for Paget's sarcoma is greater than the male preponderance for osteitis deformans, not so complicated.

In the group studied by Coley and Sharp, 33 patients over the age of 50 who developed an osteogenic sarcoma survived an average of 24 months following diagnosis. A separate group of 15, in whom the tumour arose in a Pagetic bone survided on the average for only 14.8 months.

Bad though the prognosis is for sarcoma in general, it is even worse when encountered as a development of osteitis deformans. This relates to the advanced age of many patients, the occurrence of the tumour in sites unsuitable for treatment by amputation, the presence of multiple primary tumours, and the frequently delayed diagnosis.

Stevens and Lennox (1958) reporting a single case of survival for seven years following amputation, mention two other similar cases of which they have knowledge. Cowie, Barr and Dudley report a similar case.

TABLE X

AUTHOR	NO. OF PATIENTS DEVELOPING SARCOMA	TOTAL NO. OF PATIENTS	PERCENTAGE DEVELOPING SARCOMA
Packard Steele & Kirkbride (1901)	5	66	7.5
Speiser (1927)	6	150	4.0
Kay, Simpson & Riddoch (1934)	1	34	2.9
Dickson, Camp & Ghormley (1945)	3	367	0.8
Newman (1946)	2	82	2.4
Cook	1	15	6.6
Currie	1	70	1.3

Without giving supporting figures these authors give the following estimates -

Newman	2.4%
Dacosta, Funk, Bergeim and Hawk	9.5%
Geschichter & Copeland	5.7%

In general, more recent estimates are lower than earlier ones, the explanation being the increasing detection by radiography of uncomplicated cases of Osteitis Deformans.

TABLE XI

Site of Tumour	Femur	Humerus	Skull	Tibia	Scapula	Vertebrae	Ilium	Ribs	Pelvis	Radius	Ulna	Sacrium	Clavicle
Single Sarcoma	11	11	6	6	3	1	3	0	0	2	0	1	0
Multiple Sarcoma	13	9	9	7	3	5	3	3	3	1	2	0	3
TOTAL	24	20	15	13	6	6	6	3	3	3	2	1	3

The Table is a quotation of the figures given by Sumney & Pressley who reviewed all the published cases which they could find up to 1946. There has been no comparable study since then. Most of the larger reviews were available to them except those by Dickson Camp & Ghormley with 357 cases in 1945, Newman with 82 cases in 1946 and Rosenkrantz et al who reviewed 111 cases in 1952. Together these authors found another 5 sarcomata out of a total of 570 cases.

Table X gives some assessments of the incidence of sarcoma and Table XI shows its distribution.

Among the X-Rays of the 70 patients studied here, one instance of sarcoma of the pelvis occurred in a case of many years standing.

Collins believes that while the entity of the Paget's sarcoma cannot be denied, the risk to the individual patient has probably been assessed too highly in the past.

OSTEO-POROSIS CIRCUMSCRIPTA.

Osteo-porosis Circumscripta is common and appears in the skull films of 10% of cases - Collins (1956). Of Cook's (1956) 15 cases of Paget's disease of the jaws, 14 had skull involvment with osteo-porosis circumscripta in five of these 14. Without quoting figures Ledoux-Lebard et al (1955), Busalotti and Doria (1956), Gaucher and Gauthier (1958) and Lievre and Épiney (1950) all declare it to be a manifestation of osteitis deformans. Some believe that osteo-porosis circumscripta is a result of any rapid resorptive process and not specifically a Pagetic lesion though granting that that is probably the commonest cause. This is the view held by Snapper, Fairbank and Windholz.

Dickson and others have obviously accepted that osteo-porosis circumscripta is a form of osteitis deformans. Of 117 cases in their series known to have

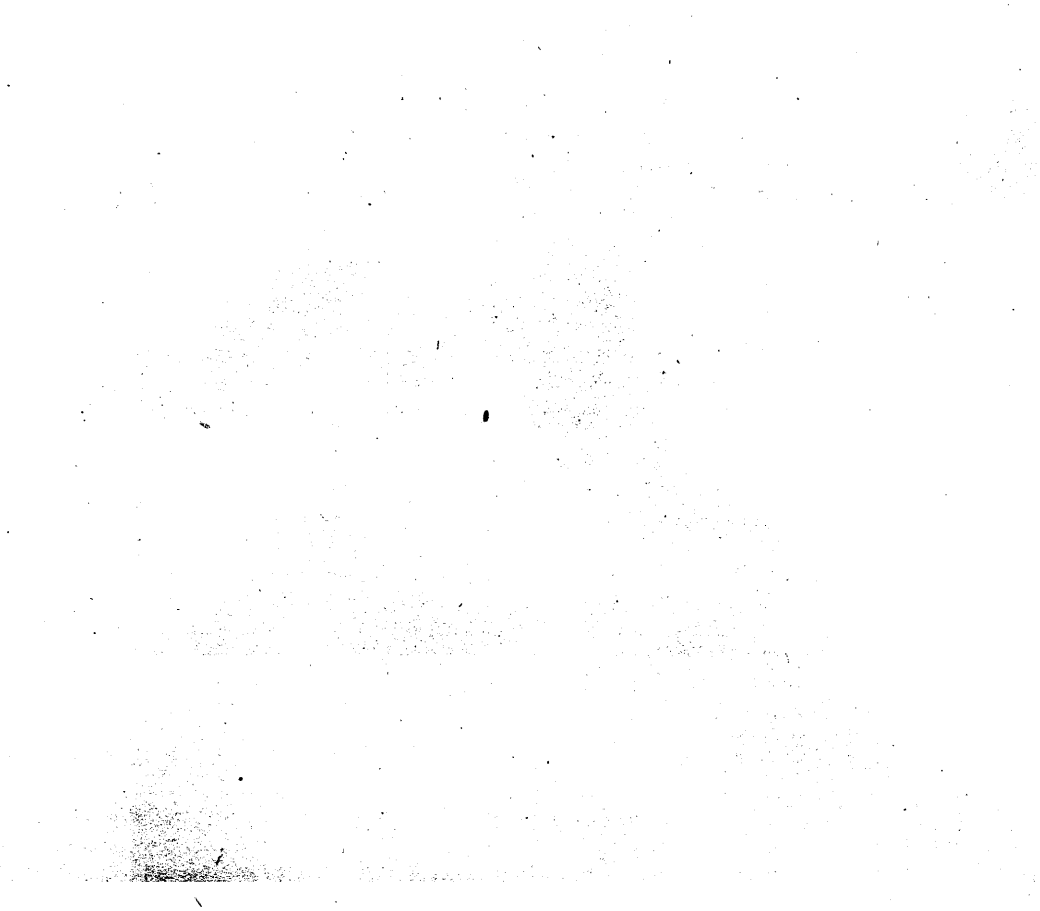
skull involvment, 26 showed osteo-porosis circumscripta and of these 26, only 5 five showed evidence of osteitis deformans elsewhere.

Roberts and Cohen (1926) and Hodges (1959) have described similar appearances in the tibia and humerus and one wonders if these may be the same lesions described by Fairbank in the radius and fibula. It is, of course to be differentiated from the similar appearances produced by Hand-Schuller-Christian's disease.

Followed over the years typical Pagetic changes are generally seen to appear in these circumscribed areas of osteo-porosis (Nauden E.P. and Calvel, 1956). Collins and Wynn (1955) in 1,369 anatomical (as opposed to radiological) examinations at post-mortem in subjects over the age of 40 years, encountered five instances. The patients had been 43, 57, 61, 68 and 80 years old. Four were men and there was one woman. Only one was recognised to have osteitis deformans in other sites.

The term denotes the demonstration by radiography of the existence of a patch of greatly diminished density in the skull cap, usually in the occipital or frontal regions and its relation to osteitis deformans has given rise to much discussion. Schmorl noted in several cases a change in the bone which he described as "haemorrhagic infarcation", and some have taken this to be the probable anatomical basis of the X-Ray abnormality. Collins and Wynn are inclined to doubt this and Windholz (1945) is doubtful also. There are no X-Rays relating to Schmorl's observation. The radiographic abnormality

was first noted by Schuller and Sosman (1926) but historical examination revealed that osteitis fibrosa could be the cause of it. That osteo-porosis circumscripta is commonly associated with osteitis deformans is beyond all doubt. Collins says that 10% of patients with osteitis deformans have osteo-porosis circumscripta.



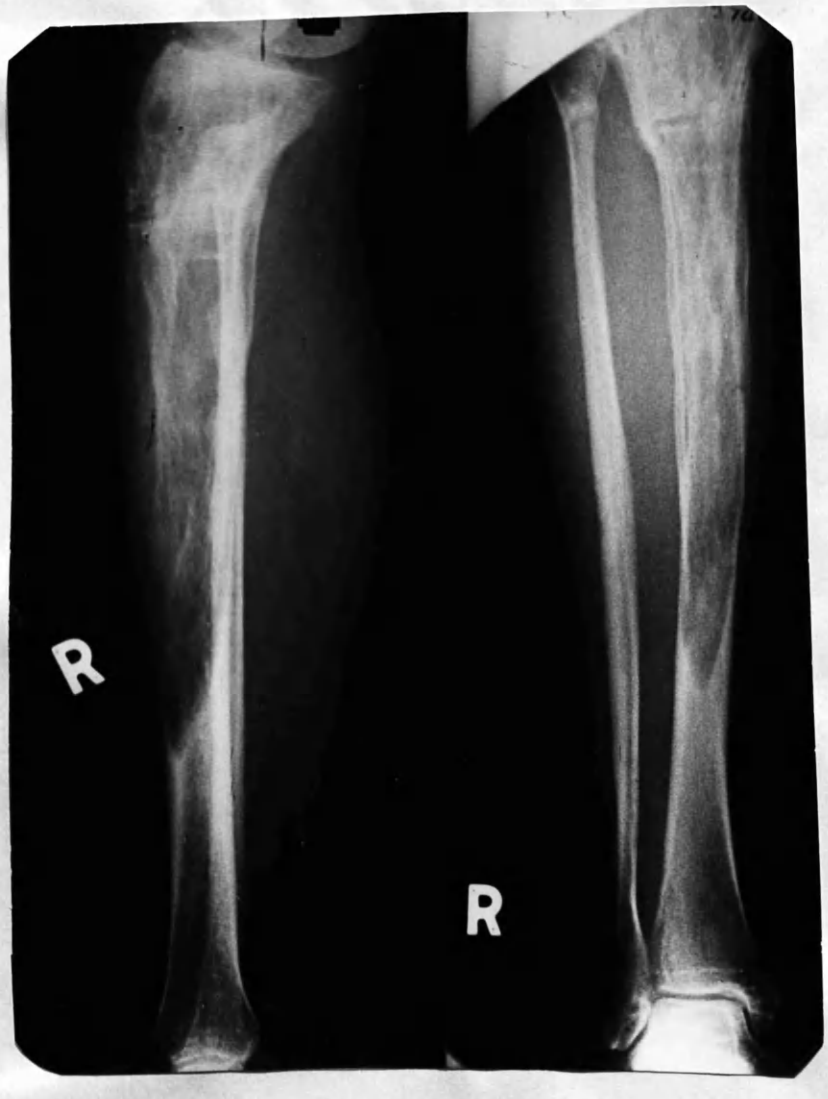


Fig. 7.

Fig. 7. *The sharp demarcation of pagetic bone from normal bone is seen to have the pointed lance head extremity - a feature thought by Brailsford to have diagnostic value.*

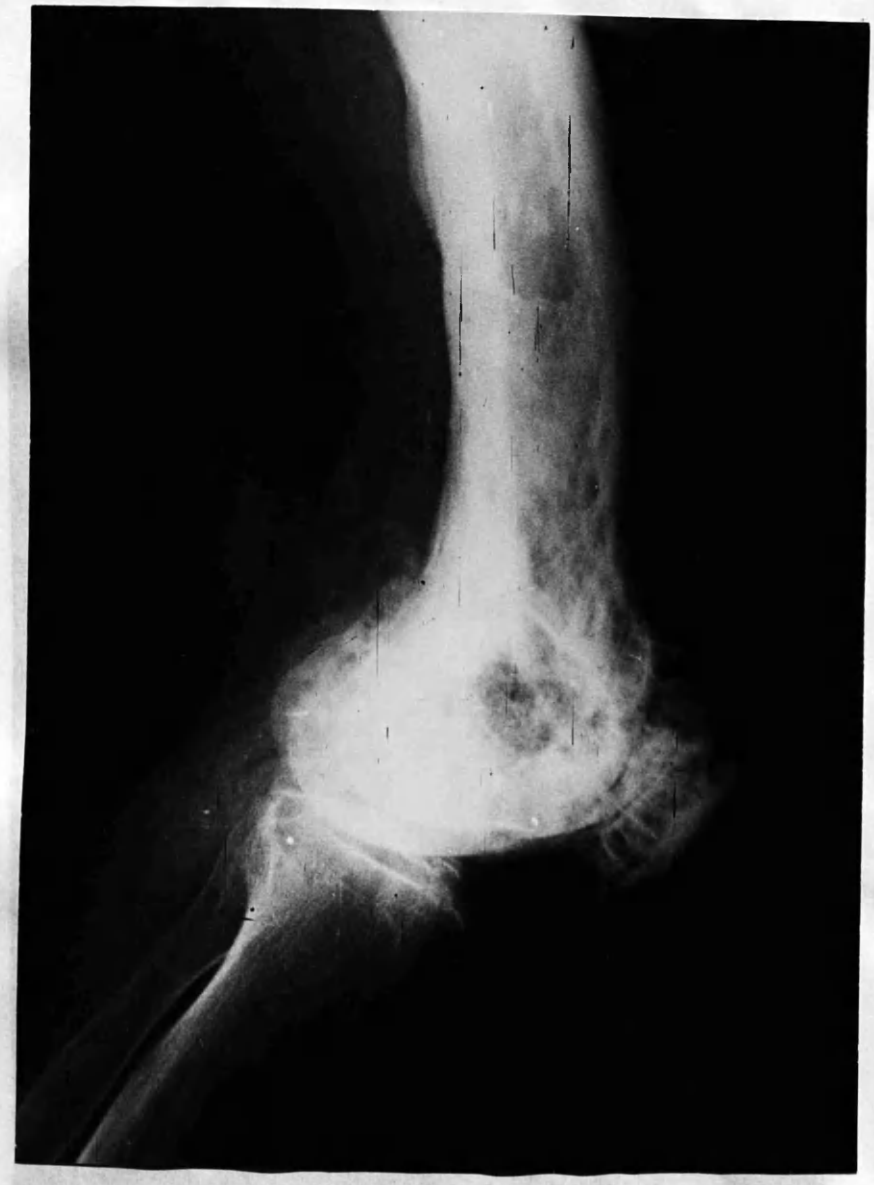


Fig. 8.

Fig. 8. *Here marked involvement of the femur and patella in Case No. 20 shows the honeycomb or spongy texture of the remodelled bone. The patella, shows the coarse striation often more strikingly revealed in X-Rays of the pelvis and sacrum.*

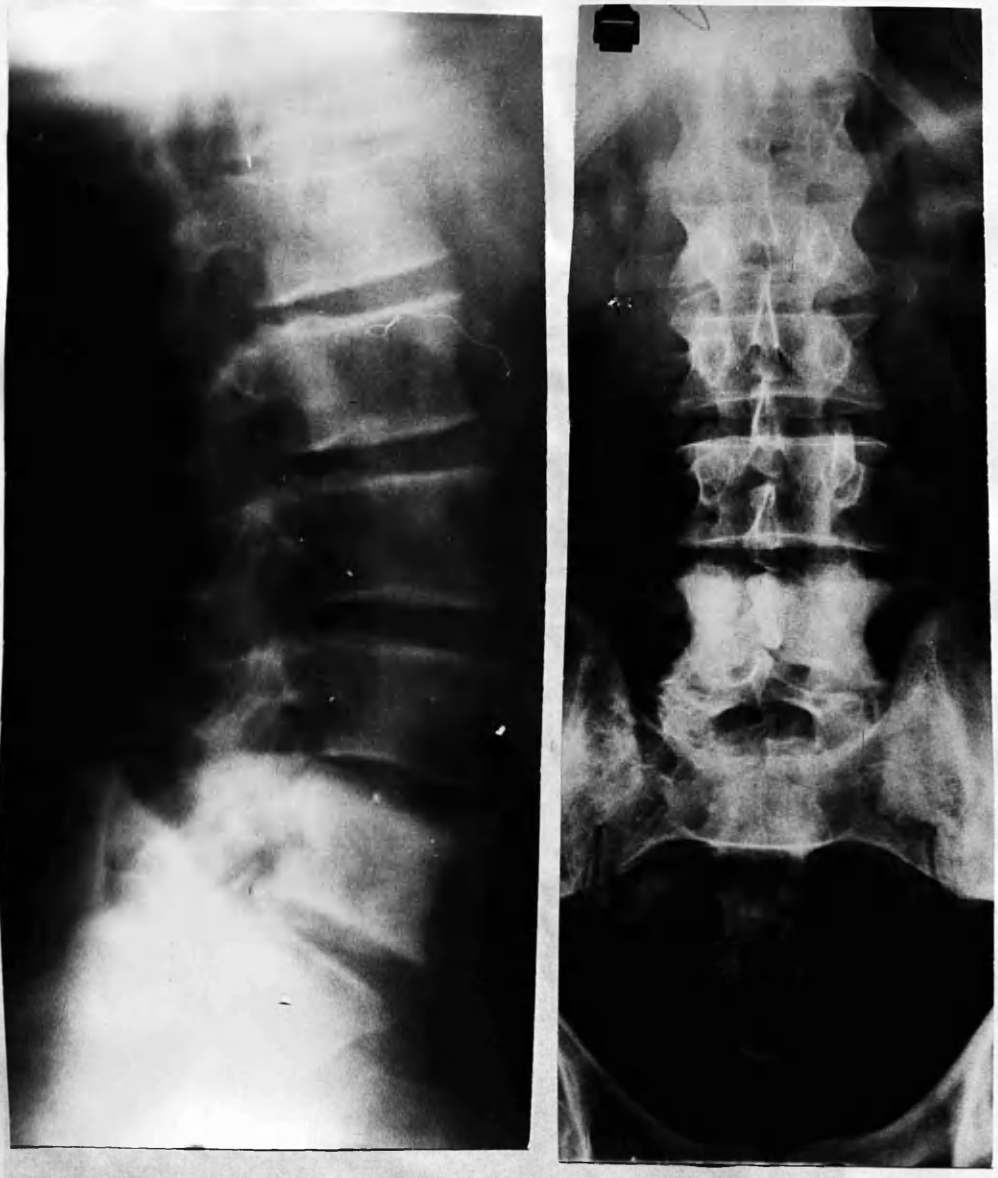


Fig. 9.

Fig. 9. *Shows Osteitis Deformans affecting a single vertebra and producing a homogeneous increase in density.*

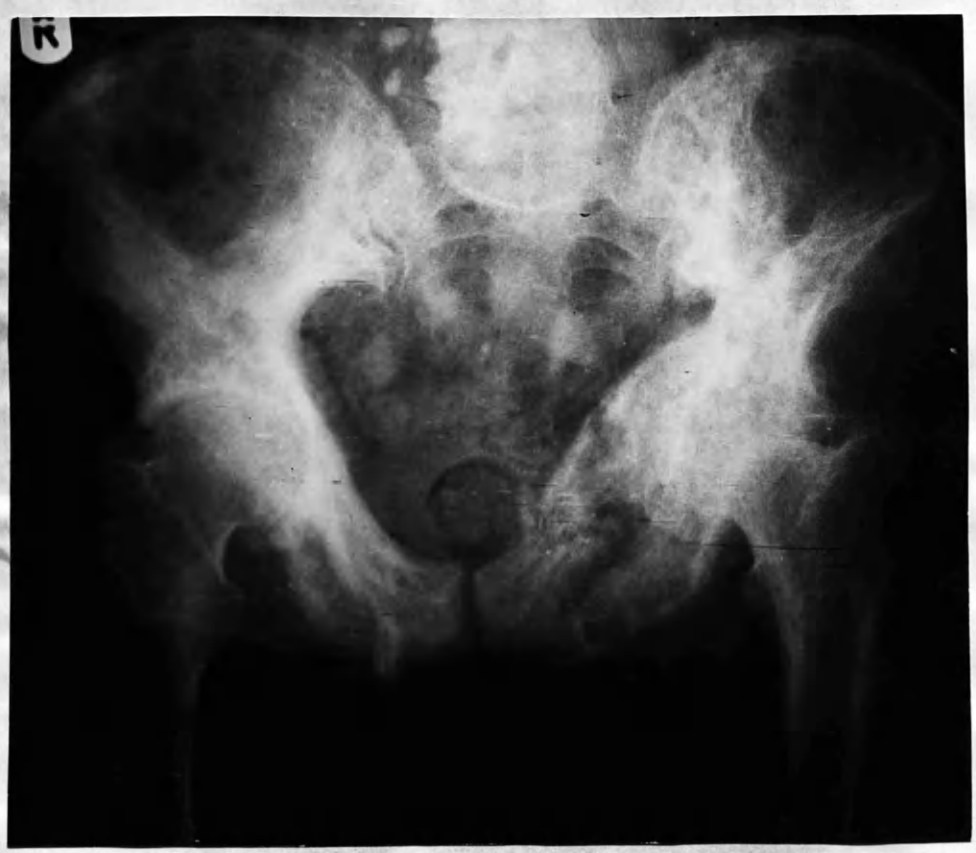


Fig. 10.

Fig. 10. *Shows the texture of the bone with varying degrees of resorption and sclerosis and in addition a pathological fracture of the pelvis.*

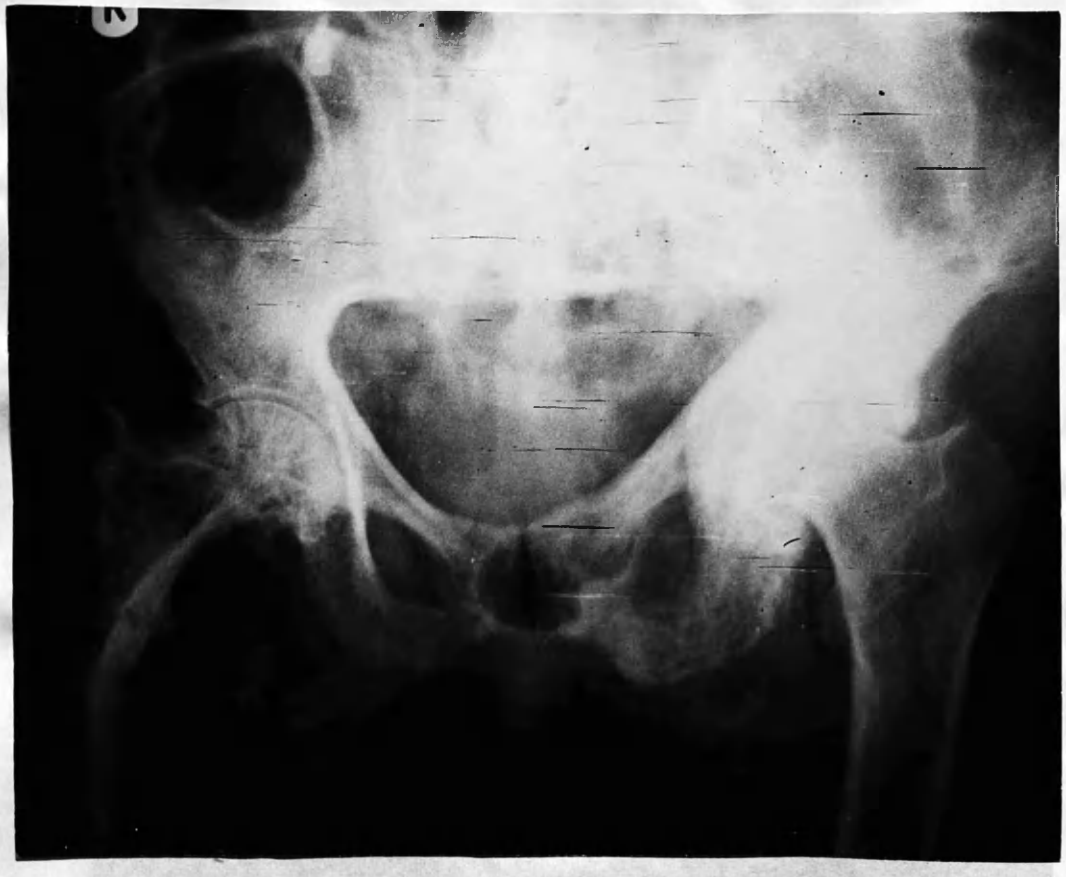


Fig. 10A.

Fig. 10 'A'. *Shows an affection of the L-side of the pelvis and the R femur.*

X-RAY CHANGES

Brailsford (1938), Snapper (1949) and Wilton (1954) have written specially valuable and lucid accounts of the radiographic abnormalities in osteitis deformans, and all these authors hold views that are broadly in agreement.

Bone resorption seems to be the earliest recognisable abnormality. Halisteresis, a term first coined in 1923 by Dawson and Struthers in their classic studies of bone dystrophies is the description applied by Brailsford to this change. It is most commonly seen in the tibia and often has a downward pointing lance head extremity which is a feature of diagnostic importance. The bone becomes more translucent and the trabecular pattern discernible where it has not previously been so. With advancing disease there occurs thickening, broadening and elongation of the limb bones. The texture assumes a honeycomb or spongy quality and, in some areas, coarse irregular striation is a striking feature. Remodelling of the trabecular structure in a quite disorganised fashion is another result and this produces the appearance so readily recognised on X-Ray. Gutman and Kasabach found it in 10 of their 116 patients.

A rather less common change produces a homogeneous increase in density of the bone and when this occurs it is generally in the vertebral column, often in a single vertebra - Delitala (1946) and Collins (1956) have

discoursed on the frequency with which this occurs and feels it is not sufficiently appreciated. The films of the mandible in Case No. 23 (see Figure 3) shows this change in a less common site.

Synchronous absorption and bone proliferation leads to the changes already mentioned in the limb bones. Deformity is a product of the proliferation rather than of any plasticity of the bone and when it affects the pelvis and vertebrae, increasing size of the bones is occasionally of help in differentiating a doubtful case from one of secondary carcinoma (Sutherland). The cortex is thickened and the marrow may be diminished.

In the long bones pseudo-fractures are frequent.* The term denotes a radiographic defect in the bone disposed at right angles to the long axis, and having the appearance of a knife cut extending sometimes to a considerable depth. See Figure 4. These can often be followed for many years without detectable change. They are said to be partial fractures by some, prevented from healing by proliferative changes which never progress to calcification (Wilton), and by others to be the site of penetration of the cortex by large nutrient vessels. In any case the appearance of the pathological fracture bears such a similar character that they may reasonably be thought to occur at the site of such lesions.

Fairbank describes the appearance of cystic defects occurring in the fibula and radius followed after many years by typical osteitis deformans. Jaffe too says

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* *See Fig. 4.*

that cystic defects may be seen and he attributes this appearance to the presence of large accumulations of marrow fat. I have not seen this and have encountered no other reference to it.

Late in the disease the bone greatly increases in density and with increasing sclerosis some foci become avascular and come to resemble sequestra.

In special sites there are features of note. The spine, especially if arthritic, may assume massive proportions and if ossified the ligaments become involved in the Pagetic changes (Snapper). Compression of affected vertebrae is common. Increased density affecting a few vertebrae or even only one, the remainder being apparently normal raises interesting questions relating to pathogenesis as well as diagnosis. In the sacrum the diminished number but increased density, thickness and irregularity of the striations are noteworthy.

Wilton believes that unilateral affection of the pelvis is often associated with scoliosis. The pelvis may occasionally have a generalised ground glass appearance but more commonly there is a mixture of bone resorption and new bone formation as seen elsewhere. Certain deformities, however, commonly occur, for example a triradiate or triangular pelvic brim.

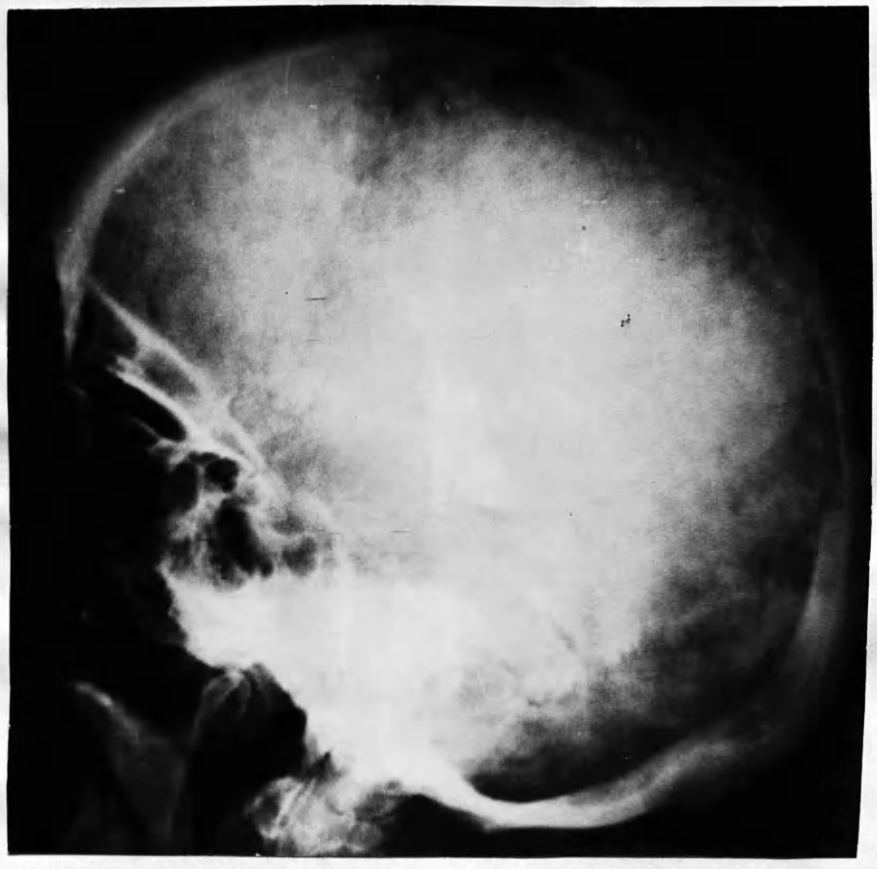

Fig. 11.

Fig. 11. *Shows the typical appearance of the skull lesion. One can see areas where resorption predominates markedly.*

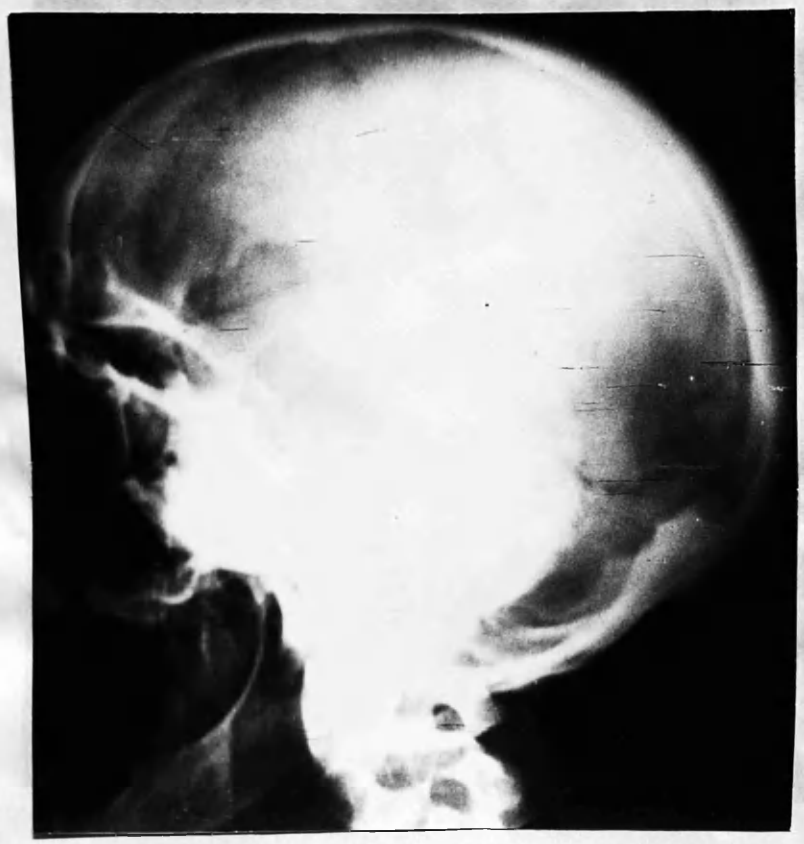

Fig. 12.

Fig. 12. *This was the only instance of Osteo-Porosis Circumscripta found in the total series of 70 radiographic examinations.*

TABLE XIII

SITE OF OSTEITIS DEFORMANS	AUTHOR AND TOTAL NUMBER OF CASES STUDIED			
	1	2	3	4
	Schmorl 138	Collins 46	Gutman Kasabach 116	Currie 70
Cervical Spine	7	-	5/46	2/16
Dorsal Spine	16	-	26/64	8/18
Spinal Column	50	-	-	-
Sacrum	57	-	-	20/26
Lumbar Spine	26	-	-	25/49
Lumbo-sacral Spine	-	76	51/92	-
Skull	28	65	82/105	15/22
Pelvis	22	43	90/101	49/52
Femur R.	31)	35)	59/91	14/40
Femur L.	15)	)		19/37
Tibia	8	30	34/63	11/29
Clavicle	13	11	15/63	2/18
Sternum	23	7	-	1/13
Fibula	-	4	4/63	1/29
Scapula	-	2	18/63	0/11
Humerus	4	2	37/63	1/9
Radius	-	2	7/27	0/8
Mandible	-	2	-	21/20
Ribs	7	2	4/63	1/35
Patella	-	2	1	1/36
Ulna	-	-	5/27	0/8
Hands	-	-	1/8	0/4
Feet	-	-	1/6	0/3
Maxilla	-	-	-	1/1
Phalanx	-	2	-	-

Table XIII. Columns 1 and 2 show the distribution found on complete skeletal survey by Schmorl and Collins. Retrospective studies analysed in columns 3 and 4 show the number of times a bone was found to be affected out of the total number of examinations of that bone. Of the vertebral lesions found by Schmorl, 26% were in the lumbar region, 17% in the dorsal and 7% in the cervical regions.

In the skull the earliest changes Brailsford noted were osteo-porosis and increased density along the suture lines. I have not seen this change myself or any other reference to it. At a later stage the skull bones are thickened, woolly in outline, generally decalcified but with many round patches of denser calcification, the whole picture suggesting a mass of small balls of cotton wool.*

MORBID ANATOMY

The principal abnormalities of osteitis deformans affect the skeleton. Any bone may be involved but it is exceptional to find changes in the small bones of the extremities or in the ribs. The distribution of Pagetic lesions throughout the skeleton is of interest and is shown in Table XIII. Ideally a complete skeletal survey is desirable, but apart from the work by Schmorl and Collins, this has generally not been done, most other surveys being retrospective. Gutman and Kasabach have observed the number of times any given bone was found affected and the number of times that bone was examined, and I have recorded the same information from the material available to me.

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* *See Fig. 11.*

Brailsford notes that the distribution of the lesions throughout the skeleton is approximately that of persistent red marrow in the adult, and of the distribution of embolic effects and secondary metastases.

Dickson et al believe that every bone may be involved in some degree and Illingworth and Dick (1936) had the same view. While admitting that they know of two cases of completely generalised affection, Albright and Reifenstein (1948) think it important that the disease has a focal origin.

The gross changes seem to spring from the widespread enlargement of the Haversian canals. They enlarge greatly, intervening bone is absorbed and contiguous canals coalesce. The resultant wide spaces at the same time fill with vascular fibrous tissue. In some bones where active resorption and reformation of bone proceed apace the periosteum is thick and hyperaemic. At operation bleeding from the periosteum and bone surface is free and may be sufficient to cause difficulty and anxiety. The cut surface of the bone is pink or fleshy and the marrow may on occasion be pale, very moist, and almost myxomatous in appearance with here and there small cavities resulting from liquefaction. In florid affections the cortical bone is soft and cuts easily with a handknife. The surface of the bone is porous from the multiplicity of large perforating vessels and the skull cap, when filled with water, leaks like a sieve through the vascular channels.

Figs. 13A and 13B.

Fig. 13A. *Shows a small sequestrum in a sclerotic bone. Reproduced from "The Illustrated Medical News" 1889. V2. p 188 (Mr. A.A. Bowlby, F.R.C.S.).*

Fig. 13B. *This beautiful drawing by Stephen Paget is from the same source and was used by Sir Jonathan Hutchison to illustrate the textural changes and remodelling in the bone.*

The marrow cavity in the long bones if often diminished by the thickened cortex at first, but later it is enlarged, and in the skull the distinction between the tables and diploe is obliterated. The vascular channels on the inner surface become progressively deeper as time passes and finally the vessels may be enclosed.

This intense proliferative stage gives way to one of progressive sclerosis in which increasing calcification produces ivory hard bone. The sclerosis may obliterate the blood supply in parts and small sequestra may result.*

In the spongy bone there are thick lustreless trabeculae with irregular denticulate margins. These are disposed in haphazard fashion, regardless of mechanical requirements. This may be readily seen in the vertebrae and Schmorl thought this to be an early occurrence in many of the cases which he discovered.

Deformity is common and would seem to result from the proliferative changes with thickening and elongation of bones whose ends are at fixed points. That elongation occurs was shown as long ago as 1887 by Clutton. The convexity of the curve in a deformed long bone is always opposite to the main mass of soft tissue. The deformities produced are remarkably constant. Plasticity of such degree as to permit mechanical deformation can scarcely be invoked as the explanation of deformity in an affected tibia alongside a normal fibula.

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* *See Figs. 13A and 13B.*

The cortical bone is thickened and in curvatures the thickening is most marked on the concave side but this is not always so. When it is, some would argue that here is evidence of the new bone formation being not an integral part of the disease but on the contrary an attempt to compensate for the mechanical weakness produced by resorption and the replacement of bone by disorganised and incompletely calcified osteoid tissue.

Freund (1929) and Jaffe both noted cellular proliferation in the deeper zones of articular cartilage when the underlying bone was affected. New bone formation appears to have a periosteal origin in some cases, and this bone gives the surface a filligree-like texture occasionally.

Sizeable local collections of marrow fat were thought by Jaffe to cause the cystic defects seen occasionally on X-Ray.

In the skull the vascular foraminae are enlarged. The neural foraminae are not contracted though they may be irregular. The suture lines are obliterated and the skull cap enlarges by progressive deposition of new bone on the outside. This in turn becoming affected by the changes of osteitis deformans.

Referring again to Table XIII it might seem that the tendency for Pagetic changes to develop in any particular part of the skeleton is connected with exposure to mechanical stress. This idea finds general acceptance. While the distribution is beyond doubt the association may well be fortuitous. Obvious anomalies spring to mind, for example, the skull is frequently affected and the calcaneum rarely. A unilateral affection of the pelvis may be associated with affection of the contralateral femur.* Béclère and Galliard (1901) gave one of the earliest accounts of a widespread affection thoroughly studied radiographically. In their case, exceptionally, the small bones of the extremities were affected and these authors were specially impressed by the contiguity of apparently normal with grossly affected metacarpals and phalanges and found this difficult to reconcile with views implicating mechanical stress in the pathogenesis. Sugarbaker says that generally the total bone mass runs parallel to the mechanical stress and the association observed is to be expected on these grounds alone. On the other hand Kay reporting a familial instance of Paget's disease, records that in one generation twins were affected, osteitis deformans appearing in the right radius of the right-handed twin and in the left radius of the left-handed twin. The parietal bossing of the skull might be related to the pull of the temporalis muscles but again why should the great strength of the masseter be associated with such relatively infrequent effects.

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* *See Fig. 10A.*

Monostotic Affections

When the changes of osteitis deformans are confined to a single bone the case is described as a monostotic affection. The relation of these to the more usual type of case has been disputed. Monostotic lesions are common.

Collins estimates the frequency at 10% of the total. Mercer believes, with many, that if followed up for a sufficient period of time osteitis deformans will be found to develop in other parts of the skeleton. He says this proves to be so in 75% of cases initially thought to be monostotic.

The solitary focus may be at a late sclerotic stage when first discovered and it cannot therefore be said that such lesions are simply the earliest evidence of a disease inevitably destined to become more widespread.

Some authors, especially in France, would separate this group, believing that there are two separate diseases. Godinot (1956) followed 10 cases for periods of up to ten years and did not find that the diseases become generalised. There seems in a significant number of such cases to be a history of recent injury. Knaggs (1926), Lièvre (1936), Helfet (1952) and Snapper and Gaudin (1956). Lièvre has collected 9 cases following injury.

Two most interesting reports concern the results of a bone graft replacement of single lesions. In both of these Pagetic changes developed in the new bone though the donor site remained free of any such abnormality - a strong argument in favour of local factors as opposed to general ones being of etiological importance (Stadford 1958, Godinot 1956).

In both cases this exceptional treatment was resorted to by reason of doubts regarding the diagnosis. Both had been adequately followed up by the time of reporting and in retrospect, osteitis deformans seems beyond question the correct diagnosis and is supported by convincing histological evidence. Stadford's case later developed other Pagetic lesions.

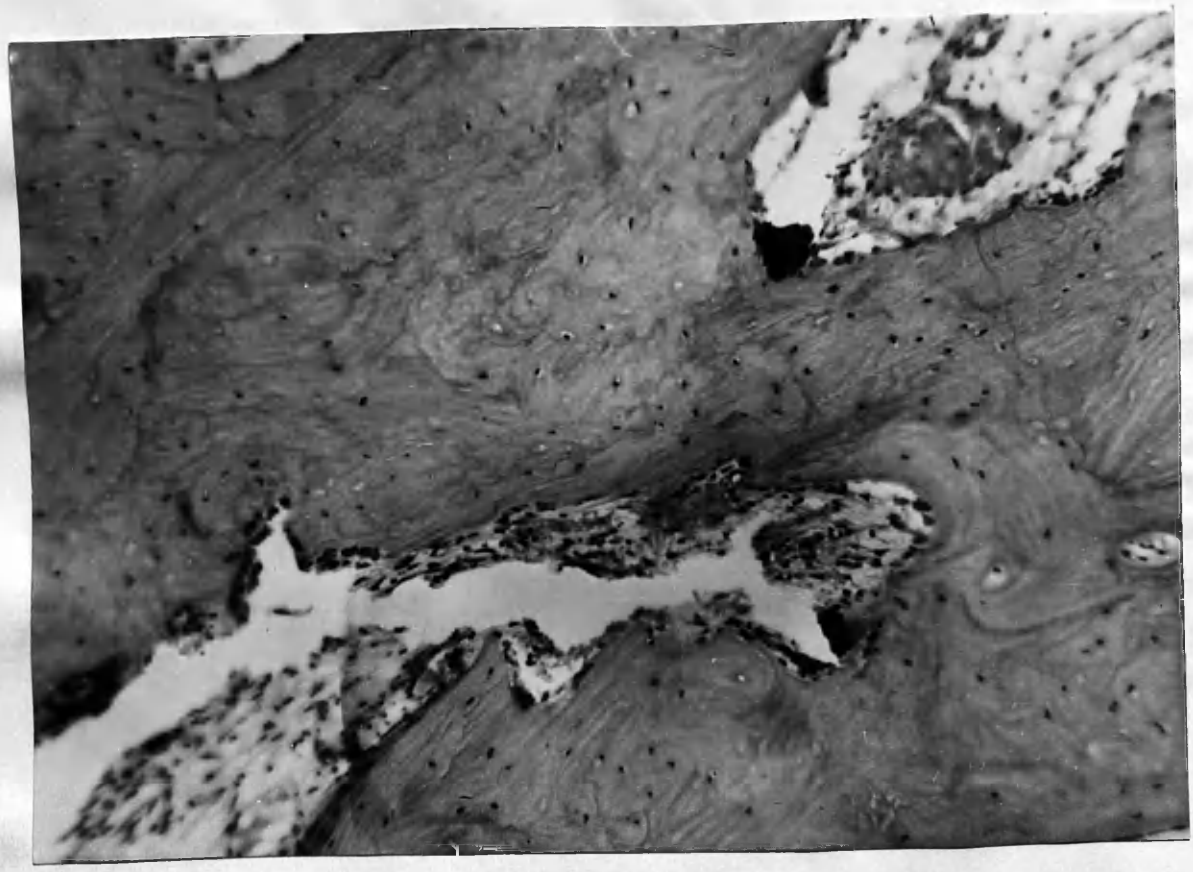

Fig. 14.

Fig. 14. *This section of bone taken at operation from the distal extremity of the proximal fragment in the fracture illustrated in Fig. 6 shows the mosaic pattern well. Though this appearance is characteristic of osteitis deformans when present to more than a minimal extent it is by no means an invariable finding. It seems to require that the balance between absorption and reformation should permit time for the maturation of the new formed bone.*

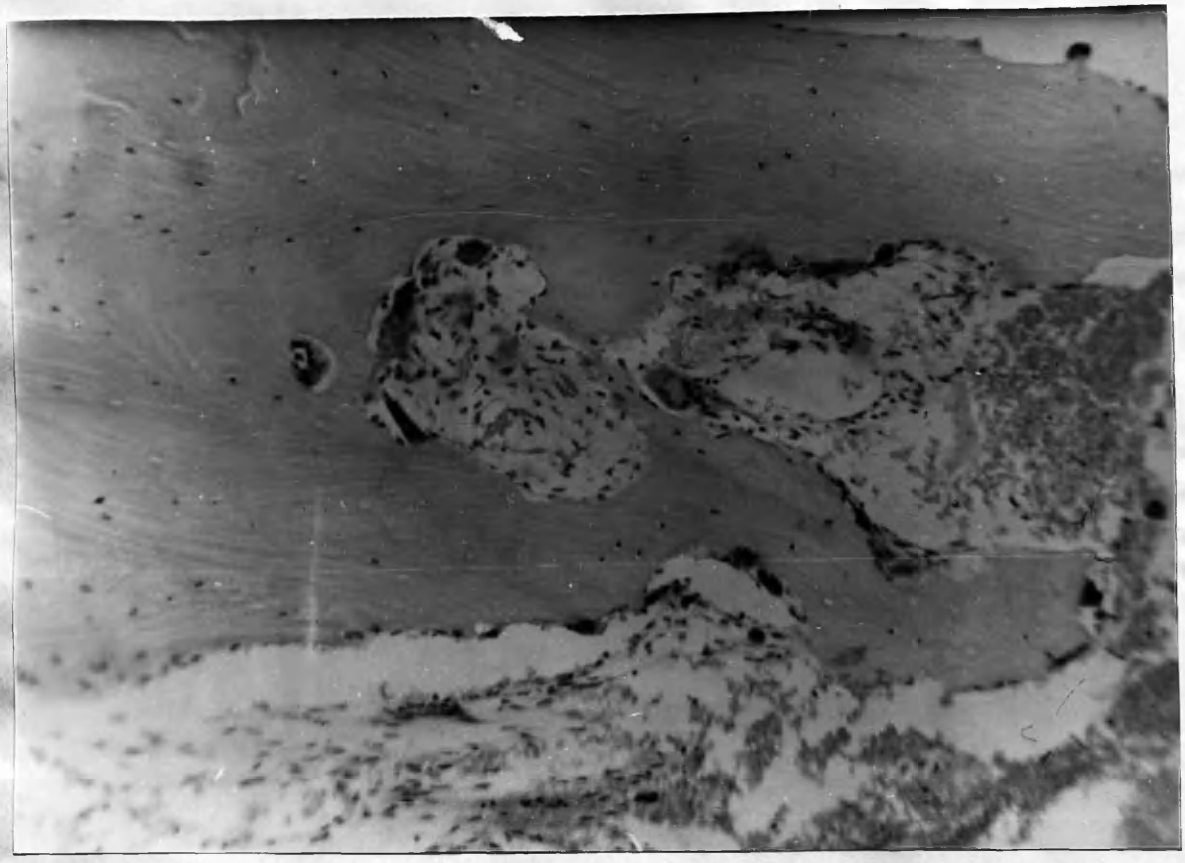

Fig. 15.

Fig. 15. *Shows intense cellular proliferation in the spaces between the trabeculae. There are many mullinucleated osteoclasts and in some parts of the section there is such an aggregation of cells as to produce a syncitium like appearance. The mosaic pattern is faintly discernible.*

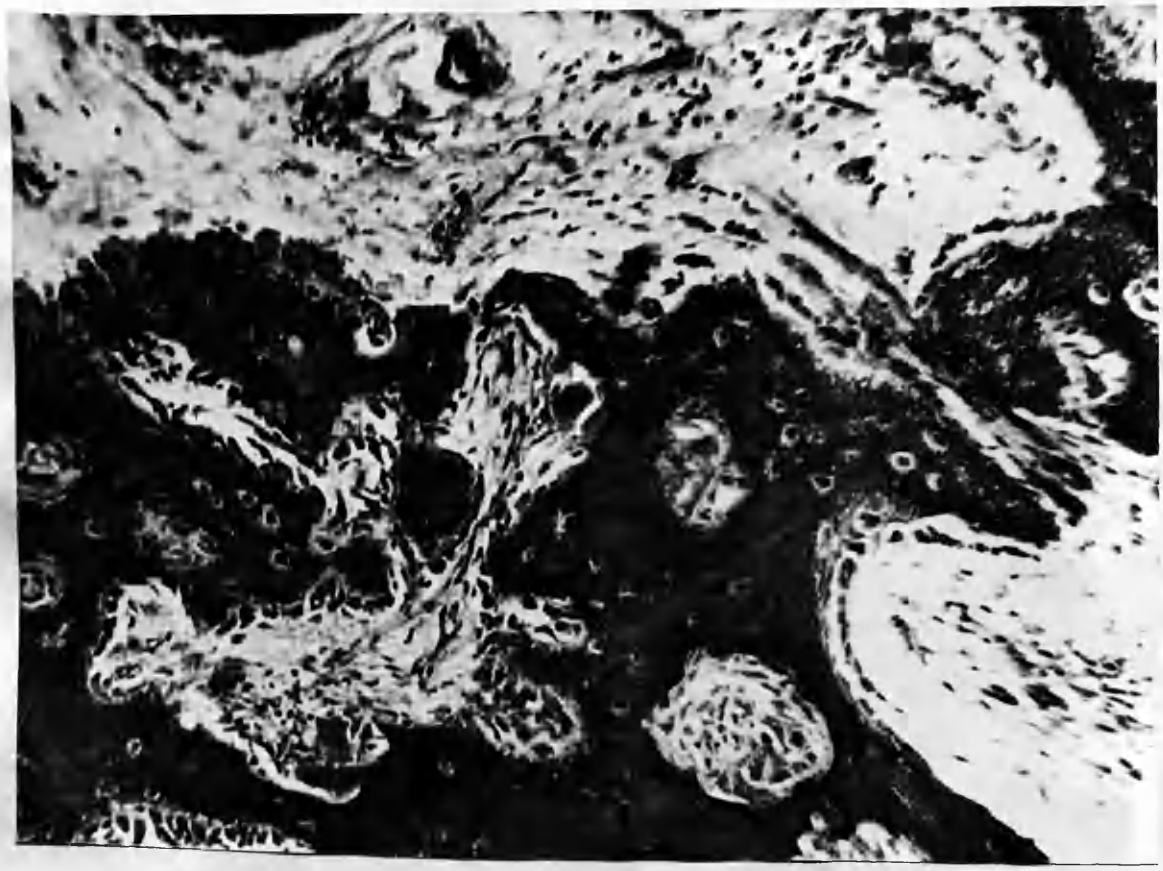

Fig. 16A.

Fig. 16 'A'. *Shows a higher magnification. The fibroblasts in some parts lie regularly alligned like metallic particles in a magnetic field or like fragments carried in a fluid stream. This is a common appearance. It also shows lacunnae in the new bone, here and there occupied by osteoclasts but more often by dense aggregations of osteoblasts. (Case No. 25).*

Fig. 16 'B'.

Fig. 16 'B'. Shows also the tendency for the fibroblasts or perhaps primitive osteoblasts to be arranged in streams - several almost syncitium like masses are seen here and there, presumably of an osteoblastic nature. There is a superficial resemblance to ossifying callus.

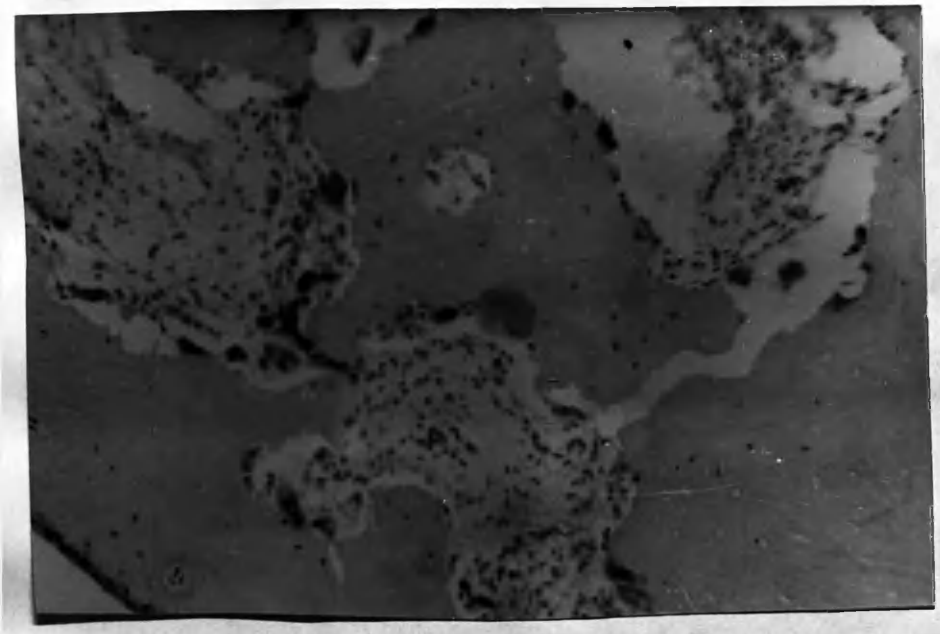

Fig. 17A.

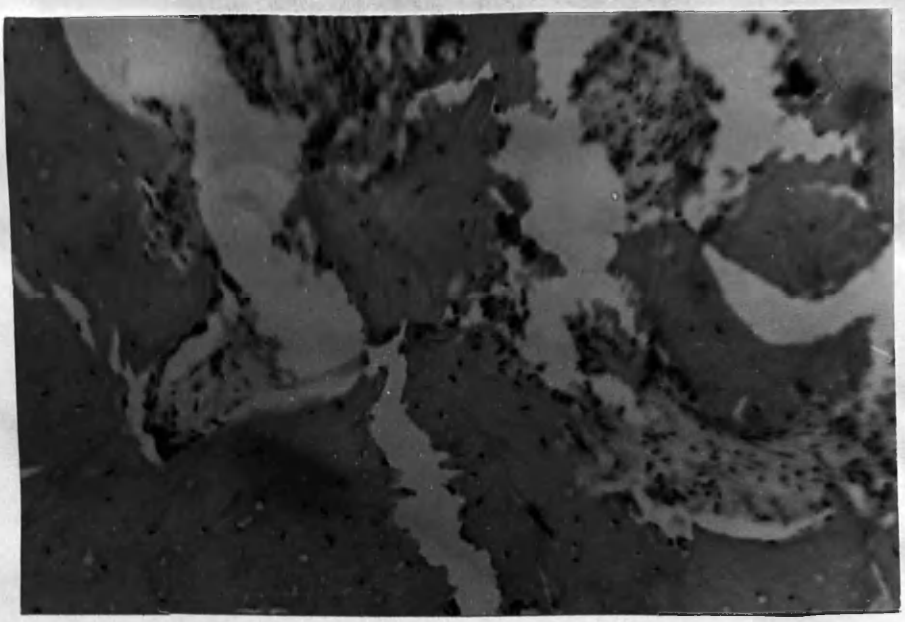

Fig. 17B.

Fig. 17 'A'. *Osteoclasts are abundant and fibrous tissue even more so. The fibrous tissue is highly cellular and the cellarity of the non calcified tissue between the bone islands is more striking than the numbers of osteoclasts.*

Fig. 17 'B'. *The new formed bone is highly cellular. There are no Haversian systems. The irregular and fragmentary nature of the trabeculae is well shown. Small dark staining round cells are numerous - perhaps primitive osteoblasts.*

HISTOLOGICAL CONSIDERATIONS *

A histological picture of generalised osteitis fibrosa was drawn by Von Recklinghausen in 1891. His belief in the specificity of this lesion found general acceptance and it was some time before further advances were made in differentiating the related bone dystrophies. Deliberate investigation of the parathyroid glands seems to have begun with the work of Sandstrom (1880). These early anatomical studies for many years lay dormant and it was not until the close of the century or the early years of the twentieth century that the first publications on the physiology of the parathyroid glands began to appear. Perhaps the most renowned among workers in this field was Erdheim. He observed the association of skeletal decalcification and parathyroid hyperplasia and deduced that these were cause and effect. Correct as this observation is in some instances further clarification was needed before the pathological differentiation of several confused pictures could be accomplished. The subsequent investigation by McCallum and Voegtlin (1908 and 1909) among others on the effects of removal of the parathyroid glands led to increasing suspicion and those patients whose bone dystrophies were associated with the presence of a parathyroid adenoma should be separately classified.

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* *See Figs. 14 - 17*

Following the preparation independently of active glandular extracts by Berman, Hansen and Collip, Mandl's successful operation in 1925 for removal of a parathyroid adenoma from such a patient vindicated these suspicions.

The separate identity of the bone dystrophy in hyperparathyroidism was now clearly demonstrated. A consequence was the impetus given to further work in this field, work which bore fruit in the discoveries by Schmorl in Dresden and Knaggs in this country. To these two in particular we are indebted for confirming the identity which the clinical studies by Sir James Paget had so clearly conferred upon osteitis deformans.

Irregular islands of newly formed bone aggregated in disorderly fashion and glued together by dark staining cement lines form a mosaic which is a striking and extensive feature of osteitis deformans. These cement lines as Schmorl called them and the mosaic pattern which they delineate were independently recognised by Knaggs, the latter saying in this connection - *"the bones are decorated by curvi-linear markings"*.

The mosaic pattern and the predominance of new bone formation over osteoclastic resorption are the most remarkable items in the histological picture. New bone is formed rapidly and extensively and itself becomes involved soon in the successive cycles of resorption and reformation.

It rarely seems to have the chance to mature or fully calcify, except when the cycle is interrupted by the occurrence of dense sclerosis which arrests further progress of the disease.

The number of osteoclasts never seems enough to account for the extent of bone destruction and those who question if this is indeed the function of these cells would seem to find support here. The fibrous tissue in the enlarged and confluent Haversian canals is often abundantly endowed with small round cells and in Cooke's 15 cases of Paget's disease of the jaws focal collections of lymphocytes were a striking feature in 7 cases. Small spicules of bone are found lying free in this fibrous tissue.

Cone (1922) notes vascular degeneration generally but specially marked in the bones.

Weinmann and Sicker (1955) noted plasma exudation into the marrow and emphasised the abundance of lymphocytes, plasma cells and macrophages. Wilton (1954) thinks that fibrosis is probably less common than generally believed and the cells regarded by most as fibroblasts are regarded by him as immature osteoblasts. Peters (1959) thinks that the osteocytes are abnormal in their lack of ramifying processes. He says the mosaic lines are the remains of absorbed and replaced trabeculae. Most authors are reticent on this point. He considers that there is extreme endarteritis. Freund and others have noted

cellular proliferation in the deeper parts of the articular cartilage covering the ends of affected long bones.

Frost (1960) in an interesting study of osteocyte death in vivo has noted that this is common in osteitis deformans. He reached this conclusion following counts of empty lacunnae in bones in various diseases but it is not clear if he refers only to sclerotic bone in Paget's disease though this seems likely.

TABLE XIV

CASE NUMBER	Haemoglobin gms. %	Packed Cell Volume	Mean Corpuscular Haemoglobin Concentration	Erythrocyte Sedimentation Rate - mm/hour Wintrobe	White Blood Cell Count / c.mm /	Polymorphonuclear Leucocytes	Lymphocytes	Eosinophils	Monocytes	Basophils	A.B.O. Blood Group
1	10.8					24	73	-	3	-	O +
2	11.8	38	31	54	21,200	Incr					
3											O +
4											
5	13.3	38	35	1	3,500	58	38	1	3	-	A -
6	13.4	40	33	5	3,300	60	36	3	1	-	A +
7	12.5	37	34	3	4,900	56	38	3	3	-	O +
8	14.2	44	32	13	5,100	60	36	3	1	-	A +
9	10.7	35	31		5,700	75	20	2	3	-	B +
10	13.3	37	35	29	7,500						A +
11	17.4	48	36	4	11,200	69	25	4	2	-	O -
12	12.5	40	31	12	5,000	60	34	4	2	-	O +
13	15.1	49	31	9	5,200	53	42	2	2	1	A +
14	16.1	49	33	16	8,200	72	26	1	1	-	B +
15	17.3	53	33	5	6,400	45	44	11	-	-	O +
16	9.7	32	29	13	25,400	78	13	7	2	-	O +
17	15.4	46	33	5	7,000	56	31	9	1	-	O +
18	10.7			31	9,000	74	22	3	1	-	A +
19	15.2	40	38	3	3,000	64	28	2	6	-	AB+
20	14	40	35	10	3,800	58	30	6	6	-	A -
21	14.6	40	36	26	8,300	44	46	4	4	2	A +
22	14.7	44	34	13	2,800	63	28	1	8	-	A +
23	7.8	26	30	19	3,700	66	33	1	-	-	B +
24	13.6	41	33								
	12.4	40	35	10	9,000	59	34	2	5		O +
25	12.5	42	30	32	4,500	62	32	4	-	-	A +
26	15.8	45	35	24	5,200	63	25	3	9	-	O +
27	12.2	40	31	1	5,200	26	65	2	7	-	O +
28	13.2	41	32		4,800	74	20	-	6	-	B -
29											

HAEMATOLOGICAL DATA

Peripheral Blood Counts.

Haematological data relating to the present series are recorded in Table XIV. No consistent pattern of abnormality emerges. Similar observations on 6 cases by Busalotti and Doria (1949) and by Poilleux and Sluczewski (1949) on 9 cases were equally lacking any unusual feature. Piney (1925) found eosinophilia and besophilia in 3 out of 5 cases and O'Reilly and Pace (1932) found monocytosis occasionally. Neither offered any interpretation of their findings which do not seem to have been repeated.

These haematological data do not seem to shed any light on the obscure problems of Osteitis Deformans.

A.B.O. Blood Groups.

This observation was made in the 29 cases personally cared for. Only in the event of an extreme abnormality emerging, could any significance be attached to the results of such an investigation in so small a series and in fact the results are within the expectations of random sampling.

ETIOLOGY.

There is much well established knowledge relating to Osteitis Deformans but of a fragmentary nature. The fields of theory and discovery have yet to yield some polarising thought which might orientate these apparently dissociated facts and reveal their integration.

In 1929 Janes and Sorrel said: "*.....nothing is known as to the cause of this affection. Heredity plays no part. No bacteria have ever been demonstrated nor has any definite relationship to the endocrine glands been established in the autopsied cases. Attempts to assign a neuropathic origin have failed through lack of clinical and pathological evidende.*"

The position has not materially altered since then. The occasional concurrence of pain, swelling and warmth, led Paget to believe that osteitis deformans was an inflammatory disease. The fibrous hyperplasia was appropriate to a chronic inflammation. Morpungo and Fiocca claimed to have isolated a specific diplococcus and to have prepared a vaccine. Da Costa et al (1921) tried unsuccessfully to repeat this work. There is little else recorded along these lines in the earlier literature on osteitis deformans and the idea lapsed. However, in 1954 Rutishauser, Veynal and Rouiller concluded that a virus infection was probably the cause and in 1959 Busalotti and Doria returned to Paget's original concept.

Following the early abandonment of the inflammatory theory Knaggs was inclined to blame the effects of endogenous toxins and thought these might arise by metabolic error. Certainly it is known that osteitis fibrosa can result from intoxication by chloroform, lead, phosporous, ammonium chloride and the acidosis of renal insufficiency. In none of these instances, however, do the characteristic features of osteitis deformans appear.

Before the Wasserman reaction was known and at a time when syphilis was more common and apparently more virulent, that disease was occasionally incriminated (Lannellogue and Fournier (1903) or stoutly exonerated (Robin (1903)). Robin at that time noted the characteristic changes in the proportions of ash and organic matter in Pagetic bone and pointed out that bones affected by syphilis displayed no such abnormalities.

Lancereaux and Gils de la Tourette believed in the neuropathic nature of osteitis deformans, the latter having found slight abnormalities of staining in the posterior columns of the spinal cord.

Moore (1951) favoured the view that there was some organic or functional imbalance of the automic nervous system. He arrived at this theory by a process of exclusion and then offered it only very tentatively, admitting himself the absence of any consistent soft tissue changes to accord with a major upset of this type.

TABLE XV

STUDIES OF MINERAL METABOLISM

AUTHOR	OBSERVATION
Goldthwaite, Painter & Osgood 1904	Calcium and magnesium retention
Da Costa 1915	Calcium retention. Urinary excretion of calcium diminished
Locke, 1921	Calcium and magnesium retention. Urine normal.
Cuthbertson, 1927	Calcium phosphorus and magnesium retention. Loss of sulphur.
Van Hazelt Andrews, 1927	Calcium retention. Urinary excretion of calcium raised.
Hunter, 1931	Urinary excretion of calcium raised in 80% of cases.
Mercer & Duthie, 1955	Urinary calcium excretion raised.
Simpson, 1959	Negative calcium balance not infrequent.

TABLE XVI

STUDIES OF CALCIUM AND INORGANIC PHOSPHATE LEVELS IN THE BLOOD

AUTHOR	OBSERVATION
Kay, Simpson & Riddoch, 1934	There is a tendency for the calcium to be slightly raised and often the inorganic phosphate to be slightly low.
Gutman & Kasabac , 1936	Calcium - 9-11 origin % in 69 patients 11.1 - 11.5 origin % in 8 patients Inorganic phosphate - 2.7 - 4.2 origin %
Newman, 1946	Calcium - 9.4 - 12.2 origin %) Inorganic phosphate - 2.6 -) 6.75 origin % in 36 patients tested
Albright & Reifenstein, 1948	Calcium and phosphate usually normal though occasionally the inorganic phosphate is slightly raised.
Mercer & Duthie, 1955	Calcium and phosphate are within normal limits.

TABLE XVII

CASE NUMBER	Serum Calcium mgm/100 ml.	Serum Inorg. Phosphate mgm/100 ml.	Serum Alk. Phosphatase Units/100 ml. (King-Armstrong Units)
1	12.0	4.15	26.0
2	12.4	4.4	9.8
3	10.7	6.7	23.6
4	9.6	5.5	44.7
5	8.6	3.3	26.0
6	8.4	-	48.0
7	8.8	-	33.0
8	9.7	4.7	18.0
9	8.6	5.8	26.5
10	10.4	4.2	7.0
11	9.6	3.5	26.3
12	9.9	2.95	34.2
13	10.1	3.3	52.9
14	9.6	3.7	38.0
15	10.0	3.9	111.0
16	9.8	4.1	3.6
17	10.5	3.2	40.6
18	9.9	4.1	23.0
19	9.4	4.6	41.2
20	10.9	3.2	19.8
21	11.4	4.8	60.0
22	10.7	-	37.0
23	11.4	4.6	8.7
24	10.4	5.2	3.6
25	11.6	3.2	77.0
26	11.8	5.1	13.8
27	9.8	-	-
28	9.8	6.2	42.2
29	9.9	4.8	26.0

TABLE XVIII

SUMMARY OF GLUCOSE TOLERANCE TESTS

CASE NUMBER	FASTING LEVEL	½ HOUR	1 HOUR	1½ HOURS	2 HOURS	2½ HOURS	AGE
1	125	179	163	115	116	-	66
2	120	135	200	193	187	-	90
3	78	119	151	98	-	-	71
5	-	-	-	-	-	-	66
6	-	-	-	-	-	-	-
7	-	-	-	-	-	-	-
25	101	139	168	182	168	-	84
8	110	132	116	107	98	-	70
9	123	152	148	137	123	120	73
10	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-
12	-	-	-	-	-	-	58
24	95	158	108	90	85	85	53
13	87	126	154	124	95	-	68
26	83	127	119	94	87	-	73
14	82	135	149	130	100	-	-
15	94	119	129	122	90	-	-
16	92	108	133	152	143	-	-
17	90	137	157	171	117	-	-
18	112	165	155	149	152	149	75
19	92	139	129	127	90	-	81
20	86	137	139	137	92	-	82
21	86	120	152	136	108	-	64
22	-	-	-	-	-	-	-
23	172	217	228	217	244	-	72
28	173	245	240	217	187	-	60
29	178	237	265	233	226	-	58

Vitamin A deficiency has been proposed but Snapper from wide experience in North China says vitamin deficiencies there are exceedingly common, while osteitis deformans is rare.

A Primary Endocrine or Metabolic Upset?

Some relevant biochemical data are listed in Tables XV, XVI and XVII, the last relating to the cases in the present series.

The raised alkaline phosphatase was first noted by Kay in 1929 and in the following year he noted that the level tended to parallel the extent of the disease. The significance of this is, that it reflects the degree of oestoblastic activity and so also the extent of the reparative phase in the disease.

The bones themselves differ in composition from normal bones. They contain a higher proportion of organic matter and a lower proportion of mineral ash. Lake (1958) gives the figures of 37% of organic matter in normal bones as opposed to 42% in Pagetic bones. The amount of fat in Pagetic bones is slightly raised (Snapper and Jaffe). The magnesium content of the bones is said by Kay Simpson and Riddoch to be diminished. They give the normal figure as 0.8 mgm % as opposed to 0.14-0.68 mgm % for Pagetic bones. Lake, however, believes the magnesium content of the bones is increased

and makes the interesting speculation that this may be connected with the tendency to sarcoma; magnesium salts having a stimulating effect on the proliferation of tumour cells in culture.

Albright and Reifenstein believe there is increased urinary excretion of calcium and phosporous during exacerbations and that this accounts for the tendency to form renal stones. McCusick (1960) agrees with this.

An interesting observation by Kissen and Kneeger (1954) is the raised citric acid level in the blood of patients with Paget's disease - 9 out of 19 investigated (60%) as opposed to 5% of a control series. They believed the rise bore no relation to immobilisation or to the presence of osteo-porosis.

The data relating to the blood chemistry reveals no discernible relation between osteitis deformans and hyperparathyroidism and most would agree with this. Clinically and radiologically the distinction is generally not difficult. Histologically, while the indeterminate picture of osteitis fibroses prevails in both, in osteitis deformans the abundance of new bone formation, the widespread mosaic patterns and the anarchic remodelling regardless of mechanical

requirements contrast with the picture in hyperparathroidism, wherein the bone structure, no matter how rarified, continues to respect functional demands and wherein cystic changes and osteoclasmata are frequent.

There still exists, however, in some quarters a desire to associate osteitis deformans with functional parathyroid abnormality. Berman (1932) argues that as the effects on bone of the adrenal and parathyroid glands are antagnostic the disease might possibly reflect an imbalance of these two influences, absorptive changes prevailing when the parathyroid is dominant and sclerosis supervening with the increasing influence of the adrenal. He thought the good response to treatment by adrenal extract might be explained in this way.

Ballin (1933) considered that parathyroidectomy had benefitted some of his cases although he gave no details as to the extent of the removal of parathyroid tissue. He thinks there are intermediate cases bearing some characteristics of osteitis fibrosa cystica, and some characteristics of osteitis deformans and that the differences are of degree only. Helfet has argued that the primary abnormality is an incapacity of the kidney adequately to excrete phosphate. Secondary

Secondary hyperparathyroidism results with loss of calcium from the skeleton and the elimination of calcium phosphate in the urine. Sclerosis results from hypoparathyroidism when the glands are exhausted. He advised treatment with aluminium salts by mouth to diminish phosphorus absorption from the bowel and claimed good results. Ghormley and Hinchley (1944) had good results clinically in 8 out of 12 cases treated according to Helfet's recommendations. Helfet says that radiological evidence of improvement is obtained but only after a long delay, of about two years. Albright and Reifenstein are among the most vigorous antagonists of the view that an endocrine abnormality can be found to explain the occurrence of osteitis deformans. They say the disease is not generalised. Here is a severely affected bone and yet contiguous bones are normal. A circulating hormone affecting bones should change all the bones in some degree. The development of osteitis deformans does not accord with such a cause. They describe the distribution as 'spotty' and emphasise the sharp demarcation of affected from normal bone. They admit to having under their care 2 cases in whom, exceptionally, the entire skeleton is affected. In one of these they submitted the patient to parathyroidectomy and although hypoparathyroidism was induced the Paget's disease was in no way improved.

Illingworth and Dick (1960) say, *"every bone in the body is affected in some degree"*, and they believe that an endocrine cause will yet be established.

The argument has several times been advanced that anterior pituitary hormones might play some part. It may be recalled that the somatotrophic hormone has diabetogenic effects and Moehlig (1936, 1952), Moehlig, Murphy and Allen (1935), and Moehlig and Abbott (1946), have recorded an increased incidence of familial tallness, obesity and diabetes in patients with osteitis deformans and in their families. Of 31 patients with osteitis deformans on whom glucose tolerance tests were done a diminished tolerance was found in 27. Similar findings are recorded by Sèrre and Mirouze (1952), Kissin and Kreeger (1954) and Mirouze (1955). Lievre (1936) and Berman (1936) also record an association with diabetes. A contrary opinion is expressed by Schneeberger (1950) who found no statistically significant difference between the incidence of diminished glucose tolerance in patients with osteitis deformans and in a control group of similar age.

Of 111 patients reviewed by Rosenkrantz et al 9 patients had diabetes and 8 others had a family history of diabetes.

Table XVIII contains observations made on the present

TABLE XIX

CASE NUMBER	Total Protein G/100 ml	Albumin G/100 ml	Globulin G/100 ml	A.G. Ratio	ELECTROPHORESIS
1	-	-	-	-	-
2	-	-	-	-	-
3	6.4	4.0	2.4	1.66	Marked decrease of Alpha 1 globulin.
4	-	-	-	-	-
5	6.8	4.4	2.4	1.83	Alpha 1 and Alpha 2 globulin slightly decreased.
6	5.6	3.9	1.7	2.29	Proportional decrease of Alpha fractions.
7	5.8	4.0	1.8	2.22	Proportional decrease of all fractions.
8	6.4	4.4	2.9	1.51	Slight decrease of gamma globulin fraction.
9	6.0	4.0	2.0	2.0	-
10	8.8	3.6	5.2	0.6	Consid. increase gamma globulin. Reduced alpha globulin. Slightly reduced album.
11	6.8	4.8	2.0	2.4	Normal pattern.
12	6.8	4.6	2.2	2.09	Slight increase of gamma globulin. Slight decrease of alpha globulin.
13	7.6	4.6	3.0	1.5	Increase gamma globulin.
14	8.4	4.8	3.6	1.33	No abnormalities.
15	6.8	4.4	2.4	1.83	No abnormalities.
16	6.8	3.8	3.0	1.26	Gamma globulin decreased, alpha globulin increased.
17	6.0	5.0	1.0	5.0	Decreased gamma globulin.
18	8.4	4.0	4.4	0.9	Increased gamma globulin. Albumin slightly decreased.
19	6.0	4.6	1.4	3.28	Slight reduction of globulin fractions.
20	6.8	4.6	2.2	2.09	Normal pattern.
21	6.4	3.8	2.6	1.34	Normal pattern.
22	6.4	4.0	2.4	1.66	No abnormalities.
23	5.6	3.4	2.2		
24	6.4	3.4	3.0	1.13	Gamma globulin increased.
25	5.6	4.2	1.4		Normal pattern.
26	6.8	4.8	2.0	2.4	Normal pattern.
27	-	-	-	-	-
28	5.6	3.0	2.6	1.16	(Reduction of albumin fraction, a slight increase of alpha 2 and beta globulins. Other fractions normal.)
29	5.6	3.4	2.2	1.5	Normal.

series of cases.

Recently Schrade, Boettle, Biegler (1960), whose interest was the humoral abnormalities associated with arterio-sclerosis, found diminished glucose tolerance in 56% of 192 non-diabetic arterio-sclerotic patients. The diminished glucose tolerance appeared to be paralleled by age, body weight and the degree of hyperlipidaemia. Arterio-sclerosis and diminished glucose tolerance is apparently an association to be expected.

Poilleux and Sluczewski noted a low total plasma protein in the majority of their cases, the gamma globulin fraction in particular was diminished. Figures obtained from the present series are given in Table XIX. No consistent abnormality emerges. Layani, Aschkenasy, Bengui, de Mende and Bonnemay (1956) have done electrophoretic studies in 32 patients. They say the albumin globulin ratio is higher in osteitis deformans than normal and that when the blood phosphatase level was very high the gamma globulins were often depressed and the alpha and beta globulins raised, but they offer no explanation. Their results differ from these of Busalotti and Doria (1959) who in 6 cases studied found a constant diminution of the albumin, globulin ratio and the gamma globulins higher than normal. It would appear that there is no consistent quantitative or qualitative abnormality of

the plasma proteins in osteitis deformans. The diabetes and the proliferative changes might conceivably result from excess somatotrophic hormone. The occurrence of the disease when gonadal function is falling off might be associated with low plasma protein levels and with increased anterior pituitary activity. An anti-insulin substance recently isolated from the plasma by Steinke et al. is thought by them to be the growth hormone. Mirouze says in this connection, "*le diabete sauf par le tronchement d'alterations vasculaires ne semble pas capable d'engendrer une osteose Pagetique ....*" He declares his belief "... *comme Rosenkrantz, une hypersecretion ante hypophysaire somatotrope mais avec un bilan azote negatif a l'origine du diabete et de l'osteose.*" Before leaving this question the observation published by Luxton (1957) is of interest. He believed that he had established a statistically significant association of osteitis deformans and lymphadenoid goitre. As the latter disease is now thought possibly to be an expression of auto-immunisation the normal or near-normal gamma globuline in osteitis deformans are of importance, indicating that this disease is unlikely to belong to the same group.

A Heritable Disorder of Connective Tissue?

McCusick who has a special interest in diseases that might be described as heritable disorders of connective

tissue has suggested the inclusion of osteitis deformans in this group. He says, *"a quality of reasonableness, although not constituting proof makes it attractive to persons familiar with bone and with the clinical behaviour of Paget's disease to speculate that the disease is fundamentally an abiotrophy of the collagen matrix of bone which breaks down with the passage of years."* Examining his suggestion a little further we note that he accepts without reservation the familial nature of osteitis deformans. He notes the many reports of angioid streaks in the retina in cases of pseudo-xanthoma elasticium and that angioid streaks are also found in osteitis deformans. They are often an isolated observation, but P.X.E. and osteitis deformans are diseases with which they are regularly associated and all three conditions have occasionally been found in the same patient. McCusick argues that the angioid streaks in osteitis deformans are evidence of a generalised defect whose main effects are seen in the skeleton but which affects the connective tissues throughout the body.

The association of angioid streaks with pseudo-xanthoma elasticum has been noted by Groenbladd (1929), Scholtz (1941) and Berlyne (1960) and with osteitis deformans by Terry (1934), Lambert (1939), Morrison (1941),

Scholtz (1941) and Mackie (1956). While the concurrence of all three conditions is recorded by Woodcock (1952) and Schaffer (1957).

First described by Doyne (1889) and named by Knapp (1892) these retinal abnormalities are very variously interpreted. Some, including McCusick believe them to result from rupture of the elastic fibres in Bruch's membrane. Hagedorne (1939) believed this and offered supporting histological evidence. Such evidence for obvious reasons is exceedingly difficult to obtain and other authors, lacking it, have not hesitated to express their own views - often differing from Hagedorne. Knapp thought retinal haemorrhages were responsible. Law (1938) believed that haemorrhage was a factor and that there were also abnormalities of pigmentation and that plication of the retina might be a cause. Mackie believed a pigmentary disturbance to be responsible and Verhoeff (1948) said they are *"ridges comprising the inner layers of the choroid produced by cicatricial contraction of fibrous tissue which had replaced the deeper layers associated with extensive obliteration of the vessels and a few sub-choroidal haemorrhagic extravasations"*. Cowper (1954) thinks the streaks result from tears in Bruch's membrance or pigmented choroidal vessels.

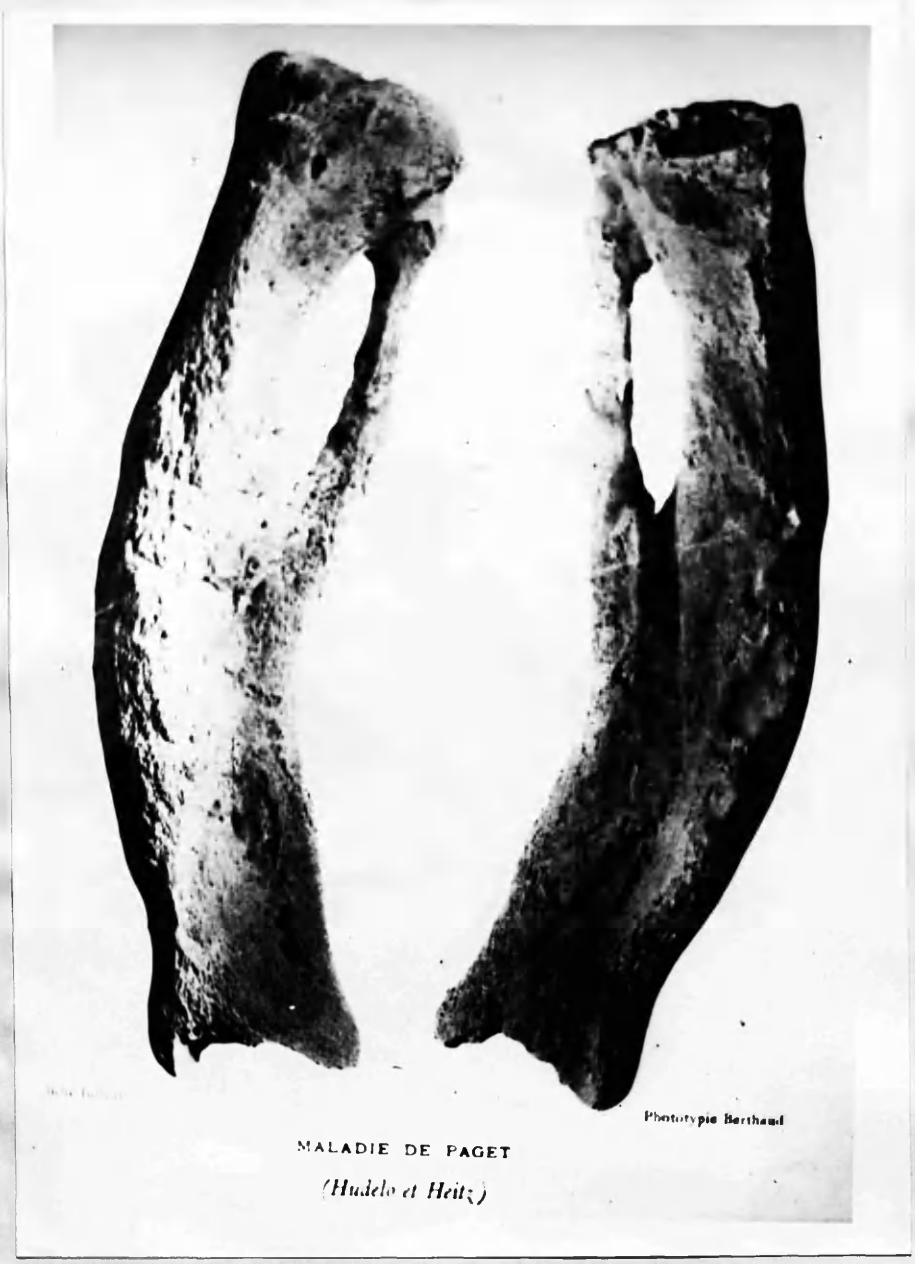

Fig.18.

Fig. 18 *Is reproduced from the article by Hudelo et Heitz and shows well the distinctive appearances of Pagets bone.*

Fig. 19.

Fig. 19 These early X-Rays of the same bones are of interest also though unfortunately not lending themselves easily to reproduction.

With regard to pseudo-xanthoma elasticium the precise histological abnormality here too is in doubt and it is disputed if the connective tissue abnormality affects the elastic fibres at all, or if there is an elastotic degeneration of the collagenous fibres. The inheritance of P.X.E. is by a Mendelian recessive gene and there is a female preponderance.

These facts combined with the doubt surrounding the nature of angioid streaks suggest that speculation along the lines indicated by McCusick must be very circumspect. I have searched for angioid streaks in 14 patients and found them in the left eye only, in one patient.

It may be appropriate to recall here Freund's belief that fibrous tissue proliferation is by itself the fundamental abnormality and that the process has a relation to the autonomous proliferation in neoplasia. Laserre (1950) and Léyani and Dunrupt (1950) also shared this idea. The analogy with Hodgkin's lymphadenoma was long ago suggested by O'Reilly and Race (1932). An interesting case report in this connection is in an early paper by Hudelo and Heitz (1901)* in whose case the tibia and fibula in one patient with osteitis deformans underwent such proliferative change as to become in parts fused into one mass of Pagetic bone.

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* *See Figs. 18 and 19.*

Primary Vascular Disturbance?

A current theory of the pathogenesis of osteitis deformans would implicate a primary intra-osseous vascular abnormality and this view is probably the one most widely held. That vascular abnormalities are present in Pagetic bones is beyond all doubt. The observation is not new. The increased vascularity apparent on dissection at operation or post-mortem is well known. If osteoporosis circumscripta is admitted as an early lesion then Schmorl has noted its extreme vascularity and described it as resembling a haemorrhagic infarct. In 1901, Béclère and Galliard following an early radiographic study of a severely affected case with extensive arterial calcification said "..... *ces lésions osseuses de la maladie de Paget paraissent frapper les divers segments du squellette individuellement; il semble que se soient des lésions secondaires consecutives a l'alteration et a l'incrustation calcaire des arteres nourricieres des os ...*" and again referring to the contiguity of affected with normal small bones in the extremities " ..... *cette singuliere répartition des lésions osseuses du squellette de la main jointe a l'intégrité des extremités articulaires ne s'accorde guère avec l'idée d'un trouble trophique d'origine nerveuse - elle s'explique mieux par l'hypothese d'une lesion artérielle intéressant l'artère nourricière .....* "

Unlike most writers at that time, Moore (1923) was familiar with the report by Beclere and Galliard and like many others he was impressed by the great size and tortuosity of the temporal vessels in some cases of skull involvement. He inclined to the view however that the vascular changes were secondary effects.

"Cone (1922) writes "*static thermal and vascular conditions are responsible for the localisation of the bone involvement and I would add that the blood vessels are the source of the disease in toto*". He had taken a sustained interest in Paget's disease and while unable to explain how vascular changes might produce the bone abnormalities he was impressed by the severity and extent of the vascular degeneration observed in his post-mortem studies saying " ..... *clinical observation coupled with the pathological findings in more than 900 autopsies convince me that Paget's disease is the result of chronic cardiovascular disease .....*". He wondered if thrombosis of the nutrient artery occurred with venous stasis and the opening up of collateral channels. In 1935, Reboul in an early monograph on arteriography illustrated the increased vascularity of the legs and leg bones in particular in a case of osteitis deformans. This publication too went generally unnoticed.

Edholm, Howarth and MacMichael (1945) showed that in an affected limb the blood flow may be increased as much as twenty times and at the same time there is a marked rise in cardiac output. Léquime, Denolin and

Verniory (1952) and Lequime and Denolin (1955) suggested that the local abnormality must be something of the nature of an arterio-venus aneurism. Sornberger and Smedal (1952) in a comprehensive review of the literature noted these changes and their absence in monostotic cases. Edholm and Howarth (1953) subsequently produced further evidence in support of their previous demonstrations. They showed the increased vascularity of the bones by gross anatomical dissection and microscopic examination and by radiography following injection of post-mortem specimens. Arteriography in 3 cases reported by Stortsen and Janes (1954) supported the same view and at the same time they recorded their observations on the increased venous pressures in affected limbs and the increased oxygen tension of the venous blood. Similar observations were made by Lequime, Denolin and Verniory and by Edholm and Howarth. Rappaport, Kuida, Dexter, Henneman and Albright (1957) recorded that when the circulation in an affected extremity was occluded a slowing of the pulse and a rise in diastolic blood pressure occurred. They too, noted that the arterial and venous oxygen concentrations in the blood of an involved limb showed a diminished difference.

In 1959 Mercer and Duthie by intravenous injection of radio-active phosphorus, shortly before operative exposure of vertebrae affected by osteitis deformans were able to demonstrate an undue concentration of isotope in the affected bones and concluded that as there had been no time for assimilation the increased concentration reflected the increased blood content of the bone.

The general trend of opinion among those recent authors quoted here has been towards the belief in multiple small fistulae.

In 1954 Rutishauser, Vaynal and Rouiller, who were well aware of the general belief in the fistulous nature of the vascular anomaly, made a detailed histological study of Pagetic bones. They recorded hypertrophy of the periosteal and endosteal plexuses and increased penetration of the cortex by branches from these. In section they found a great increase in the number of arterioles and arteriolar capillaries. The abundant arterioles being of much wider diameter than the few discernible in normal bone. In the fibrous zones they found arcades of arteriolar capillaries and large venous sinusoidal spaces were common. There was a tendency for many vessels to be arranged in parallel. An effect of these changes is to produce in the bones a sudden loss of peripheral resistance to the circulation. This increases the pulse pressure and the cardiac output and these authors

say there is no need to invoke the existence of a fistulous type of lesion " ..... *la vascularisation d'un os Pagetique se caractérise par l'extraordinaire accroissment de nombre des vaisseaux et par le grand diamètre de la plupart d'entre eux ....."* *"..... des communications directes entre arterioles et sinus veineux n'ont pas pu être mises en evidence ....."*

In 1955 Bricaud, Castaing Cabanieu, Cottin and Brausted published observations supporting these views.

DISCUSSION

From the foregoing it emerges that well attested evidence supports current views on many points - the incidence of the disease in the community, the prevalence of subclinical affections, the distribution of cases by age and sex, the skeletal distribution of bone changes and the frequency of pathological fractures and sarcomata. In other matters there is insufficient evidence to support firm conclusions and opinions differ widely. Writings on the etiology especially reveal their diversity.

Synchronous resorption and reformation of bone is a physiological phenomenon. The continuous and perfect remodelling of the meta physis during growth of a long bone shows how delicate a reciprocal adjustment normally exists. The factors governing the resorption of bone with narrowing of the shaft and extension of the medullary cavity and simultaneously the contiguous proliferation by which the metaphyseal expansion enlarges and migrates distally must surely be meticulously integrated. Some asynergysm of these processes might conceivably result in such a dystrophy as osteitis deformans. Elting and Peeters have both favoured this concept. Where one of these two opposite tendencies predominates a mono-phasic lesion results. Osteoporosis circumscripta may be

such a lesion. It has been argued that its occurrence in the skull is related to the absence of mechanical stress.

Many would incriminate resorption as the primary abnormality and assign to new bone formation a compensatory role invoked by the mechanical weakness which resorption produces. Mechanical strees, they argue, is the stimulus to osteoblastic activity and if this is eliminated as for instance by immobilisation after a fracture resorption proceeds apace and the affected bones rapidly decalcify except at the fracture site where local factors determine prompt callus formation and calcification. Albright and Reifenstein are the originators of this concept. They said that in such circumstances if this concept is correct hypercalcaemia may be expected. Indeed they did encounter this and of menacing degree in 2 cases under their care. Their experience is often quoted but I have found no other records of such occurrences. I have had the opportunity to treat 3 pathological fractures of the femur occurring in the course of osteitis deformans and in none of these has there been any reaction to immobilisation resembling that occurring in Albright and Reifenstein's 2 cases. See Fig. 20.

That bone resorption is the first change has been argued by many others notably Schmorl, Collins, Brailsford and Wilton but the cause of this absorption

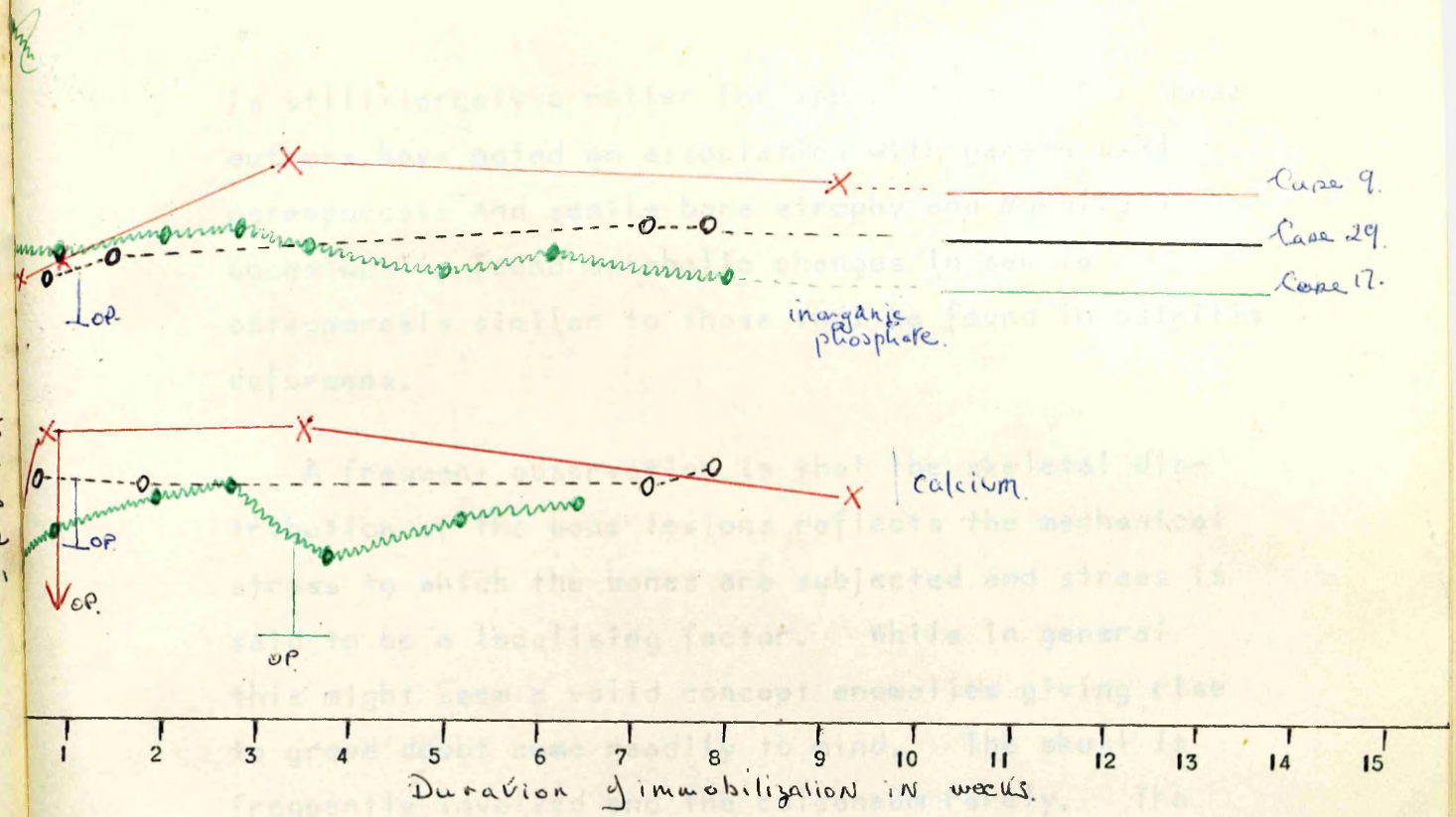

Fig. 20 *Shows serial estimations of serum calcium and inorganic phosphate done during immobilization following fracture. These were operated on at the time indicated. (OP) Neither the stress of operation nor the immobilization seems to have had any noticeable effect on these levels.*

is still largely a matter for speculation. All these authors have noted an association with generalised osteoporosis and senile bone atrophy and Moehlig has occasionally found metabolic changes in senile osteoporosis similar to those that he found in osteitis deformans.

A frequent observation is that the skeletal distribution of the bone lesions reflects the mechanical stress to which the bones are subjected and stress is said to be a localising factor. While in general this might seem a valid concept anomalies giving rise to grave doubt come readily to mind. The skull is frequently involved and the calcaneum rarely. The pelvic lesion is often unilateral and may be associated with affection of the femur of the opposite side. The great power of the masseter muscle might be expected to produce something more notable than the occasional mainbular lesion. In Case No. 9 osteoporosis circumscripta occurs in the occipital region in a patient spending much of her time lying flat on her back with the affected region resting on pillows. Sugarbaker (1940) suggests that the total bone mass is distributed parallel to the mechanical stress and it is to be expected that the random distribution of Pagetic changes might well give an appearance suggesting stress as a cuase, when in fact the association is fortuitous. On the other hand Kay in affected twins found osteitis deformans in the right radius in the right handed twin

and in the left radius of the left handed twin.

When treated at all, patients seem to get symptomatic treatment in most cases but a few rationally based methods have been tried and the results obtained might afford some clue to the nature of the disease. Helfet sees support for his views in the satisfactory response to the administration of aluminium salts. By diminishing phosphate absorption in this way he prevents the occurrence of secondary hyperparathyroidism and mitigates the effects of the renal impairment of phosphate excretion. Berman has had some success by treatment with adrenal extract. Albright and Reifenstein have given detailed accounts of the diminution in the local blood flow and histological return to something like the picture of normal cancellous bone following administration of A.C.T.H.

Oestrogens and androgens have both given benefit in some cases (Poilleux and Sluczewski) and it has been argued that these may help by diminishing anterior pituitary activity.

CONCLUSION

Osteitis deformans is a common disease. Subclinical forms are very prevalent. Males are more commonly affected than females and the greatest incidence of the disease is in old age. There is no self limiting factor and florid lesions are commonly encountered in patients of great age. Onset in early adult life is by no means rare.

The jaws are affected in many cases - the maxilla as well as the mandible. Leontiasis ossea is frequently due to osteitis deformans.

Osteoporosis circumscripta is usually a manifestation of osteitis deformans.

There is a notable absence of peripheral ischaemic changes in the limbs of pagetic patients considering the age of the majority.

The impairment of hearing and vision so commonly regarded as effects of osteitis deformans has probably been over-emphasised.

The role of mechanical stress in determinating the skeletal distribution of pagetic changes is in doubt.

The cause of osteitis deformans is undetermined.

Many believe that an explanation will yet emerge revealing a causal endocrine abnormality. Changes in carbohydrate metabolism commonly found are thought by some to support this belief. These do occur in patients with osteitis deformans but also they have been shown to relate to age and to arteriosclerosis in the absence of osteitis deformans and endocrine abnormalities may prove to be a fortitous association.

Vascular alterations seem likely to be secondary to the bone changes.

S U M M A R Y

INFORMATION OBTAINED BY A STUDY OF 29 PATIENTS WITH OSTEITIS DEFORMANS IS RECORDED. TO THIS IS ADDED DATA RELATING TO THE X-RAYS OF A FURTHER 68 PATIENTS.

THE LITERATURE ON OSTEITIS DEFORMANS IS REVIEWED AND AN ATTEMPT MADE TO APPRAISE CURRENT KNOWLEDGE OF THIS DISEASE AND THE RESULTS OF THE PRESENT STUDY.

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