DEPARTMENT OF PATHOLOGY, KAROLINSKA SJUKHUSET, STOCKHOLM

ON THE GENESIS OF OSTEITIS DEFORMANS (PAGET)

By

ÅKE WILTON

INTRODUCTION

Among the diseases affecting the skeleton osteitis deformans (Paget) is of interest from a bone physiological point of view. The disease is a typical disease of aged people, and therefore a detailed study of the reactions in the aging bone tissue is possible. As the disease usually has a long duration and causes progressing deformities, the significance of strain in the forming of the skeleton can be better studied than in any other disease of the bones. The author (1931, 1933 and 1937) has investigated the reactions in the bone tissue of a variety of bone diseases and has for many years examined and followed-up cases suffering from Paget's disease. The object of this article is to show in what way the skeleton is affected at the earliest stages of the disease, how the pathological changes progress and to discuss the etiology of the disease on the basis of the findings.

SUMMARY OF EARLIER HYPOTHESES

Paget (1877 and later) considered that osteitis deformans is of an inflammatory nature, an osteitis, and based his opinion on Butlin's interpretations of the histopathologic changes. *Lunn* (1885) believed that the disease was caused by inherited constitutional factors. Other investigators (i.e. *Stilling*, 1890, *von Recklinghausen*, 1891, *Looser*, 1926) came to the same conclusion as *Butlin*, namely, that an inflammatory process is the originating cause. Other causative factors suggested are syphilis, gout, chronic rheumatism, trauma, intoxication owing to metabolic or intestinal disturbance, carotene deficiency etc.

The histopathologic changes recognized in Paget's disease were for a long time classified as a form of osteitis fibrosa cystica, although of "hyperostotic" type (*Christeller*, 1926). This misinterpretation has since been corrected, mainly by *Schmorl*. In view of the observation

that parathyroidal hyperplasia is present in osteitis fibrosa cystica, Paget's disease has also been interpreted as due to a disturbance in the internal secretions (hyperfunction of the thyroid gland, *Meyer-Borstel,* 1929, disturbance of the hypophyseal function, *Rummert,* 1934, and others).

The inflammation theory is still much discussed. Objections to it were already raised as early as 1888 (*Goodhart*), and since then other investigators, for example *Stenholm* (1924), have abandoned the theory. A detailed study led *Schmorl* (1932) to the conclusion, that the disease is a local, non-inflammatory, primary bone disease of unknown origin softening the bone. This interpretation has been objected to by Erdheim (1935), who revived the classic inflammation theory after a study of *Paget* changes in the skull. Other authors, such as *Haslhofer* (1937), maintain, like *Erdheim,* that osteitis deformans is a chronic osteitis. *Weinmann* and *Sicher* (1947) are of the opion that an hyperplastic osteitis may not be entirely unjustified.

TABLE I

Case no.		Sex	Year of birth	Year when Paget symptoms appeared or the disease was diagnosed	Age when this occurred	Year of death	Duration of disease years	Cause of death
Living cases	Dead cases							
1		fm	1874	1925	51			
2		fm	1875	1937	62			
3		m	1892	1943	51			
4		m	1880	1943	63			
5		m	1881	1943	62			
	6	m	1863	1898	35	1929	31	Arteriocardiosclerosis + bronchitis purulenta
	7	m	1858	1918	60	1931	13	Cystopyelonephritis purulenta
	8	fm	1861	1921	60	1926	5	Bone sarcoma with metastases
	9	m	1855	1922	67	1937	15	Arteriocardiosclerosis
	10	m	1869	1928	59	1931	3	Unknown
	11	m	1850	1919	69	1931	12	Arteriocardiosclerosis
	12	m	1855	1932	77	1937	5	Fractura collum femoris + bronchopneumoniae
	13	m	1865	1933	68	1944	11	Hypertrophia prostatae + cystopyelonephritis
	14	m	1863	1944	81	1945	1	Unknown

THE AUTHOR'S INVESTIGATIONS

The author's material consists of 19 clinically diagnosed cases of *Paget*'s disease, in 14 of which it was possible to corroborate the diagnosis. Table 1 gives information with regard to the 14 definitely established cases (11 men and 3 women).

The first part of the investigation consisted in macroscopic and microscopic studies on skeletal parts taken at autopsy from two brothers and a sister suffering from *Paget*'s disease (cases 6, 7 and 8) (Wilton 1937).

Subsequent investigations were in the form of frequent roentgen examinations on living *Paget* cases and examination of autopsy cases in the light of previous roentgen observations.

Roentgenologic observations.

After comparing the roentgen pictures of skeletal parts appearing normal at the first examination with those taken later, when the bones displayed changes typical of *Paget*'s disease, the author has come to the conclusion that the earliest observable roentgenologic sign of this disease is that the coarse-fibred lines of spongy bone (the Meyer lines, fig. 1), running in the directions in which the strain is exerted, without being noticeably thickened appear with abnormal clarity in the roentgen picture (fig. 2, cuneiform bones). Later on, the lines coarsen and become confluent, giving rise to sclerosis (cf. calcaneous in figs. 1 and 2). At this early stage, it is hardly possible to diagnose *Paget*'s disease on the basis of the roentgen appearances, seeing that a similar type of sclerosis is also seen in other diseases of bone, such as healed osteitis fibrosa cystica. At a later stage in the disease the *Paget* roentgenogram is characterized by the presence of decalcified and rarefied foci in addition to the sclerosis already mentioned, and it is not until this stage has been reached that *Paget*'s disease can be diagnosed with complete certainty (*Polgar* 1933). As the disease progresses the skeletal parts involved gradually become deformed in a manner showing characteristic features for each individual bone ("fish vertebrae", "heart-shaped pelvic inlet", "bowlegs with sabre tibia", and so on).

In *Paget* patients with scoliosis, in whom the weight-bearing conditions in the pelvic bones and lower extremities, as a consequence of this deformity, are unevenly distributed, the *Paget* changes are most pronounced on the side where the strain is greatest (fig. 3).

The disease may appear to be stationary for long periods at a time, but it nevertheless slowly progresses, earlier deformities becoming

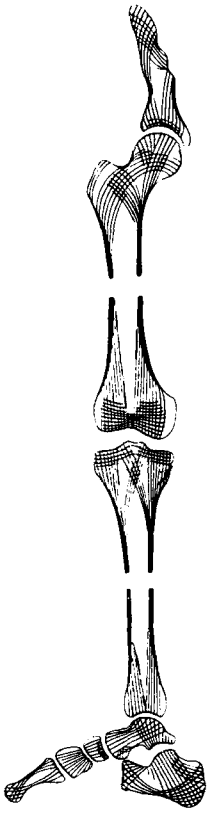

Fig. 1.
From *Meyer* (1867). The figure shows the coarsely fibred spongiosa (so-called Meyer lines) in the pelvis and the bones of the lower extremities.

more pronounced and new parts of the skeleton gradually being involved.

In the following macroscopic and microscopic analysis the roentgenologic changes have been divided as follows into stages which naturally cannot be strictly delimited from one another.

Stage 1: Abnormally clear Meyer lines.
Stage 2: Sclerosis.
Stage 3: Sclerosis and rarefied foci.
Stage 4: Progressing deformities.

Examination of sections.

Stage 1. The bone structure in bones showing the earliest roentgenologic lesion is usually of a normal yellowish-white colour. Microscopically, the fine-fibred spongy bone which, in control cases, encloses the Meyer lines in a fine network is seen to have wholly or

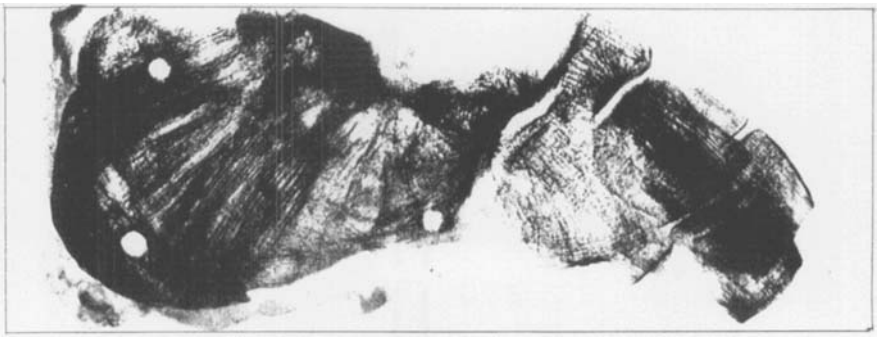

Fig. 2.
Roentgenogram of the bones of a foot with *Paget* lesions. The cuneiform bones display the earliest lesion, in the form of abnormally clear Meyer Lines. In the calcaneus a subsequent stage is seen, with coarsened Meyer lines which in places have become confluent giving rise to "sclerosis".

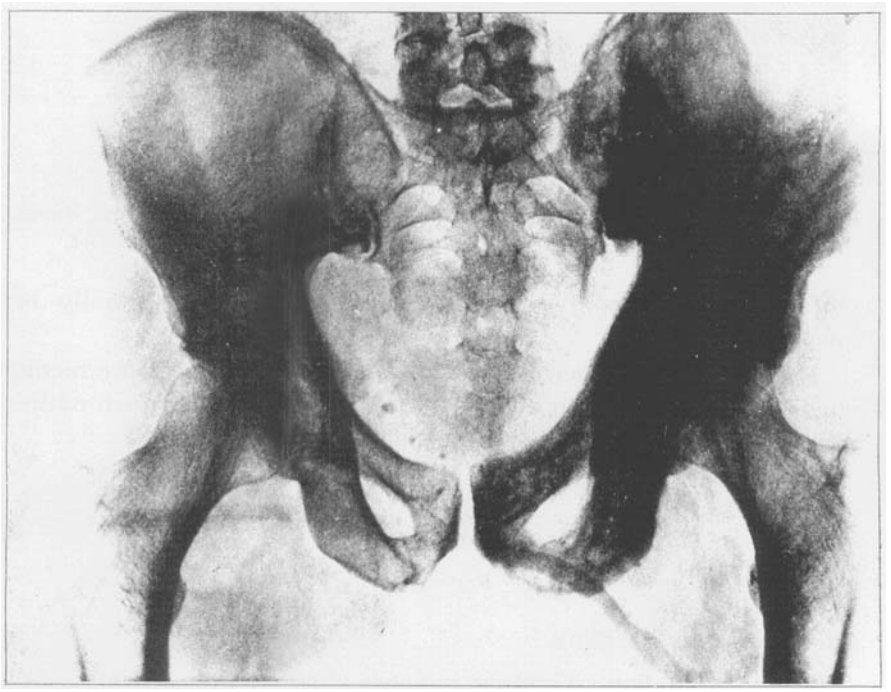

Fig. 3.
Typical roentgenogram of a *Paget* pelvis displaying sclerosis and rarefied foci. The lesions are most advanced on the right side, where the strain, on account of scoliosis, is greater than on the left side. On the right side also, the pelvis is deformed.

partially disappeared (fig. 4). The coarse-fibred lines also display atrophy in places, and the bone appears slightly brittle. At this early stage, there are no or insignificant resorption processes and the microscopic appearances most closely resemble those seen in senile atrophy of bone.

Stage 2. In the next stage of the *Paget* process the bone, macro-

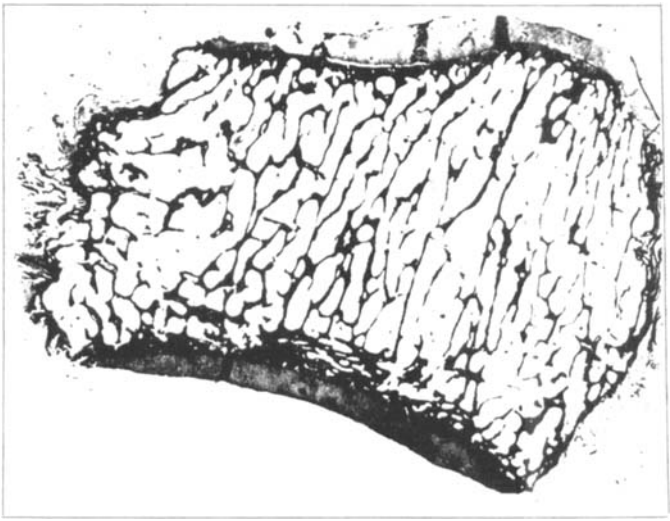

Fig. 4.
The earliest roentgenologic sign of Paget's disease of bone (cf. Fig. 2 cuneiformi bone) proves to be due to atrophy of the fine-fibred spongy bone.

scopically speaking, is reddish in colour, and dark red spots resembling hemorrhages are often present. When the bone is examined microscopically this change is recognised as due to osteolytic foci, with wide vessels surrounded by highly vascularized, poorly differentiated bone tissue in the calciferous bone trabeculae (fig. 5).

The immature bone tissue is growing and after having undergone the maturing process forms new calcareous bone (cf. Wilton 1937) to strengthen the structural parts where the strain is greatest, i.e. the compact bone and the Meyer lines, as a result of which the sclerosis seen on the roentgen picture arises, At this stage, lacunar resorption is also observable in the microscopic sections side by side with the new bone formation. The bone tissue proliferating in the marrow spaces is highly vascularized and contains immature spindle-shaped bone cells resembling connective tissue cells. When the marrow cavities are filled with tissue of this kind the morphologic appearances that have

been termed "osteitis fibrosa" and "marrow fibrosis" arise. These appearances may resemble granulation tissue (fig. 6) and this explains why *Paget*'s disease has previously been thought to be due to an inflammatory process. Inflammatory cells are, however, not distinguishable, either at this stage or at other stages.

Stage 3. At a subsequent stage, the processes of new bone formation

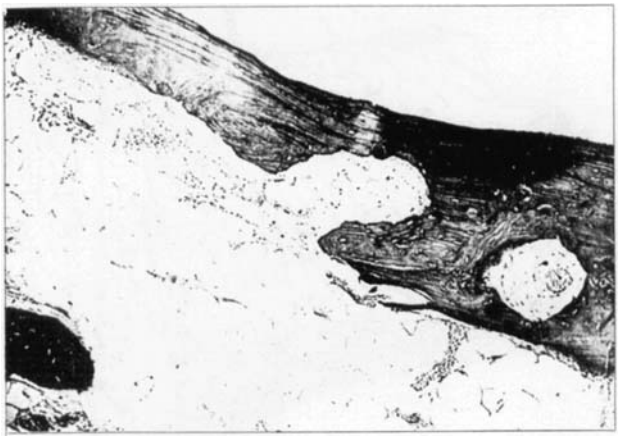

Fig. 5.
Early histo-pathological stage of Paget. Around the vessels in the calciferous bone there have arisen foci of dissolution with immature bone tissue, which is proliferating out into the fat marrow.

and resorption become more active. The lacunae become confluent and form large cavities, on the walls of which new bone formation and resorption take place in close proximity to one another. If the new bone is formed close to the old calcareous bone, broad "cementing lines" arise. A study of microscopic sections gives the impression that the resorption processes take place without conformity to any known law. By combining roentgenologic, macroscopic and microscopic studies and observing the strain on bones affected with *Paget*'s disease the author has come to the conclusion that the intensive reconstruction processes are brought about by static insufficiency with its resultant alteration in the weight-bearing conditions. New bone formation takes place in those structural parts where the alteration has involved increased strain, and bone resorption where the strain has been lessened. The parts not subjected to strain become more or less completely resorbed during this stage, and this is the explanation of the rarefied and decalcified foci seen in the roentgen picture.

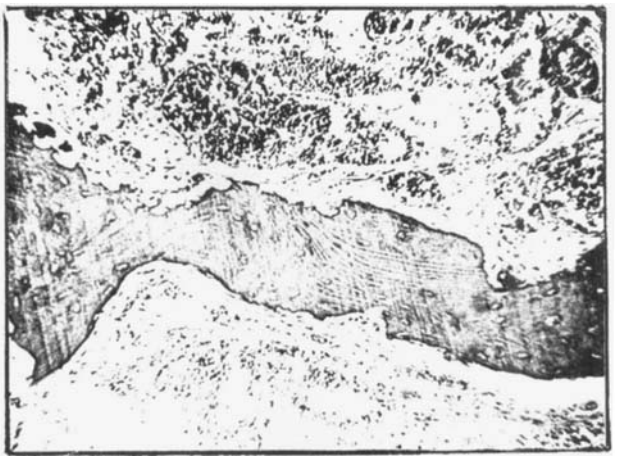

Fig. 6.
Section from a part of the talus which had a dark-red cut surface. The marrow spaces are occupied with blood-filled vessels and immature bone tissue, resulting in the morphologic pictures described as "osteitis fibrosa" and "marrow fibrosis".

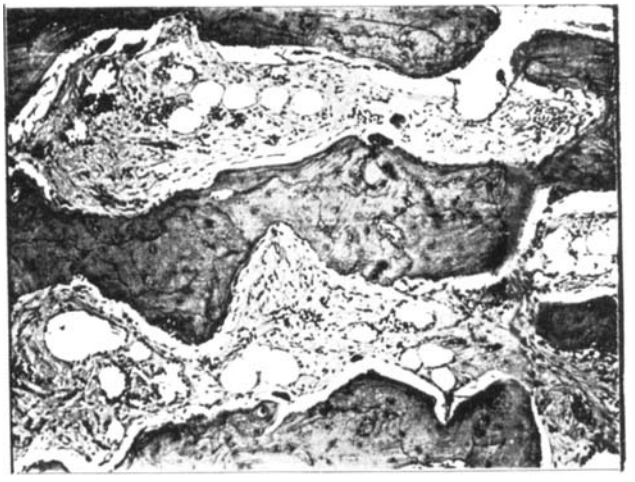

Fig. 7.
Paget in a later stage. Mosaic structure, "marrow fibrosis", processes of bone dissolution and new bone formation are to be distinguished.

Because of the intensive reconstruction processes the previous microscopic structure of the calcareous bone changes, the bone appearing to be composed of a large number of small pieces of bone (so-called mosaic structure, fig. 7) separated from one another by broad cementing lines with irregular deposits of mineral salts (cf. Engfeldt et al., 1952).

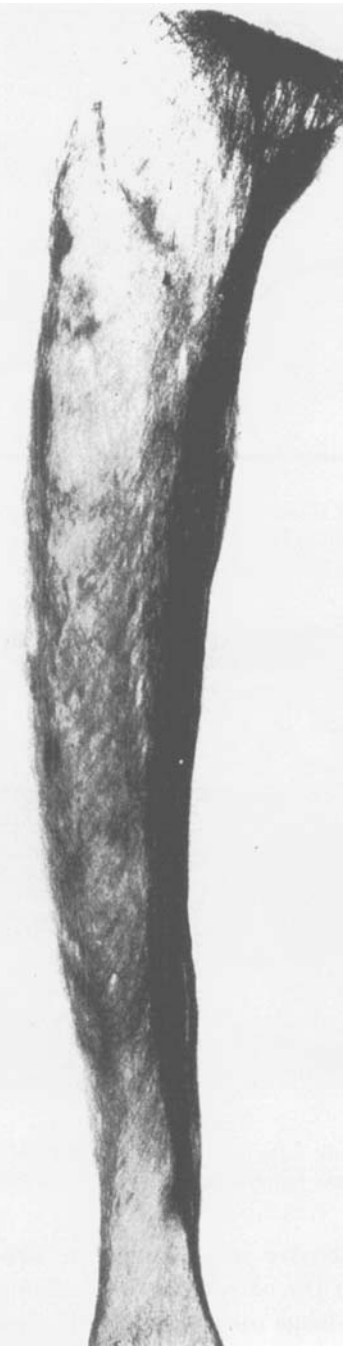

Fig. 8.
Roentgenogram of the medial part of a *Paget* tibia with sclerosis on the posterior (concave) side where the strain is greatest and rarefied foci on the anterior (convex) side where the strain has been lessened.

Fig. 9.
A femur in an advanced stage of *Paget*'s disease. The bone shows the same necrobiotic and necrotic features as in advanced senile osteoporosis.

Stage 4. At the stage where deformity has developed, the principles governing the reconstruction processes become more evident. In the sabreshaped deformation of the tibia, for instance, sclerosis of the compact bone and the Meyer lines arises on the posterior (concave) side where the strain is greatest while the bone resorption processes dominate on the convex side where the strain has been lessened

(fig. 8). The progressing *Paget* process is characterized, histopathologically, by bone production of lower quality, and "primitive" bone is often formed in the "marrow fibrosis". The cementing lines become broader while at the same time the new-formed matrix consists to an ever increasing extent of hyaline masses poor in collagen in which bone salts are deposited in the same way as in the cementing lines. Gradually this type of matrix, as in advanced senile osteoporosis, becomes necrobiotic (fig. 9).

DISCUSSION

The most characteristic feature of *Paget*'s disease is the advancing deformation of various parts of the skeleton. *Paget* declared that deformities arise because the diseased skeletal parts, owing to their softness, have a lowered resistance to load. The author is of the same opinion and as each skeletal part has its own special loading characteristics each bone will always be deformed according to a certain pattern.

Various explanations have been advanced to account for the "softening" and the resulting static insufficiency. Those investigators who consider *Paget*'s disease to be a form of osteitis regard the static insufficiency as dependant upon inferior new bone formation due to the inflammatory process. As no signs of inflammatory changes are observed in *Paget*'s disease this hypothesis has no objective grounds.

The author accounts for the *Paget* changes and the *steadily progressing* static insufficiency as follows:

The ability of any part of the skeleton to support its load is determined by 1) the quantity and 2) the quality of the bone structure. A continuous rebuilding of the bone takes place as it performs its functions. The total *quantity* of the bone is determined by the inherent relative speeds of deposition and resorption. The capacity to produce new bone depends on the growth rate (new formation of bone-producing cells). In the early ontogenetic stages of development the capacity for bone growth (potential powers of new bone formation) and its growing activity (active new bone production) are considerable, but these decrease as development proceeds.

High-quality bone structures require fully developed organic matter and *regularly* deposited mineral salts. From what has been observed the formation of both the organic and inorganic matrix apparently takes place as the result of the activity of the bone cells. With gradually increasing functional maturity these gain the power to produce a high-quality matrix (Wilton, 1931). In the senile stage of life the bone cell's power of maturation gradually diminishes and the growth power

is small, leading to formation of inferior matrix and atrophy of the finely fibred spongy bone (Wilton 1937).

The first sign of the *Paget* disease is a generalized atrophy of the finely fibred spongy bone without any morphologic signs of resorption processes, that is to say, a morbid change that is caused by the bone's reduced capacity for development. As this type of atrophy, under physiologic conditions, begins at a much more advanced age than that at which osteitis deformans begins, the conclusion reached by the author is that *Paget* lèsions arise because *the bone tissue enters its senile phase abnormally early*. The normal strain therefore has the effect of overstrain. The bone tissue is, admittedly, senile, but at this early stage of the disease it still retains its capacity for reaction and reacts in the same way as old, overstrained bone tissue with an atrophied endosteum and periosteum (osteolysis around the vessels in the calcareous bone, with formation of proliferative bone tissue; Wilton, unpublished). Owing to the new bone formation, the skeletal part can function for a time in a normal manner, and few or no clinical signs of skeletal insufficiency arise. With progressing age the bone tissue's capacity for reactive processes diminishes, leading to the gradual development of skeletal insufficiency and deformity with the progressing skeletal insufficiency. Continual reconstruction processes occur, and we then get the characteristic histopathologic picture, with its numerous foci of resorption and new bone formation, "marrow fibrosis", "mosaic structure", and so on. The bone tissue's capacity for reactive processes diminishes still further, the life of the newly formed bone tissue becomes shorter and shorter, and the bone becomes liable to necrobiosis. The *Paget* process at this stage is indistinguishable from the changes displayed by highly senile bone tissue.

The occurrence of osteitis deformans in families has been known for a long time. *Da Costa* and his co-workers made a study of the cases of *Paget*'s disease described in the literature, where the disease had attacked two or more members of the same family. *Kerr* supplemented this review with other similar cases (Table II). Still other cases, such as those described by *Hankes* (1935) (4 brothers) may be added to these reviews. In my material, three of the cases were brothers and sister.

The fact that two or more members of the one family may suffer from such a rare disease as *Paget*'s disease is strong evidence in support of the view *that the abnormally small development capacity of the bone tissue is caused by hereditary factors.*

Many facts argue in favour of local factors also having a certain importance in the arisal of *Paget* changes. As *Schmorl* has already

TABLE II

Author	Relationship of cases
Da Costa.	
Fournier	Father and son
Smith	Do.
Oltinger and Agasse-LaFont	Father and 2 sons
Roberts	Son, father, and brother
Fritz	Son, father, sister, and 3 great-aunts
Lunn	2 brothers
Robinson	Do.
White	Do.
MacKenzie (cited by Smith)	Do.
Dubreuilh and Laubie	2 brothers and son of 1 of them
Parry	2 sisters
Stahl	Do.
DaCosta	Do.
Kilner	Brother and sister
Lindsay and Gordon	Man and 2 paternal uncles
Kerr.	
Chauffart	Mother and daughter
Berger	Mother and son
Wallet	Brother and sister
Abbey	2 brothers

pointed out, *Paget* lesions first begin, and become most pronounced, in those parts of the bone structure that are exposed to the greatest strain. In *Paget* patients with scoliosis the *Paget* lesions are severest on the side bearing the greatest weight. These observations suggest that the strain exerted on the bone structure may be a local genetic factor.

SUMMARY

Fourteen cases of *Paget*'s disease have been examined and followed-up. It is shown that the first sign of the disease is a generalized atrophy of the finely fibred spongy bone without any signs of inflammatory processes. On the basis of the investigation the author advances the hypothesis that the genesis of *Paget*'s disease is an abnormally small development capacity of the bone tissue caused by hereditary factors.

RESUME

14 cas de la maladie de *Paget* ont été examinés et suivis. Il s'est montré que le premier signe de la maladie est une atrophie généralisée de l'os spongieux finement fibré, sans aucun signe de processus in-

flammatoire. A la base de ces investigations, l'auteur émet l'hypothèse que la gènese de la maladie de *Paget* est la capacité anormalement faible de développement du tissu osseux due à des facteurs héréditaires.

ZUSAMMENFASSUNG

Vierzehn Fälle von Pagets Erkrankung wurden untersucht und weiter beobachtet. Es wird gezeigt, dass das erste Zeichen der Erkrankung eine allgemeine Atrophie der feingefaserte Spongiosa ist und dass Zeichen entzündlicher Prozesse nicht vorhanden sind. Auf Grund seiner Untersuchungen stellt der Verfasser die Hypothese auf, dass die Ursache der Paget Erkrankung in einer erblichen Schwäche der Entwicklungsfähigkeit von Knochengewebe zu suchen ist.

LITERATURE

Butlin, H. T.: Lancet 1885: 1, 519.
Christeller, F.: Verh. dtsch. path. Ges. 1926.
Engfeldt, B., Engström, A., Helander, C. G., Wilton, Å., and *Zetterström, R.:* Acta path. Scand. 1952: 31, 256.
Erdheim, J.: Beitr. z. Path. Anat. 1935: 96, 1.
Goodhardt, J. F.: Trans. path. Soc., London 1878: 39, 175.
Haslhofer, L.: Henke und Lubarsch: Handb. d. spec. Path. Anat. u. Hist. 1937: IX/3, 551.
Kerr, J. W.: Public Health Bulletin 1933: 209, 1.
Looser, E.: Verh. dtsch. path. Ges. 1926.
Lunn, J. R.: Trans. Clin. Soc., London 1885: 18, 272.
Meyer-Borstel, H.: Fortschr. Röntgenstr. 1930: 42, 589.
Paget, Sir James: Trans. Roy. Med. a. Chir. Soc., London 1877.
– Ibid. 1882.
– Illustr. Med. News. London 1889: 2, 181.
Polgar, E.: Röntgenpraxis 1933: 5, 487.
v. Recklinghausen, F.: Festschr. d. Assist. f. Virchow. Reimer. Berlin. 1891.
– Untersuch. ü. Rachitis u. Osteomalacie. Fischer. Jena. 1910.
Rummert, O.: Fortschr. Röntgenstr. 1934: 49, 85.
Schmorl, G.: Verh. dtsch. path. Ges. 1909.
– Verh. dtsch. path. Ges. 1926.
– Verh. dtsch. path. Ges. 1930.
– Fortschr. Röntgenstr. 1931: 43, 202.
– Virch. Arch. 1932: 283, 694.
Stenholm, T.: Path.-Anat. Stud. ü. d. Osteodystrophia fibrosa (sog. Ostitis fibrosa v. Recklinghausen) Thesis. Almquist o. Wiksells boktryckeri, Uppsala. 1924.
Stilling, H.: Virch. Arch. 1890: 119, 542.
Weinmann, J. P. and *Sicher, H.:* Bone and Bones. The C. V. Mosby Company, St. Louis, 1947.
Wilton, Å.: Acta path. Scand. 1931: 8, 258.
– Ibid.: suppl. 15.
– Tissue Reactions in Bone and Dentine. Kimpton. London. 1937.