The Mechanism and Incidence of Cardiovascular Changes in Paget's Disease
(Osteitis Deformans)

A Critical Review of the Literature with Case Studies

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Although abundant evidence of concomitant cardiovascular disease is scattered throughout the literature on osteitis deformans, appreciation of the etiologic relationship between the two diseases has been lacking. This paper shows that cardiovascular disease accompanying extensive osteitis deformans may result from: (1) excessive demand on the heart from increased vascularity of affected bones; (2) the influence of concomitant arteriosclerosis apparently exceeding the normal for the age concerned; (3) characteristic thoracic spine deformities which compromise cardio-respiratory function, and (4) hypertension. Fifty-four cases are presented. The incidence of cardiovascular disease exceeds that in the general population of the same age and corresponds with the extent of skeletal involvement.

Many physicians conversant with the osseous characteristics of Paget's disease are not well acquainted with concomitant changes in the heart and blood vessels which occur in the same disease. Incontrovertible evidence of such changes is scattered throughout the voluminous literature on osteitis deformans that has accumulated since Sir James Paget's original paper, but to date little attempt has been made to correlate these various findings and opinions, nor has any extensive study on the incidence of such changes been made. We have, therefore, reviewed the literature on Paget's disease with particular reference to the nature and incidence of the attendant cardiovascular changes, and presented a series of consecutive cases in which studies of heart size and electrocardiographic examinations have been made in an attempt to correlate previous observations and establish the incidence of related cardiovascular disease in osteitis deformans.

Occult,\textsuperscript{1-3} monophasic,\textsuperscript{4-10} monostotic,\textsuperscript{11-15} and polyostotic or advanced classic forms of the disease have been described.\textsuperscript{16-26} However, it is the vascular and cardiac changes that occur in the very extensive or classic form of the disease with which we are primarily concerned.

Relationship between Paget's Disease and the Circulatory System

The characteristics of osteitis deformans, per se, have been thoroughly reported and discussed in periodicals and texts,\textsuperscript{27-31} so that an attempt will not be made to elaborate on this aspect of the problem. The appreciation of the influence of osteitis deformans and attendant conditions on the cardiovascular system has been delayed and complicated by several factors: (1) there is a high incidence of degenerative vascular changes in the "normal" elderly population, which must serve as a basis for comparison; (2) the marked limitation of activity that usually accompanies the classic form of Paget's disease tends to mask the presence of cardiovascular changes in the group in which they would otherwise be most likely to manifest themselves; (3) the classic form of the disease is so uncommon (in contrast to the localized disease)\textsuperscript{32,33} that it is difficult to obtain a large series of cases for study; (4) deformities of the thoracic spine characteristic of the classic form of Paget's disease make the determination of the presence of cardiac
enlargement difficult on roentgenologic and physical examination.

The following conditions, any one or all of which may be present in a given case of osteitis deformans, either increase the work of the heart or decrease the ability of that organ to perform its function and, therefore, over a period of time, diminish cardiac reserve and predispose to enlargement and failure: (1) increased blood flow in the bony lesions of osteitis deformans in certain phases of the disease; (2) arteriosclerosis; (3) deformities of the thoracic spine and chest, and (4) hypertension.

Increased Vascularity and Hemodynamics in Osteitis Deformans

A. Incidence

Sir James Paget remarked the increased vascularity of affected bones, and described the appearance of the long bones in his first case which came to necropsy as follows: "The outer surface of the walls of the bones was irregular and finely nodular, as with external deposits or outgrowths of bone, deeply grooved with channels for the larger periosteal vessels, finely but visibly perforated in every part for the transmission of the enlarged small vessels. Everything seemed to indicate a greatly increased quantity of blood in the vessels of the bone."22

Increased heat over affected tibiae was recorded in three of the seven additional cases reported by Paget in 1882.21

Evidence of increased vascularity of affected bone in the form of increased redness, warmth, or dilated overlying vessels was noted by many subsequent observers,8, 12, 15, 16, 31-44 and came to be recognized as a clinical feature of the disease.10, 45-47 The replacement of bone by fibrous and vascular tissue99, 48, 49 was observed to be accompanied by hyperemia, increased vascularity and also by fibrosis of the bone marrow.1, 2, 6, 16, 17, 24, 32, 35, 41, 45, 50-55

Instances of excessive heat and redness have been observed in this series, and have been interpreted as clinical evidence of increased blood flow in affected bone.

It is usually difficult to accomplish satisfactory hemostasis when it is necessary to operate on pagetic bone. Two patients in this series had surgical treatment and in both instances there was excessive bleeding. This problem has been encountered by others 39, 40, 55, 56 and emphasizes the degree of abnormal vascularity of bone affected by osteitis deformans.

Although the presence of excessive vascularity in bones affected by osteitis deformans was soon well established,46, 39, 48, 54, 57, 58 the degree of increased blood flow, its relationship to the radiologic stage of the disease and influence on the general circulation remained to be determined.

In 1923, Sherwood Moore39 made the first attempt to determine, quantitatively, the circulatory changes in Paget's disease by measuring the volume flow to the limbs. An average of many observations showed the blood flow to the affected limb to be over twice that to the sound limb, and he concluded: "Increased vascularity of bone in Paget's disease can be considered as established beyond doubt. . . . It certainly exceeds increased vascularity observed in infectious states of bone."39

In view of the fact that recent experiments have emphasized the difficulties encountered in measuring the blood flow through extremities in human beings,59 the work of Moore should, perhaps, be accorded more qualitative than quantitative significance, but it remains an important early observation.

Awareness of the effects of increased vascularity due to Paget's disease developed slowly. One of our patients, a 68 year old man, had extensive Paget's disease of 20 years' duration and when last admitted to the hospital was in congestive heart failure. The possibility of a relationship between the excessive blood flow due to Paget's disease and the congestive heart failure was considered, as shown by the entry of Dr. L. M. Hurxthals on the hospital record of December 27, 1943: "The right leg is hot, probably indicating marked blood flow there due to Paget's disease. This added blood flow may be a factor in heart failure."

The most comprehensive study of the vascular changes in bone affected by osteitis deformans and their influence on the general circulation has been made by Edholm, Howarth, and McMichael.58 In 1945, they meas-
ured the cardiac output and bone blood flow in a 66 year old man who had advanced, extensive osteitis deformans accompanied by congestive heart failure of undetermined etiology. Left ventricular enlargement, marked capillary pulsation in the nail beds and a high pulse pressure were present. An electrocardiogram was normal. On venous catheterization, the right auricular pressure was elevated, and the cardiac output was 13.3 liters per minute. Occlusion of the circulation to the lower extremities (both of which were affected by extensive osteitis deformans) caused a drop in the right auricular pressure, pulse rate and cardiac output. Blood flow through the nutrient arteries of the affected bones was found to be from 10 to 20 times the normal. They concluded: "The data presented here indicated that there occurs in generalized* Paget's disease an increase in bone blood flow of sufficient magnitude to produce effects on the general circulation similar to those resulting from free arteriovenous communications. Further work is required to study the relationship between the increased flow and the radiologic stage of the disease. The absence of significant increases in cardiac output in cases of localized Paget's disease suggests that it is only when the disease becomes generalized that the circulation as a whole is greatly increased, and in such cases the signs of heart failure may develop."54

Further studies by Edholm and Howarth57 provide additional evidence of excessive vascularity and bone blood flow in osteitis deformans. Two complete necropsies on cases that had been followed and studied revealed "tremendous development of the bone vascular system in the affected limbs which we further demonstrated by intra-arterial injections of radiopaque material." These observations were further substantiated by biopsy specimens and studies on the effect of intravenous epinephrine on skin temperature in the normal limb and in limbs affected by osteitis deformans. They concluded: "We have confirmed our previous findings that the total limb blood flow is very greatly increased when the bones in the limb are affected by osteitis deformans."

B. Effects

The increased vascularity that is characteristic of the involved portions of the skeleton in osteitis deformans (at least in certain phases of the disease)58 has been shown to have no significant effect on the general circulation when the area of bony involvement is small. When a large proportion of the skeleton is involved, the attendant increase in blood flow may be accompanied by elevation of the cardiac output37, 51, 60 to several times the normal basal rate of approximately 4 liters per minute.61, 62

The factor of increased demand on the heart thus becomes an important consideration in extensive Paget's disease of long duration, in which case it reduces cardiac reserve, predisposing to enlargement and failure.50, 63

Arteriosclerosis and Cardiovascular Disease in Osteitis Deformans and the General Population

A. Incidence

The voluminous literature on the nature and incidence of arteriosclerosis attests to the controversial nature of the subject.64–68 Statistics on the incidence of arteriosclerosis tend to be unreliable, particularly in the living, since there is not an entirely satisfactory method for the determination of its presence (once a definition of the nature of the process has been accepted) and various observers report their findings on the basis of different methods and standards.67 In addition, intimal lesions are of more clinical importance than medial calcification,68–70 and the problem is complicated by the fact that there are multiple causes of arteriosclerosis when the term is used in its liberal sense.61, 65, 71–80

Our interest in a possible relationship between arteriosclerosis and osteitis deformans was aroused from the observation that marked calcification of the arteries is nearly always found on the roentgenograms of patients with extensive Paget's disease, and from the fact that since the time of Paget, clinicians have

* Since osteitis deformans is not a systemic disease, "extensive" appears to be a preferable term.*
thought both the incidence and severity of arteriosclerosis to be greater in patients with osteitis deformans than among the general population of a similar age.9, 27, 29, 30, 81

The question of a real increase in the severity and incidence of arteriosclerosis in Paget's disease has not been adequately determined because so many observers were inclined to state their impression that the incidence and severity were out of proportion to the age groups concerned,9, 12, 14, 24, 31, 33, 39, 45, 47, 50, 51, 55, 81-88 yet did not provide adequate statistical evidence. Still others dismissed the question with the caveat that the advanced age of the patient was in itself sufficient explanation for the severe arteriosclerosis,21, 27 while some presented fairly sizable groups of cases supporting the contention that the incidence of arteriosclerosis is significant, the age of the patient notwithstanding.14, 20, 25, 82, 89, 90

For this reason, we have calculated the incidence of arterial calcification as seen in the roentgenograms of patients in our series with regard to the extent of bony involvement. The findings are, in turn, compared with the reported clinical and autopsy incidence of arteriosclerosis in the general population of the same age (fig. 1). Although our series is far too small to be of statistical significance, the fact that in local Paget's disease the incidence of arterial calcification on the roentgenograms is slightly less than the clinical incidence of arteriosclerosis in the general population of the same age,91 yet in extensive Paget's disease, it exceeds the autopsy and clinical incidences for the age concerned,91, 92 lends support to those who believe that the severity and incidence of arteriosclerosis in extensive Paget's disease exceed the normal, age notwithstanding.

B. Effects of Arteriosclerosis in Osteitis Deformans

1. Heart. Locke stated that in osteitis deformans, cardiovascular disease is undoubtedly the most common cause of death.27 As the etiologic role of arteriosclerosis in chronic cardiovascular disease is well recognized, it will be alluded to only in broad outline.

Arteriosclerotic disease of the coronary arteries may lead to varying degrees of chronic myocardial ischemia.82, 91-97 Decreased cardiac reserve, angina pectoris, myocardial fibrosis, dilatation with or without hypertrophy and, finally, failure may result, depending upon the degree of insult.96-101 Coronary disease also predisposes to thrombosis, acute ischemia, conduction defects and infarction.54, 94, 102 These may also result in dilatation, failure or death.103

Although the finding of increased incidence of calcification in the aorta and peripheral vessels is not direct evidence of excessive calcification of the coronary arteries, the arterial calcification in Paget's disease is not influenced by the proximity to involved bones.90 Since in the "heterochronic aging"91, 64, 78, 104 of the arterial tree the coronaries are known to be ahead of the peripheral vessels,77, 104 excessive coronary artery calcification may be expected in Paget's disease.102 Figure 2 shows the incidence of coronary artery disease in the general population in comparison with cardiac enlargement in osteitis deformans. Since not all cases of coronary disease have cardiac enlargement, it suggests that coronary disease in osteitis deformans must either exceed the normal for the general population of the same age or that other factors such as increased blood flow and chest deformities also play a part. We believe the excessive cardiac enlargement in Paget's disease to be the result of the combination of factors in most cases.

Arteriosclerosis and calcareous deposits which chiefly involve the aortic and mitral valves very often appear in advanced Paget's disease27, 88, 90, 104, 107 and the resulting stiffness and deformity may impair the function of these structures.91, 94, 104, 108-111 The work of the heart is thereby increased, most likely at the very time that the myocardium is deprived of an adequate blood supply by coronary artery disease.

A recent study by Harrison and Lennox102 in England revealed that calcification of the mitral valve is more frequent in osteitis deformans than among the general population of a similar age group. These workers stated that intracardiac calcifications contribute to the high incidence of cardiovascular morbidity and mortality in Paget's disease.

In this connection, it is of interest that
Paget's disease was present in 3 of 12 cases of intracardiac calcification reported by Windholz and Grayson.113 This is a much higher incidence than could be expected in view of the relative infrequency of Paget's disease. It should be noted that they113 considered the calcifications to be unrelated to either rheumatic fever or arteriosclerosis.

2. Other Organs. The effects of arteriosclerosis in osteitis deformans are not limited to the heart. Symptoms which are referable to any organ or portion of the body may result from changes in its blood supply.

Peripheral arteriosclerosis causes a loss of elasticity in the vascular tree which results in benign or senile hypertension, characterized by a high systolic and more or less normal diastolic pressure, absence of progression or evidence of overt cardiac or renal damage and minimal retinal changes.114 This type of hypertension is usually thought to have little effect on the heart itself, yet Burgess114 has shown that the most frequent cause of death in these patients is cardiac failure, that they are subject to cardiac hypertrophy and enjoy somewhat less than normal life expectancy. Other authors have also stated that systolic as well as diastolic hypertension adds a burden to the heart.66

Arteriosclerosis of the renal vessels and consequent interference with the renal blood supply has been shown to be a cause of hypertension.66, 78, 116-120 Some authors consider hypertension to be associated with Paget's disease.121, 122

In the light of present knowledge it appears that a final decision cannot as yet be reached with regard to the relationship between arteriosclerosis that characteristically accompanies extensive Paget's disease and the development of hypertension of a degree that predisposes to cardiac hypertrophy and dilatation.

The presence of a diabetic type of glucose tolerance curve in Paget's disease has frequently been reported.64, 66, 83, 89, 123, 124 The significance of this observation has recently been challenged but the mean age of the control group in this experiment exceeded that of the group with Paget's disease by 14 years.125

Although a calculated correction was made for age discrepancy, the series was small and it appears likely that some degree of alteration in carbohydrate metabolism does occur in Paget's disease. The reason for such an alteration has not been demonstrated, but it has been suggested that arteriosclerotic changes in the kidneys, accompanied by a high renal threshold for glucose or variation in the activity of the pituitary gland may play a part.89

Although some competent observers believe that arteriosclerosis is never a cause of diabetes,126 other authorities state unequivocally that arteriosclerosis of the pancreas may be a cause of the milder type of diabetes which occurs in the aged.78, 97, 127-129 In support of this premise, it may be recalled that the tendency for diabetes to appear parallels the progress of arteriosclerosis in Werner's syndrome.130 It, therefore, is possible that the tendency for a diabetic type of glucose tolerance curve to develop in Paget's disease may be explained, at least in part, on the basis of arteriosclerosis of the pancreas. This interpretation should be tempered by the fact that glucose tolerance normally diminishes with advanced age125, 131 and with marked limitation of activity,131 both of which are often present in advanced osteitis deformans.

Deformities of the Dorsal Spine and Chest

A. Incidence

Severe cervicodorsal kyphosis accompanied by marked deformity and restriction of movement of the thoracic cage is recognized as characteristic of the advanced, classic form of osteitis deformans.29, 31, 32, 54, 122 It was a prominent feature in 7 of the 12 cases reported by Paget up to 1882.27, 28 and in 66 of 99 "authentic cases" in the literature up to 1900 reviewed by Packard, Steele and Kirkbride.84 This association has subsequently been confirmed by numerous authors,1, 4, 6, 18-21, 24, 27, 28, 55, 61, 65, 68, 124, 132-135 and was present to some degree in two of the four cases of classical osteitis deformans in the present series.
B. Effects

Awareness of the direct and indirect effects of severe deformities of the cervicodorsal spine and chest on the cardiorespiratory system has developed very slowly, and in so far as osteitis deformans is concerned, began with the comments of Paget on his first case. He stated that the spine was curved and rigid, while "the chest became contracted, narrow, flattened from before backwards, and the movements of the ribs were lessened." After observing further examples of respiratory embarrassment in his additional cases reported in 1882, Paget concluded that death "did not appear due in any degree to the disease of the bones unless it were that the difficulty in breathing was aggravated by the deformity of the chest." There are numerous references in the literature to disease of the chest caused by deformity and restricted movement of the thorax in Paget's disease. Occasionally, there has been further hindrance to respiration from paralysis of intercostal muscles as the result of a bony overgrowth at the neuroforamina.

Although severe deformities of the dorsal spine and chest became a recognized cause of right heart failure and a materially shortened life expectancy as well as decreased function of the lungs, the various mechanisms involved were not clarified until rather recently. Earlier observers had inclined to the view that the cause of right heart failure in these patients was mechanical, namely, loss of aid to the right heart from the normal respiratory movements, increased resistance in the pulmonary circuit due to kinking or compression of vessels and compression of one lung and compensatory emphysema of the other.

The advent of pneumonectomy and the subsequent observation that obliteration of half of the pulmonary circuit failed to precipitate right heart failure made it clear that the anatomic interference with the pulmonary blood flow did not adequately explain the known facts concerning pulmonary cardiac failure in the hunchbacked. Chapman, Dill and Graybiel made a step forward in the clarification of this problem by emphasizing the importance of decreased oxygenation.

Further elucidation has recently been provided by the discovery of the fact that an abnormally low oxygen saturation of the blood has a marked vasoconstrictive effect on the pulmonary arterioles and precapillaries. Experimental evidence of this vasoconstrictive effect stems from the observation that in the normal individual, inhalation of half the normal oxygen concentration will double the pulmonary arterial pressure without raising the cardiac output. McMichael pointed out that the oxygen saturation of the blood in patients with chronic emphysema is nearly always below 80 per cent, and may be as low as 30 per cent. He discussed these findings in relation to right heart failure and emphasized, along with others, that a rise in pulmonary arterial pressure causes more embarrassment to the right ventricle than a corresponding rise in systemic pressure does to the left ventricle. This is true because a rise in systemic pressure automatically enhances the coronary flow, whereas, the right ventricle is not benefited as a result of its increased work. McMichael summarized the effect of pulmonary vasoconstriction which results from relative anoxemia as follows: "Poor ventilation of the lungs may induce this vasoconstrictive reaction and this may be the key to the problem of many forms of pulmonary heart disease. The difficulty of moving a kyphoscoliotic thoracic cage with consequent limited ventilation may have the same action on the pulmonary arterial pressure as the poor ventilation of emphysematous lungs, or lungs in which the bronchioles and alveolar ducts are strangled by peribronchial lymphatic carcinoma."

It may be stated, therefore, that in classic osteitis deformans, the frequent, severe deformities of the cervicodorsal spine and chest,
accompanied by fixation of the thoracic cage and respiratory distress, occasionally augmented by paralysis of intercostal muscles, may predispose to right heart failure through anatomic interference with pulmonary blood flow, and as a result of spasm of the pulmonary arterioles and precapillaries from the attendant low oxygen saturation.

Anemia in Osteitis Deformans

On the basis of pathologic reports, a significant degree of anemia might be expected as a complication in extensive Paget's disease because of replacement of bone marrow by fibrovascular tissue and encroachment on the marrow cavity by bony overgrowth and osteoid tissue. MacCallum\textsuperscript{153} stated that, "The marrow actually loses its blood-forming elements and becomes converted into a vascular fibrous tissue which produces much soft, bone-like tissue." Numerous other authors have confirmed the fact that metaplasia and fibrosis of the marrow and encroachment on the marrow cavity are common in advanced osteitis deformans.\textsuperscript{1, 9, 14, 15, 21, 24, 31, 44, 49--52, 54, 124}

These pathologic findings notwithstanding, marked anemia, attributable to osteitis deformans, is a rare occurrence. Because Paget's disease progresses very slowly, if at all, there may be time for compensatory phenomena to counteract the effect of the gradual loss of erythropoietic tissue from the bone marrow so that anemia, comparable to that found when marrow is replaced by neoplasm, is rarely seen. Whatever may be the reason, we have not found any cases of anemia due to Paget's disease in this series in which the red blood count and the hemoglobin reached less than 50 per cent of normal, which is considered necessary to cause cardiac enlargement from anemia.\textsuperscript{153, 154} Moreover, we have been able to find only one case in the literature in which severe anemia was attributed to Paget's disease.\textsuperscript{52} In this case, there was extensive replacement of the red marrow by fibrous tissue, and death resulted from "osteosclerotic anemia which developed as a result of Paget's disease." In view of its demonstrated infrequency, it appears that complicating anemia is not a significant cause of cardiac enlarge-

ment and heart failure in extensive osteitis deformans.

Report of Cases

This series is derived from the selection of all cases of osteitis deformans which appeared in the files of the New England Baptist Hospital from January 1, 1941, to December 31, 1947, and includes a detailed study of the records in each case. During this interval, there were 106 patients for whom a definite diagnosis of Paget's disease was made. Eighty-eight of these patients had been studied at the Lahey Clinic at some time before their hospitalization, and their outpatient records were also utilized for this study.

The incidence of cardiac enlargement and other studies are reported for 54 of the 106 patients for whom standard 72 inch posteroanterior chest films were available. The 52 patients for whom chest films were not taken, comprising a number in whom cardiac enlargement was found on physical examination, were not included in this series.

For the purpose of determining the influence of the extent of the disease on the cardiovascular system, the 54 cases were arbitrarily divided into three groups: (1) local disease, in which osteitis deformans was confined to one bone or anatomic part such as the skull or pelvis, (2) moderately extensive disease, in which the process involved more than one long bone or part, but less than the classic form, and (3) classic osteitis deformans, in which the skull, spine, pelvis and extremities were widely involved.

The mean age at examination was 58 years for group 1 (36 cases), 63.4 years for group 2 (14 cases) and 68.8 years for group 3 (four cases).

Because of the high incidence of degenerative vascular disease in the general population of the sixth, seventh and eighth decades, the age of the patients who have Paget's disease is an obstacle to the demonstration of a relationship between osteitis deformans and cardiovascular disease. Figure 3 shows the incidence of cardiac enlargement in the general population of various age groups as determined by physical examination. These findings were derived from
the examination of 100,924 unselected life insurance policy holders by one group and 10,000 similar unselected life insurance policy holders by another group. As the decades concerned. Comparison of these figures with the incidence of cardiac enlargement in Paget’s disease as shown in figure 3 reveals the incidence in patients who had extensive osteitis deformans to be many times that of those in the general population of the same age.

Figure 4 shows the relationship between cardiac enlargement and the extent of bony involvement in osteitis deformans. There is a marked increase in the incidence of enlargement as the disease becomes more extensive, and as
enlargement, whereas the groups with moderately extensive and classic osteitis deformans had 50 per cent and 100 per cent cardiac enlargement, respectively.

Since the use of life insurance examinees as representative of the general population may be questioned because they comprise a group from which the lowest economic classes are largely excluded, and since physical examination is less accurate than the teleoentgenogram for the determination of the size of the heart, further comparisons may be useful. Kretschmer and Butler reported the incidence of cardiac enlargement from all causes to be 15.3 per cent in 314 patients who suffered from prostatic disease. Patients who have prostatic disease tend to fall in the same age group as those with Paget's disease, and when it is recalled that for a given age, males are usually more susceptible to coronary disease than females, and that prostatic disease itself (when it causes obstruction) may be a cause of cardiac enlargement, the contrast with the incidence of cardiac enlargement in extensive osteitis deformans becomes even more significant.

There is further well documented evidence that overt heart disease and cardiac enlargement are not the rule in the aged general population. Willius studied 700 patients whose ages varied from 75 to 96 years, and could not find clinical evidence of heart disease in 45 per cent; however, the incidence of congestive failure was 12.1 per cent. Boas

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seen from figure 3, this increase is much greater than could be expected solely from the age groups of the patients concerned. Of the cases with localized disease, 28 per cent had cardiac

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CARDIAC ENLARGEMENT IN PAGET'S DISEASE (SORNBERGER & SMEDAL)

CLINICAL INCIDENCE CARDIAC ENLARGEMENT IN GENERAL POPULATION (SYDENSTRICKER and BRITTON, 1930)*

A LOCAL PAGET'S DISEASE
B MODERATELY EXTENSIVE PAGET'S DISEASE
C CLASSIC PAGET'S DISEASE

Fig. 3. The clinical incidence of cardiac enlargement in the general population versus cardiac enlargement in various stages of Paget's disease (see text for explanation).

Dotted line: Cardiac enlargement in Paget's disease (Sornberger and Smedal).

Solid line: Clinical incidence of cardiac enlargement in the general population (Sydenstricker and Britten, 1930). (The authors stated the incidence by decades for each sex. This graph represents the arithmetic mean of their figures for each decade.)

Dash line: Idem. (Proc. Life Ext. Examiners, 1939). (The incidence was stated by five-year periods. This graph represents the arithmetic mean for each decade.)


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Fig. 4. The relationship between cardiac enlargement and the extent of bony involvement in Paget's disease.
discussed the aging of the cardiovascular system, and pointed out that in old age the body demands less oxygen, the caloric intake is less and the individuals in this group avoid extreme temperatures and physical activity. He concluded that such patients do not have a need for the great cardiac reserves of youth, and that usually, the functions of the heart and arteries suffice to meet the needs of the presumably the duration) of bony involvement (figs. 3 and 4). A summary of the reported incidence of cardiac enlargement and arteriosclerosis in Paget’s disease may be found in table 1.

Electrocardiographic tracings were available in 21 of the 54 cases in this series. The incidence of normal tracings and those showing coronary disease in the various stages of bony involve-

<table>
<thead>
<tr>
<th>Author</th>
<th>Arteriosclerosis</th>
<th>Cardiac Enlargement</th>
<th>Evidence</th>
<th>Extent of Bone Disease</th>
<th>Age (mean, Yrs.)</th>
<th>Duration (mean, Yrs.)</th>
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<td>5 of 5 100</td>
<td>1 of 5 20</td>
<td>Clinical</td>
<td>++ (1 case)</td>
<td>52</td>
<td>10</td>
</tr>
<tr>
<td>Sornberger and Smedal, 1948</td>
<td>37 of 54 69</td>
<td>21 of 54 39</td>
<td>x-ray</td>
<td>++ to +++</td>
<td>59.6</td>
<td>—</td>
</tr>
<tr>
<td>—</td>
<td>4 of 4 100</td>
<td>4 of 4 100</td>
<td>x-ray</td>
<td>++</td>
<td>65</td>
<td>17.5</td>
</tr>
<tr>
<td>—</td>
<td>12 of 14 86</td>
<td>7 of 14 50</td>
<td>x-ray</td>
<td>++</td>
<td>63.4</td>
<td>—</td>
</tr>
<tr>
<td>—</td>
<td>21 of 36 58</td>
<td>10 of 36 28</td>
<td>x-ray</td>
<td>+</td>
<td>58</td>
<td>—</td>
</tr>
</tbody>
</table>

* Paget reported five cases, but only one in detail which came to autopsy.
† Bortz reported 21 cases, but only 14 came to autopsy.
‡ While there were three cases of Paget’s disease in the series of 12 cases of intracardiac calcification, only two of the three were identified as examples of Paget’s disease.
§ This patient had rheumatic heart disease with congestive failure.

body under basal conditions in advanced old age.

A comparison of the incidence of cardiac enlargement in extensive osteitis deformans with that in the general population of the decades concerned, therefore, refutes the factor of age per se as an explanation for the increased incidence in Paget’s disease. When age is discounted, it may readily be seen that the incidence of cardiac enlargement in osteitis deformans is correlated with the extent (and

Figure 2 shows the clinical incidence of coronary heart disease in the general population in comparison with the incidence of cardiac enlargement in the various stages of Paget’s disease. The incidence of cardiac enlargement in osteitis deformans exceeds the clinical in-
idence of coronary artery disease in the general population when the bony involvement is extensive, in which case it also exceeds the clinical and autopsy incidence of arteriosclerosis in normal subjects for the ages concerned (fig. 1). This difference becomes more significant when the fact that marked coronary artery disease may be present at autopsy without previous\textsuperscript{92, 141} clinical evidence is considered, and when one considers that in 2,000 consecutive autopsies only 69 per cent of the patients who had significant coronary artery disease showed cardiac enlargement.\textsuperscript{111} It is apparent, therefore, that coronary sclerosis, per se, in the degree which is normal for the age concerned, could not account for the entire incidence of cardiac enlargement in Paget's disease. The other factors which help to bring advanced and classic forms. In the meantime, these data may be accorded qualitative significance, and the determination of the precise incidence of cardiovascular disease in extensive osteitis deformans must await the publication of further studies.

The cardiothoracic ratio as measured on postero-anterior chest films, taken in an upright position at a distance of 72 inches, has been used as the index of cardiac enlargement in this series. It is generally conceded that this is an inexact method, although it is far more dependable than clinical findings.\textsuperscript{12, 13, 144} The chief source of error attendant upon the use of the cardiothoracic ratio lies in the fact that minimal enlargement may escape detection.\textsuperscript{144} Since error from the use of this method would tend to result in finding too few cases of cardiac

---

**Table 2.** Electrocardiographic Findings in Paget’s Disease

<table>
<thead>
<tr>
<th>Stage of Disease (bony involvement)</th>
<th>Mean Age (at examination)</th>
<th>Number of Cases with Electrocardiogram</th>
<th>Normal</th>
<th>Coronary Artery Disease</th>
<th>Left Ventricular Hypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number</td>
<td>Per cent</td>
<td>Number</td>
<td>Per cent</td>
</tr>
<tr>
<td>Localized</td>
<td>58.0</td>
<td>14</td>
<td>6 43</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Moderately extensive</td>
<td>63.4</td>
<td>6</td>
<td>2 33</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Classic</td>
<td>68.8</td>
<td>1</td>
<td>0 0</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21</td>
<td>8 3</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* The complication of bundle branch block prevented determination of presence of left ventricular hypertrophy.

about this high incidence of enlargement in Paget’s disease are thought to be the increased cardiac output that often accompanies extensive osteitis deformans,\textsuperscript{37, 40, 56} and more severe arteriosclerosis than is warranted by age alone.\textsuperscript{12, 29, 39, 82, 89, 90} Rarely, chest deformities and possibly hypertension related to arteriosclerosis may contribute to cardiovascular morbidity and mortality in advanced Paget’s disease.

**Methods and Sources of Error**

It is realized that the figures presented on the incidence of cardiovascular disease in osteitis deformans do not represent a series large enough to be statistically significant. This will probably be true, however, of any one series owing to the relative infrequency of osteitis deformans in the moderately advanced and classic forms. In the meantime, these data may be accorded qualitative significance, and the determination of the precise incidence of cardiovascular disease in extensive osteitis deformans must await the publication of further studies.

The fact that chest films were made for all of the patients in this series may distort the incidence of cardiac enlargement. While many chest films are taken routinely, or for conditions unrelated to the heart, an indeterminate error will result from the fact that patients who have symptoms referable to the heart are often selected for chest films, and the apparent incidence of cardiac enlargement may thereby be increased. This error can be eliminated only by reporting a series in which chest films are taken routinely on all patients with extensive Paget’s disease. However, this error is compensated to some degree by the use of the cardiothoracic ratio which does not indicate cases with minimal cardiac enlargement.

A possible source of error in the determina-
 tion of the size of the heart in osteitis deformans is the deformity of the cervicodorsal spine and chest, commonly seen in the advanced or classic form of the disease. These deformities, when present, make the determination of the size of the heart, by roentgenologic or physical examination, difficult. To date, no way has been found to obviate this problem, except by autopsy, although it did not have any influence in this instance since only two cases in this series had marked cervicodorsal kyphosis, and in each, the cardiac enlargement was so great as to be beyond question.

SUMMARY AND CONCLUSIONS
1. An appreciation of the influence of osteitis deformans and concomitant conditions on the cardiovascular system has been retarded and complicated by several factors: (a) the high incidence of degenerative vascular changes in the normal elderly population, (b) the masking effect of limited physical activity on the symptoms of cardiovascular disease, and (c) the fact that the moderately advanced and classic forms of osteitis deformans are too uncommon to permit accumulation and study of a single statistically significant series of cases.

2. The incidence of cardiovascular disease is appreciably greater in extensive Paget’s disease than among the general population, age notwithstanding, and is manifested by cardiac enlargement and marked arteriosclerosis.

3. Cardiac enlargement and arteriosclerosis are related to the extent of the bony involvement, and are more pronounced when the latter is extensive.

4. The mechanism of cardiac enlargement in extensive Paget’s disease may be attributed to one, or more frequently, a combination of the following factors: (a) increased work of the heart as a consequence of the marked vascularity of bone in certain stages of osteitis deformans; (b) more frequent and severe arteriosclerosis than warranted by age alone, which may compromise the efficiency of the myocardium or valves, or both; (c) severe deformities of the cervicodorsal spine and chest which directly or indirectly embarrass the pulmonary circulation, and, on occasion, bring about right heart failure; (d) in some cases, hypertension which results from loss of elasticity in calcified vessels, or possibly from nephrosclerosis, may be an added burden.

5. There is not convincing evidence of a significant increase in the incidence of cardiac enlargement in localized Paget’s disease.

6. Anemia as a complication of Paget’s disease does not appear to produce cardiac enlargement in an appreciable number of cases.

7. It is suggested that arteriosclerosis of the pancreas may contribute to the production of a diabetic type of glucose tolerance curve in osteitis deformans and that Paget’s disease should, in its extensive form, be added to the conditions (diabetes, myxedema, idiopathic hypercholesterolemia and hypertension) which are considered to be accelerators of arteriosclerosis.

8. Patients in whom there is extensive osteitis deformans should be classified as having “potential heart disease” and should have periodic physical examinations, chest films and electrocardiographic studies.

9. The determination of the exact incidence of cardiac enlargement and arteriosclerosis in extensive osteitis deformans must await further study of the subject and the compilation of a statistically significant number of cases.

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