GENERALISED OSTEITIS FIBROSA
With Parathyroid Tumour and Metastatic Calcification

INCLUDING
A CRITICAL DISCUSSION OF THE PATHOLOGICAL PROCESSES UNDERLYING OSSEOUS DYSTROPHIES.

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I. INTRODUCTION AND HISTORICAL.*

It has long been recognised that the clinical picture of many bone conditions is often far from clear, the diagnosis often equally difficult, and the pathological picture extremely varied. The writers have had the opportunity of correlating the pathological findings with the clinical history in a patient with one of these obscure bone lesions, the interest of which was increased by the existence of a parathyroid tumour and the

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presence of calcareous deposits in all the organs and tissues. It has, therefore, seemed to them worth while to give an extensive account of the case, together with a discussion of some of the fundamental conceptions and problems that underlie bone pathology. Into this discussion it will be necessary to bring the consideration of numerous bone conditions which, however widely differing in their clinical characteristics, have a certain similarity in their histological changes and may, therefore, justifiably be included in a group of allied diseases. No term as yet applied to such a group has been sufficiently inclusive. French writers have given it the name "Osseous Dystrophies," while German workers, following von Recklinghausen, use the term "Rachitic Malacias." In the discussion it will soon be recognised that neither term is entirely adequate, since many conditions of bone which fall to be considered cannot be satisfactorily placed in either category.

In 1877 Paget described a chronic inflammation of bone occurring in people past middle age: the disease usually affects several bones and is accompanied by a peculiar thickening, softening, and bending of the bones, which results in a characteristic clinical picture in which spontaneous fracture is rare. The pathological changes in the bones show: (1) an extensive resorption of bone by osteoclasts; (2) an excessive new formation of bone, laid down by osteoblasts on the resorbed surface of the old bone, so that the cortex which had become rarefied may become dense, especially in the skull; (3) the bone marrow becomes transformed into fibrous tissue and encroaches on the cortex, and in this fibrous tissue osteoid bone is laid down, the lamellae of which run in every direction; (4) sub-periosteal layers of bone are formed which add to the volume of the bone in thickness; (5) occasionally cysts or spaces filled with fluid are present in the fibrous tissue and occasionally tumour-like tissue with numerous giant cells. The special points to be noted in this description are the fibrous transformation of the bone marrow with formation of new bone, and the early rarefaction of the cortex which later may become dense with irregular Haversian canals: the new bone both in the medulla and in the cortex is at first osteoid but may become calcified so that the bone regains its rigidity.

In 1891 von Recklinghausen described a lesion of bone, occurring usually in young adults, the course of which is chronic and gives a clinical picture with few symptoms, except the
frequency of spontaneous fracture: the primary and essential pathological changes are the following: (1) a fibrous transformation of the bone marrow which extends into the canals of the Haversian system and results in (2) a local destruction of osseous tissue; (3) parallel with this there is a new formation of osteoid tissue; (4) haemorrhages occur in the later stages with many giant cells in the cellular fibrous tissue, so that the structure resembles a giant cell sarcoma; (5) cysts occur through haemorrhages or through resorption of bone or a myxomatous change in the fibrous tissue. The special points to be noted in this description are the fibrous transformation of the bone marrow with formation of new bone, and the early rarefaction of the cortex which may be reduced to a thin shell of bone or entirely replaced by fibrous tissue. The great frequency of areas of giant cell tissue and cysts gave the name "Osteitis Fibrosa with multiple tumours and cysts." This disease was at first regarded as identical with Paget's Osteitis Deformans—this identity being indicated by von Recklinghausen's term "Ostitis fibrose oder deformirende"—and by some as a juvenile form of Paget's disease under the designation "Osteomyelitis fibrosa solida or cystica"—cysts being the rule in Osteitis Fibrosa and the exception in Osteitis Deformans.

The above two conditions were regarded by Paget in 1877 and by von Recklinghausen in 1891 as essentially inflammatory in origin, but in 1910 von Recklinghausen modified his view and included Osteitis Fibrosa in the group of metaplastic malacias, thereby bringing it into relation with anomalies of metabolism. It will be necessary, therefore, briefly to discuss the two most important malacic conditions—Osteomalacia and Rickets—and to consider in what respects these resemble and differ from Osteitis Deformans and Osteitis Fibrosa.

In Osteomalacia there is a gradual softening and bending of the bones, in some patients limited to the bones of the pelvis, in others affecting the bones of the limbs and trunk. In the affected bones (1) the bone salts appear simply to be dissolved out, the basement substance remaining as a finely-fibrillated material with the original lamellation; (2) the decalcified cancellous tissue becomes absorbed; (3) the cortex becomes porous, except a thin sub-periosteal layer; (4) the bone marrow is replaced by a soft, vascular-cellular tissue which also takes the place of the absorbed bone; (5) there is only a moderate amount of new formation of osteoid tissue and
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the bone marrow usually remains very cellular or becomes gelatinous with numerous hemorrhages. The special points to be noted in this description are the decalcification and resorption of the osseous tissue and its substitution by a new-formed marrow or granulation tissue, which may rarely become fibrous: there is no sign of inflammation and little of new formation: there is only a limited amount of fibrous transformation of the bone marrow and only a limited amount of osteoid tissue formation. In the literature concerning Osteomalacia, cases have been recorded with the presence of giant cell tissue and cysts, and in 1889 Hirschberg described a picture identical with osteitis fibrosa under the term “Osteomalacia with cysts”: since von Recklinghausen’s classical description of osteitis fibrosa, however, the occurrence of giant cell tissue and cysts has apparently been sufficient to classify the case as osteitis fibrosa. It must be noted that Osteomalacia occurs in persons whose endochondral ossification is complete: the softening must be due therefore to the removal of lime salts.

Rickets, on the contrary, is most frequently developed during the first two years of life. It is a constitutional disease in which the bone lesions are due to a faulty development and, therefore, proper ossification does not take place. In the affected bones the physiological growth of bone in its various phases is abnormal; (1) the growth in length and thickness is irregular and active, but actual ossification is imperfect and the lime salts already deposited may be removed—leaving osteoid tissue; (2) the enlargement of the medullary cavity by the resorption of the inner layers of bone is also irregular and excessive; and (3) fibrous tissue with osteoid tissue may develop. The bones become bent and incomplete fractures are frequent: after a time the rachitic process may stop and the porous bone and osteoid tissue become dense. The special points to be noted in this description in relation to our present subject are the possible fibrous transformation of the bone marrow and the formation of osteoid tissue, in part by the removal of lime salts, and in part by the metaplasia of cartilage and fibrous tissue.

These constitute the chief malacic diseases, the grouping of which is dependent upon that peculiar metamorphosis of a part or whole of one or several bones into fibrous tissue—with a tendency in one member of the group—osteitis fibrosa—
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to the formation of cysts and tumour-like tissue. Cysts are much rarer in Osteitis Deformans and rare in true Osteomalacia.

Von Recklinghausen divided osteitis fibrosa into a generalised and a localised type—the latter affecting a single bone, and it is when we come to the consideration of the localised type that we have to bring under review the neoplastic processes in bone, some of which are regarded by certain writers as truly metaplastic in the above sense and by others as inflammatory. Many articles on this subject bear such comprehensive titles as "Benign Bone Cysts; Osteitis Fibrosa Cystica; Giant Cell Sarcoma; Bone Aneurism; and Chronic Hæmorrhagic Osteomyelitis." It is necessary, therefore, now to consider what underlying conception allows these diseases to be so grouped together.

The characteristic of osteitis fibrosa is the presence of an inflammatory fibrous tissue in the medullary cavity, replacing the medullary cavity and producing absorption of the cortex. If the proliferative processes are dominant, von Recklinghausen thought that there resulted a very cellular tissue with the formation of giant cells—a formation which closely resembled giant cell sarcoma, and was so designated by von Recklinghausen. If, on the other hand, degenerative processes together with hemorrhages prevailed, cysts were formed; and, frequently, giant cell areas and cysts occurred in close relationship to each other. The full title of von Recklinghausen's disease, therefore, is "Osteitis Fibrosa with Multiple Tumours and Cysts": and the tumours and cysts were regarded as end-stages of the process underlying osteitis fibrosa.

It is, therefore, obvious that multiple small cysts in this fibrous tissue metamorphosis could be called Osteitis or Osteomyelitis Fibrosa Cystica, and if the multiple loculi coalesced, with hæmorrhage from ruptured capillaries, a single large cyst might be formed containing a blood-stained fluid and with or without a lining membrane. This membrane, if present, was continuous with the fibrous tissue in the immediate neighbourhood, and might contain giant cells in its structure, and bone lamellæ in its outer layers, which gradually merged into tissue typical of osteitis fibrosa. If, on the other hand, numerous giant-celled areas were present in the fibrous transformed tissue, such areas were regarded by von Recklinghausen as true areas of giant cell sarcoma. In the naked eye picture red areas resemble giant cell sarcoma, and the yellowish-white areas
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osteitis fibrosa. Such multiple tumour and cystic areas might similarly be found in all the bones if the generalised type of osteitis fibrosa existed, but these were in no sense metastases, and in no case were metastases present in internal organs. Von Recklinghausen extended his conception of osteitis fibrosa to include not only the central giant cell sarcoma and all medullary cavity cysts not due to such obvious conditions as the softening of tumours, e.g. of enchondroma and myxoma and to hydatid cysts, but even the sub-periosteal epulis of the jaw. His claim, therefore, was that the microscopic picture of giant cell sarcoma is a late stage of osteitis fibrosa.

Bloodgood holds that the term "chronic osteomyelitis fibrosa solida or cystica" is more appropriate than that of osteitis fibrosa or osteitis fibrosa cystica, and Barrie classifies benign bone cysts, osteitis fibrosa, chronic osteomyelitis fibrosa all under the one term "chronic fibro-cystic osteomyelitis," and claims that this is in all cases a late stage of "chronic haemorrhagic osteomyelitis." Barrie contrasts this condition with the malignant periosteal and endosteal sarcoma, and looks upon the so-called medullary giant cell sarcoma (myeloid sarcoma) as a chronic non-suppurative haemorrhagic osteomyelitis, i.e. an exuberant vascular granulation tissue with giant cells, and, therefore, not a tumour tissue at all. The appearances shown in this vascular granulation tissue have long been accepted as those of a medullary or myelogenous giant cell sarcoma, and their significance, nature and interpretation—whether neoplastic, metaplastic, or inflammatory formations—will be fully discussed in a later section. In the meantime it is sufficient briefly to indicate how they fall into the group of allied conditions under discussion. In the red granulation tissue of Barrie—chronic haemorrhagic osteomyelitis—there are present whitish areas and small cystic cavities: both appearances are evidences of metaplasia and, if at all active, may convert the tissue, by a fibrous tissue replacement of the granulation tissue with retraction and consequent cyst formation, into the "chronic fibro-cystic osteomyelitis" of Barrie. (Synonyms: benign bone cysts; osteitis fibrosa cystica; chronic osteomyelitis fibrosa solida or cystica.)

The group we are considering of rarefying osseous diseases, therefore, and especially one member of it—osteitis fibrosa—shows cysts the walls of which contain a giant-celled tissue rich in cells of sarcoma-like structure, which cannot be looked upon
as malignant. If, then, a portion of the contents or wall of such a cyst or of the surrounding bone contain a tumour-like tissue and the cyst wall or surrounding bone further shows fibrosis, bone resorption and new formation, what is the condition? The important diagnostic point raised here resolves itself into the question: (1) Can the medullary giant cell sarcoma—the so-called medullary or myeloid sarcoma—and even the simple epulis type of the jaw be regarded as a late stage of a localised or generalised type of osteitis fibrosa? i.e. is it metaphastic and not neoplastic or inflammatory. Or: (2) is the medullary giant cell sarcoma, which shows areas of fibrous transformation at some part, to be regarded as a late stage of chronic hæmorrhagic osteomyelitis? i.e. is it inflammatory and not neoplastic or metaphastic. Or: (3) is it a true giant cell sarcoma? i.e. a neoplastic not a metaphastic or inflammatory formation. In other words: are we to consider "Osteitis Fibrosa" a distinct pathological entity characterised by fibrous metaplasia of bone marrow and bone and include under this term benign bone cysts, giant cell sarcoma of epulis type, chronic hæmorrhagic osteomyelitis, and the generalised type of osteitis fibrosa with multiple giant-celled areas and cysts?

The subject of this paper, then, is the fibrous and fibrocystic type of "metaplastic malacia" of von Recklinghausen or "osseous dystrophy" of Miculicz, Bérand and Alamartine, and, recognising that in this clinical and pathological picture giant-celled tissue and cysts may be present, the relation of such giant-celled tissue and cysts, on the one hand, to the giant cell sarcoma of epulis type and the solitary or multiple bone cysts, and on the other hand, their relation to chronic hæmorrhagic osteomyelitis and its end-stage chronic fibro-cystic osteomyelitis.

Before passing to the consideration of the case it will be necessary to recall briefly one or two points in relation to bone structure and the physiological phases of bone growth. According to Maximow certain star-shaped mesenchyme cells migrate into the perichondrium of the embryonic cartilage: these migrant cells differentiate in two ways: (1) into fixed cells which are the forerunners of the osteo-poietic tissue and stroma, and (2) into haemoblasts, the forerunners of all the hæmopoietic cells. In the bone marrow, therefore, the connective tissue framework or reticulum, with the blood-vessels, is distinct.
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from the actual bone-marrow parenchyma, the blood-forming cells. With this framework is connected a membrane consisting of fibrous tissue or only of spindle-shaped cells, which clothes all the inner spaces of the bone. It is from this so-called "endosteam" that proceed normally the destruction and the building-up of bone. The atrophy or resorption of bone goes on normally in large measure by lacunar resorption by means of osteoclasts (poly-karyocytes) which are genetically and morphologically sharply distinct from the giant cell of the bone marrow, the mega-karyocyte, which is a derivative of the haematoblast. The osteoclasts, on the other hand, are derivatives of the connective tissue framework, especially of the endosteam: yet they are not specific formations, for in pathological conditions they can arise out of the local connective tissue. New bone formation takes place normally through osteoblasts: these also are not specific cells but are likewise of endosteal origin and, can, under pathological conditions, arise out of the local connective tissue. They produce lamellar bone on the calcified cartilage columns of normal bone or on the outer surface of old trabeculae in pathological conditions by secreting a homogeneous intercellular substance, osseo-mucin, which is separated off from the cell and gradually becomes calcified, at first irregularly, later becoming homogeneous. New formed bone, under normal conditions, does not remain at a standstill, but, through resorption and apposition, is built up into a structure adapted to meet mechanical influences, and so spongy bone becomes formed. Jores, in an experimental investigation on the influence of mechanical compression on the bones, found that compression gives rise to a stimulus which hinders the growth of bone, causing its resorption and substitution with connective tissue. When the pressure is removed there is a proliferation of bone tissue to take the place of the resorbed bone, so that compression atrophy will occur only when the period of pressure lasts longer than the period of removal of pressure.

In endochondral-formed bone the trabeculae are lamellar and their intercellular substance is kept together by the finest fibrils which become fused together by a cement substance that is no longer recognisable by the usual stains. Periosteal bone formation takes place just as in the ossification of connective tissue pre-formed bone, i.e. the first trabeculae arise not in apposition to a given ground substance such as the calcified cartilage.
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trabeculae but in the midst of connective tissue out of proliferated cells (osteoblasts); in their development abundant old dense fibrils (Sharpey's fibres) are enclosed and a network-like bone is formed, which at first is not lamellar. But later there is the partial resorption and the formation of lamellar bone around the blood-vessels.

In all organic bone diseases there is both resorption and new formation of bone so that the normal processes are repeated. In the bone destruction, according to many recent writers, three types of changes may be involved: (1) the formation of perforating canals corresponding to the Volkmann's perforating canals; (2) the lacunar resorption by means of osteoclasts; and (3) halisteresis or the simple solution of the lime salts, possibly by a bio-chemical agency. In the new formation of bone, on the other hand, two types of processes are involved: (1) meta-

plasia out of connective tissue cells, giving a network-like bone, which later becomes lamellar; and (2) the apposition of new bone by osteoblasts either on the remains of the old trabeculae or on the lamellæ of network bone. The conceptions underlying these modes of bone destruction and new bone formation will have to be discussed more fully later, but in the meantime the destructive and formative physiological processes may be extended to the analogous pathological processes, on the one hand of a rarefying osteitis, i.e. an inflammatory osteoporosis in which there is a transformation of the bone marrow into a granulation tissue which absorbs the osseous part with the formation of a sequestrum, and on the other of an ossifying osteitis in which new bone formation occurs, in consequence of inflammation in the marrow spaces, through osteoblast activity, a condition of osteo-sclerosis.

By the term "metaplasia" is understood the transformation of one tissue into another of similar morphological origin and functional character. This is distinct from differentiation or the change that occurs in the transformation of embryonal tissues. The metaplastic process is brought about by little understood factors which regulate the conditions under which the cell and tissue elements live. Such changes are often found in inflammation and, in the origin of bone out of connective tissue, chronic inflammatory conditions often play a rôle. Here the osteoblasts concerned have had no connection with performed osteogenic tissue and are the descendants of true connective tissue cells, which have differentiated in a new direction.
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In studying bone lesions, therefore, it is necessary to bear in mind that bone cells and cartilage cells are simply highly differentiated fibroblasts: the fibroblast produces collagen fibrils but may produce mucin or chondro-mucin, or osseo-mucin, becoming respectively a myxomatous connective tissue cell, a chondroblast or an osteoblast, and in tumours the fibroblast may differentiate into any of these varieties or remain as a fibroblast. In membranous bone a mass of spindle-shaped cells is formed, some of which assume the characters of bone corpuscles and give up part of their cell body to the fibrillar substance which then becomes homogeneous osseo-mucin, and later becomes ossified. Bone begins to develop in cartilage, by an ingrowth of blood-vessels accompanied by embryonic mesenchyme cells (periosteal buds) and then some of these, as endosteal cells, proceed to form bone by laying down osseo-mucin by apposition on the calcified trabeculae. In pathological conditions, the osteoblasts, or cells which have assumed the function of osteoblasts, produce in an analogous manner new bone in the Haversian systems eroded by osteoclasts, and bone is also being formed by the osteogenic layer of the periosteum. In this way, in bone lesions, bone is being formed both after the type of membranous bone and by apposition as in endochondral ossification. Whether new bone can be formed by the bone corpuscle buried in the rigid bone, e.g. in a transplant, is still a disputed point and will be referred to in a later section.

II. CLINICAL HISTORY: X-RAY AND POST-MORTEM NOTES.

A. W., male, æt. 49, mason's labourer by occupation, was admitted to Leith Hospital on 24th January 1921, on account of delayed union in a fracture of the left humerus sustained four months previously.

He gave the following history. Up till 1916 he had been a healthy man. In that year, while serving in the Labour Corps in the army in France, he began to suffer from aching pains in the limbs, especially severe in the lower limbs, along with stiffness in the knee and ankle-joints. These pains were attributed to rheumatism. The disability caused was so great that he was ultimately discharged from the army and given a small pension on account of rheumatism contracted while on active service. It is noteworthy that on his return to civil life in 1917 he was at once able to resume his ordinary labouring
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work, and that he continued to do it till he broke his arm in 1920. From time to time he suffered from so-called rheumatism in various parts of his body but never severely enough to prevent him working or to induce him to seek medical advice. On 13th September 1920, while in the act of lifting a heavy brick he felt a sudden pain in his left upper arm, and the arm gave way with an audible crack. He came to the out-patient department of the hospital for advice and was found to have sustained a fracture of the shaft of the humerus just below the junction of the mid and lower thirds. The fracture was attributed to muscular violence and was treated on ordinary lines. An X-ray photograph showed a slightly oblique fracture with little displacement, but the bone showed a curious appearance. It was rather thicker than a healthy humerus and had lost the differentiation into cortical and medullary portions to a large extent. While the peripheral portion threw a shadow less dense than the cortex of a healthy humerus, the medulla appeared to be filled up with bone so that the density of its shadow corresponded in general with that of the cortex. When examined in detail, however, the shadow of the bone was found to vary in density in an irregular manner. Thus at one part the cortical shadow was denser than at another, and at the periphery of the medullary area there appeared to be layers of slightly denser consistence than elsewhere, but these again were of variable density and irregular contour and in parts absent altogether. The bone appeared, in short, to have undergone a general thickening associated with very irregular calcification (Plate I., Fig. 1). No other abnormalities were noted at the time and the man was treated as an out-patient. Union took place very slowly, and by December, i.e. three months after the injury, was still incomplete. Early in January the patient began to complain of pains in the left arm and hand. A radiograph of the humerus taken at this time showed that a very striking amount of decalcification had taken place, especially in the lower fragment (Plate I., Fig. 2).

On 24th January, just over four months after the occurrence of the fracture, the patient was admitted to the hospital for indoor treatment.

On admission he was seen to be a sallow complexioned man, 5 ft. 4 ins. in height, with no obvious deformities. He walked with a slightly high stepping gait, suggestive of a mild degree of peripheral neuritis. He complained of pains and
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weakness in the left upper limb associated with the delayed union of the broken humerus and also of pains in the shoulders, neck and back of the head. The pains were not acute, being more of a dull aching character, not severe enough to interfere with sleep or to interfere seriously with the patient's general health. His general physique was fairly good and he was well nourished.

The left upper limb was wasted and movements at the elbow and shoulder were much restricted in range and feeble. The left humerus felt considerably thickened, especially in its distal half, and there was evident mobility at the seat of fracture. This mobility took the form of a bending at the weak spot and not of a displacement of one fragment on the other. There was a notable absence of any signs of inflammatory reaction. The bone was not tender, there was no redness or oedema and no local or general rise of temperature. An X-ray photograph taken the day after admission, when compared with that taken ten days before, showed a still more striking decalcification of the lower fragment and of the upper fragment near the fracture. The lime salts seemed to have been almost entirely removed from large areas of the bone, so that its contour could not be clearly identified (Plate I., Fig. 3). Attention was naturally directed, in the next instance, to the rest of the skeleton. No abnormality was evident except that the cranial vault seemed rather large. An X-ray photograph of the skull confirmed this suspicion and showed that the bones of the cranial vault were about twice their normal thickness, that they were less dense than usual, that the edges were hazy and ill-defined and that the density varied in an irregular patchy manner. No sign of division into outer and inner tables with intervening diploe could be made out. The general character of the change appeared similar to that in the humerus in so far as there was a uniform thickening with apparent partial decalcification. The sutures could not be seen (Plate I., Fig. 6). It was interesting to note that in spite of the evident change in the skull bones the patient was unaware that there was anything wrong with his head. He complained of occasional pains in the occipital region, but there was no tenderness of the skull and no sign whatever of any inflammatory condition in the tissues of the scalp.

He had not noticed that there had been any increase in the
size of his head. Examination of the rest of the skeleton did not reveal any abnormality. X-ray photographs of the bones of the left forearm and hand, of the bones of the right upper limb and of the bones of the lower limbs showed no definite departure from the normal.

Further examination of the patient revealed no organic disease with the exception that, on his admission to hospital, the urine contained a faint trace of albumin. This disappeared later and the amount and quality of urine secreted were normal. The heart and lungs were healthy. The appetite was good and digestion unimpaired. The nervous system was unaffected, sensation being normal everywhere, the reflexes undisturbed, and the patient's mental attributes and condition such as might be expected in an average individual in his walk of life.

The blood was examined and tested for the Wassermann reaction on two occasions and found definitely negative. The patient stated that he came of healthy stock and had six healthy children, and there was nothing to suggest the possibility of a syphilitic infection in his history or condition. In general, his appearance did not suggest illness, although he looked a little pale and sallow. He might fairly be described as showing a degree of general debility, but not more than could be accounted for by the prolonged disability due to his fractured humerus.

_Diagnosis._—It was difficult to arrive at a positive diagnosis. The wide distribution of the aching pains suggested a generalised affection, but examination revealed definite changes only in the left humerus and skull. In the hope of gaining further information a small portion of the affected humerus was removed ten days after admission. It was taken from immediately below the seat of fracture, and it was interesting to find that the bone apparently held more lime salts than the X-ray photo led us to expect, for an osteotome was required to cut it. The portion removed showed to the naked eye a finely reticulated structure. The microscopic appearances are fully described in Section III., p. 440. They may be summarised by saying that they showed a complete replacement of the normal bone by a fibrous tissue undergoing metaplasia into osteoid and osseous tissue of new formation. The operation wound healed well and the procedure did not disturb the patient's health in any way. The general features of the case seemed to suggest that we possibly had to deal with an early example of Paget's Osteitis.
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Deformans. The asymmetry of the changes and their apparent absence in the lower limbs did not conform to the descriptions of typical cases of Paget's disease, but these have usually been taken from advanced cases in which deformity was already a well-marked feature. The appearances in the early stages of Paget's disease are not yet known and it was thought that the diffuse pains from which the patient suffered were probably the precursors of bone changes which would become evident in time and might then bring the features of the case more into line with the advanced cases of which the features are so well known. No more definite conclusion was reached during the man's life.

Progress.—After the operation for the removal of a portion of bone the patient's condition improved both locally and generally. The humerus solidified at the seat of fracture and an X-ray photograph taken on 15th February, thirteen days after the operation, showed that lime salts had been redeposited in the humerus (Plate I., Fig. 4). The shadow thrown was a strong one, although patchy and irregular in density as in former photographs and the contrast between it and the photograph taken on 25th January was most striking. It should be stated that the variations in density as between one photograph and another were interpreted as indicating differences in the amount of lime salts present in the bone at one time and another. If that interpretation is correct and no other seems possible, the photographs show in a very interesting way how the lime content of a bone may vary in this disease and how quickly lime may be removed or laid down. The redeposit of lime salts was coincident with improvement in the patient's general health. The pains in the limbs and occipital region disappeared and, at his own request, the man was discharged from hospital on 12th March, seven weeks after admission, in good general condition. Seven weeks later, while travelling in a motor bus, he was severely jolted, and was thrown so that his left arm came against a rail. The arm was badly hurt and immediately felt powerless. He came straight to the hospital and was found to have sustained a second fracture of the humerus about two inches above the former one. There was no displacement. The radiograph again proved interesting, because it showed that the bone had apparently a more regular structure than before. There was a dense but thin cortical layer, while the remainder of the bone threw a
lighter shadow of almost uniform density without any sign of a medullary cavity. The appearance suggested that the lime salts had become more regularly distributed, possibly in response to the use which had been made of the arm since recovery from the first fracture (Plate I., Fig. 5).

General examination of the patient revealed no change of any note. He said that he felt well and that his pains were much less troublesome than when he was first seen four months before. He was kept in hospital for five weeks, during which time he remained well and the humerus slowly consolidated. Slight mobility was still present when he was discharged, at his own request, on 1st June. During June he attended as an out-patient for massage and his general condition did not alter. From June till October he was not seen. An idea of his condition during this time may be gained from the fact that he succeeded, unknown to us, in insuring his life on the basis that he was a healthy man suffering only from the effects of a broken arm.

On 24th October, however, he was suddenly seized with a heart attack and was admitted to the hospital, in the evening, in a state of collapse with a very rapid and feeble pulse. He was too ill to give an account of himself and died suddenly the following morning without any precise conclusion as to the cause of his collapse having been arrived at.

A post-mortem examination was made twenty-four hours after death and the chief morbid changes visible to the naked eye were as follows:—

Post-Mortem Notes.

Left Humerus.—The shaft of the humerus is thickened, more especially in its lower half, where the diameter of the shaft is 1 cm. greater than in a normal bone of corresponding length. From a point 7 cm. above the lower end, corresponding to the site of the first fracture, the shaft is slightly bent medially. The most striking feature about the bone is its pliability. In its whole length the shaft can readily be bent out of the straight without fracture and at the site of the first fracture this pliability is greater than elsewhere. On section the bone is found to be so soft that it can easily be cut with a knife. The normal structure has been replaced by a grey or greyish-yellow finely reticulated soft spongy bone. This has entirely replaced the dense cortical bone and filled up the medullary cavity except
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for a space 6 cm. by 0.5 cm. in the upper half and a smaller space 2 cm. by 0.3 cm. in the lower half (Plate II., Fig. 2). This greyish-looking bone appears to have displaced the cancellous tissue in the lower end of the humerus and to be invading along an ill-defined line the normal-looking cancellous tissue in the head of the bone. Here and there, throughout the spongy material, there are brownish patches suggesting increased vascularity and immediately below the periosteum there is a thin layer of reddish brown colour also suggesting increased vascularity. This layer shades off into a periosteum two or three times the natural thickness, which blends very intimately with the bone and strips with great difficulty, taking particles of calcareous material with it from the rough vascular-looking surface of the bone. The remnants of the medullary cavity contain some brownish gelatinous-looking marrow. The general consistence of the new material is fairly even, although there is a line, at the site of the old fracture, where it seems softer and less calcareous than elsewhere. The cartilaginous surfaces at the ends of the bone are normal in appearance except for one or two small areas of fibrillation, such as occurs in the early stages of rheumatoid arthritis.

In general, the bone may be described as replaced by, or converted into, fibro-calcareous material. The change has been more extensive in the lower half in so far as the bone is thicker and the medullary cavity has been more completely filled up than in the upper half. It seems reasonable to attribute the excessive change in the lower part of the bone to a reaction following the trauma associated with the two fractures. The remarkable disappearance of lime salts followed by their reappearance as the fracture slowly healed, seemed to indicate specially active changes stimulated by the damage to the bone.

Skull.—On handling the skull it is found to be quite pliable all over, of a consistence like that of stout leather. It is easily cut with a knife, being rather softer than the left humerus. The pericranium is slightly thickened and very firmly attached to the bone. When detached it leaves a rough, greyish red, vascular-looking surface. The sutures are obliterated. A horizontal section at the level of the frontal sinus shows that the calvarium varies in thickness from 4 to 9 mm., and is composed of greyish pink finely spongy bone of uniform appearance without any sign of division into layers.
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As in the humerus, the dense bone has been entirely replaced by soft spongy material (Plate II., Fig. 1).

The dura mater lining the vertex presents for 12 cm. along the middle line, on its cerebral aspect, a very coarsely striated appearance. This striation extends almost symmetrically on either side for 1 to 3 cm. Beyond this the dura is smooth over the rest of the skull. It shows large reddish patches of vascularisation below each parietal eminence and a number of other smaller reddish patches scattered irregularly over the interior of the membrane. In addition the dura shows a number of patches and streaks of a light yellow colour. It is easily separated into two layers, a very thin layer on the surface next the brain, and a thicker deep layer next the bone and so intimately united to the bone that it can hardly be separated from it. The reddish patches are found to be due to dilatation and engorgement of capillaries in the thin superficial layer of dura which separates readily and leaves a smooth avascular surface below. The yellow streaks and patches on the other hand are found to be due to a deposit of calcareous material on the surface of the deep layer next the bone and when the deep layer is peeled off the bone it takes this yellow calcareous material with it.

The surface of the brain is normal in appearance. The base of the skull shows no abnormality, but on chiselling the basi-sphenoid it is found to be softer and more easily divided than usual.

**Left Femur.**—The left femur shows a slight antero-posterior bowing. On section the cortical layer appears to have become a little thickened towards the medullary cavity in its upper half. It has a normal appearance and hardness when tested with a sharp metal instrument except in one or two areas along the lateral aspect, where it looks a little spongy next the medullary canal. The bone is, however, quite hard in these areas when tested. The periosteum is not thickened and strips readily. The marrow shows a number of maroon coloured areas in the upper half of the bone, and in the lower half has the appearance of a normal fatty marrow. In general, it may be said that the femur shows little definite change to the naked eye (Plate II., Fig. 3). In particular, the medullary canal is not encroached on except to a very slight extent where the cortex seems a little thick in the upper half of the bone. The bone seems hard and strong. This is noteworthy
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in view of the fact that microscopic examination shows very definite changes all through the bone.

**Sternum and Ribs.**—The sternum and ribs showed no surface change to the naked eye but were found to be very friable and easily broken on handling. On examining the cross-section the ribs showed an enlargement of the medullary canal at the expense of the cortex.

The other bones were not examined, as they seemed to be strong and of normal contour and had not shown any changes when examined by the X-ray during life.

**Parathyroid Tumour.**—In relation to the left lower pole of the thyroid gland was found a yellowish ovoid body about an inch in length. Taken at first for an enlarged gland this afterwards proved to be an enlargement of a left lower parathyroid body. The remaining parathyroids were of normal size.

The internal organs and viscera showed no special or characteristic changes to the naked eye. Along with the bones described above they were removed and preserved for microscopic examination.

**III. HISTOLOGICAL STUDY.**

**Methods.**—In order to obtain as comprehensive a view as possible of the lesions and of their structure very numerous sections, both large and small, have been examined from all the bones available. The tissues were fixed in Pick’s solution and portions of the bones were transferred to Perenyi’s decalcifying fluid for a varying period. Small fragments from the humerus including both the cortex and medulla, and from the cranial vault were also sectioned without previous decalcification. The humerus was first cut longitudinally in frontal section and the whole of one half prepared in paraffin in four divisions. Plates XII.-XIV. represent three of these four portions—the upper and lower ends of the humerus and the shaft, while three intervening discs, taken from the upper, middle and lower thirds of the shaft were cut transversely to the long axis: one of these transverse discs is shown in Plate XI. A large longitudinal portion of the shaft of the femur (Plate IX.) and several transverse discs were also sectioned: Plate X. represents one of these transverse portions and forms a very valuable contrast to the similar section of the humerus (Plate XI.). Large and small portions from the vault of the
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skull (Plate XV., Fig. 1), the basi-sphenoid, and from the rib (Plate XV., Fig. 2) were also prepared.

The paraffin sections were stained by the haematoxylin and eosin stain, by the van Gieson stain and also for the Prussian blue hæmosiderin reaction: small portions were also fixed in Zenker's fluid and stained to bring out individual points—by Weigert's elastic stain and Mallory's connective tissue, and phosphotungstic acid haematoxylin stains. Frozen sections were found of special value and nearly all the drawings were made from such sections: these were stained by the routine methods and also by the specific methods, e.g. Schmorl's thionin-blue-picric acid, Best's carmine, Scharlach R, and the alum and lithium carmine stains.

In examining the microscopic findings it is important to recognise that different stages of the disease come under observation in the various bones. The presence of these different stages in their evolution adds very greatly to the completeness and value of the histological picture and aids its interpretation. It will be convenient to begin the description of the histological changes with that of the portion of the affected humerus removed during life.

*Portion of the Affected Humerus excised on 2nd February 1921.*

This was taken from the shaft immediately below the seat of the fracture: it was readily decalcified and microscopically showed dense layers of thickened periosteum, which were directly continuous with broad strands of a loose fibrous tissue in which bone trabeculae were inserted. These trabeculae gave the impression of new-formed bone, for there were recognisable neither lamellation nor Haversian systems: they were irregular in shape and, under low power, gave the general outline of a network, but isolated oval and elongated portions were also present, the fibrillated ends of which were distinctly continuous with the fibres of the fibrous tissue in which they were embedded. Closely applied to many of the trabeculae, except at these fibrillated ends, were layers of cells of osteoblast type, while many others showed a contour deeply and irregularly indented by large, multi-nucleated osteoclasts. In the intervening fibrous tissue were evidences of recent capillary hæmorrhages together with small clusters of multinucleated cells of osteoclast type, especially sub-periosteal in their grouping. In the deeper layers of the periosteum, which was composed of very dense
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fibrous tissue, could be traced a direct transition to the underlying bone trabeculae, and in the trabeculae immediately subjacent, which were larger and more regular, a commencing lamellation could be recognised together with a difference in the staining which indicated a minimal degree of calcification. In none of the sections could any bone be recognised by its concentric or parallel lamellation or by the type of its bone cells as old bone.

We pass now to the histological changes found post-mortem: (A) the bones; (B) the parathyroids; and (C) the calcareous deposits in the organs and tissues.

(A) THE BONE CHANGES.

The Humerus.—As already noted the bone cut readily with a knife and was very readily decalcified. Plate XII. represents the head and adjoining part of the shaft: Plate XIII. the lower half of the shaft, which includes the sites of both the fractures; and Plate XIV. the lower end, while Plate XI. represents a transverse section of half of the shaft between Plates XIII. and XIV. A comparison of these figures with Plate II., showing the naked eye appearances, confirms the presence of the extreme change noted both in the cortex and medulla and these figures together with numerous drawings sufficiently indicate many of the essential features. The invasion by fibrous tissue of the cancellous head of the bone, along an irregular line, and the complete fibrous tissue substitution of the cancellous lower end are clearly to be seen, while the whole of the shaft, both cortex and medulla, with the exception of small areas in the medulla, is a solid cylinder composed of more or less dense fibrous tissue in which is embedded a reticulum of bone trabeculae, while the whole is surrounded by dense layers of thickened periosteum. The brownish areas in the drawing are seen, microscopically, to be hæmorrhagic areas containing numerous cellular elements with many giant cells, and several small cysts, in the early stages of their formation, are also present. The larger part of the areas of the bone marrow which have escaped the general fibrous tissue substitution have been transformed into a cellular marrow, the reticulum of which shows a gradual transition into the fibrous tissue. It was impossible to distinguish in the large section of the lower half of the shaft (Plate XIII.) either of the
sites of fracture under high power, but under a low power magnification they were indicated by a slight excess in the irregularity and density of the disposition of the new-formed bone, together with the size of the areas of haemorrhagic giant-celled tissue.

It may be gathered from the above brief description that all the bone found in the humerus, except a few atrophic spicules in the head, was interpreted as a new formation, while in the later description of the changes in the femur the bone present was interpreted as old bone undergoing resorption. It will be advisable, therefore, in view of the many difficulties found by all observers in this interpretation, to state what were the criteria accepted by the writers. The conclusions, based on the appearances presented in the various staining methods, especially that of Schmorl, must be allowed a certain freedom in their application and are at best generalisations.

Old bone (Plate VI., Fig. 1) showed (1) Haversian systems with definite concentric and intervening parallel lamination; (2) Bone cells uniformly distributed and spindle-shaped, with definite and regular, almost parallel, canalicular processes from the sides; (3) evidences of calcification. On the other hand, bone showing (1) a homogeneous appearance or only slight peripheral lamination; (2) cells closely arranged axially and with irregular and radiating processes; (3) transition at its fibrillated ends into fibrous tissue; (4) a minimal calcification in the axial portion: was accepted as new-formed bone (Plate VI., Fig. 3). The presence or absence of large numbers of osteoblasts or osteoclasts was not conclusive evidence of old or new bone: old bone in process of destruction shows frequently on one side a layer of active osteoclasts, and on the other side layers of osteoblasts laying down new bone in apposition, while new bone after a certain stage in its development may show the same picture. Judged by the above standard, the bone trabeculae of the humerus were almost without exception new-formed in the sense that they did not represent the bone laid down as a result of the early endochondral and sub-periosteal ossification.

Under low power, therefore, the humerus is seen to be almost entirely replaced by fibrous tissue with new-formed bone in which a complete reconstruction of the bone architecture has taken place. The pale areas in Plates XI.-XIV. are the fibrous tissue strands, while the darker, irregular, narrow
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strands forming a network are branching trabeculae of new bone—probably laid down at different times, for all stages of the transition between fibrous tissue and non-calcified bone tissue (osteoid tissue) are represented. There is no demarcation of this fibro-osteoid cylinder into a cortex and medulla: the darker zone at the periphery is composed of dense layers of periosteum in which osteoid transformation is taking place. The osteoid strands in this periosteum are much more closely deposited than in the remaining tissue, where they form an open network leaving often large stretches of fibrous tissue free from osteogenic development. The periosteal fibrous tissue is in direct continuity with the deeper fibrous tissue, and its osteoid strands are also directly continuous with the osteoid trabeculae in the peripheral and central portions.

A low power magnification also shows certain other features: amongst these are (1) the presence of areas of fatty marrow, not yet replaced by fibrous tissue, in which the connective tissue cells show tufts of fine fibrils—an early indication of the later substitution; (2) areas of fatty marrow with partial or complete replacement by a lymphoid marrow; (3) multiple dark areas (Plate XI., y, and Plate XVIII., Figs. 1-3), the largest of which are sub-periosteal, which give the picture of a spindle or polymorph-celled tissue with numerous giant cells of osteoclast type; in the interstices of this cellular tissue lie very numerous red-blood cells and pigmented phagocytic cells; (4) small cystic areas (Plate XVIII., Figs. 4-6) forming loculi in the process of confluence into larger cysts.

Summary of changes in the humerus (L.P.). The shaft shows a thickened and dense periosteum with many osteoid trabeculae in its layers; this thickened periosteum forms a sheath enclosing a mass of fibrous tissue of varying density, and in this latter is inlaid a wide-meshed spongy bone; the meshes of which are narrowest in the peripheral parts which are in direct continuity with the periosteal and sub-periosteal strands. In scattered areas through this fibro-osteoid tissue are small cysts and giant-celled tumour-like hæmorrhagic areas. Before passing to the examination of these various structural portions under high power, it is possible to give to this picture the diagnosis of “osteitis fibrosa with multiple tumours and cysts” (von Recklinghausen’s disease).

Under high power the direct transition of the fibrous tissue into osteoid tissue can be readily traced. The term “osteoid”
signifies osseous tissue not yet calcified, i.e. the basement substance is fused osseo-mucin. In this transformation or regeneration of bone there can be recognised what is so often noted in the regeneration of any tissue, that the manner of regeneration follows very closely its first development, i.e. that the first stage of the newly-formed anatomical element is an embryonal one and that this undergoes successive transformation. The series of drawings and photographs (Plate VIII., Figs. 1-6, and Plate XVII., Figs. 1-6) to illustrate this transition, have all been taken from frozen sections of the fibrous tissue present in the former medulla (Plate XI.), so that there can be no doubt that the bone trabeculae are new formations. The first change recognisable in the loose fibrous tissue is a thickening of the fibrils surrounding the fibroblast: with van Gieson’s stain this change is suggestive of a condensation with a slight granularity of the normal fibrogen, but soon there is a swelling and fusion of individual fibres with a very definite change in the cell outline. A later stage is indicated by the presence of cells now lying embedded in a homogeneous matrix containing fibrils—both cell and matrix recognisable as bone cell and osseo-mucin.

The area in which this change is taking place may be very limited, with irregular margins in which the fibres of the fibrous tissue can be traced in direct continuity with the fibrils in this homogeneous tissue. Multiple, minute areas now fuse along the whole or certain portions of their irregular surface and have intervening wide or narrow meshes of unchanged fibrous tissue, bounded by strands or trabeculae of bone which form a network. The peripheral portions of the long axis of the trabeculae now show the nearest cells of the fibro-cellular tissue arranging themselves in a definite manner as a protoplasmic, epithelial-like lining layer, the elements of which may now be called osteoblasts, and these cells lay down in a more regular manner osseo-mucin on the surface of the trabeculae. As layer after layer of cells becomes enclosed in osseo-mucin and uniformly and regularly applied to this surface, it gradually assumes a definite striping and lamellar arrangement—this is the first indication of new formation of bone by apposition, i.e. by deposition on a definite surface, as in early endochondral ossification on the surface of the calcified cartilage. The axial portion of the new bone is meanwhile undergoing a commencing calcification, and its cells show irregular processes with a very irregular grouping, in striking contrast to the peripheral, more
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uniform distribution. At the free ends of the bone strands the continuity of the fibrils of the fibrous tissue can be traced for a considerable time after peripheral lamellation of the borders has begun, while the gradual and progressive transformation of further cells and fibres into bone cells and osseo-mucin is taking place. The continuity of fibrils of connective tissue with the fibres undergoing the change into osseo-mucin can frequently be traced directly through the developing osteoid strand; these fibrillar processes are the so-called Sharpey's fibres and are very numerous in this new-formed bone.

We have here, therefore, a direct transformation (metaplasia) of connective tissue into bone tissue, as in membranous bone, without the stage of endochondral bone formation—the result is the formation of a network of bone in the strands of which the structural units may long be recognised running in all directions. Such new-formed bone is often called reticular or network-like bone, both from the apparent network the strands form and also from the original network structure of the fibres which composed the individual strands. But another mode of bone formation has been indicated—that of bone apposition, analogous to the apposition bone laid down by osteoblasts on the surface of the remaining calcified trabeculae in endochondral ossification; this second mode of formation of new bone, in contrast to the direct transformation of the connective tissue cell into an osseo-mucin forming cell, shows a transition stage to osteoblast cells which lay down bone on a surface already prepared for the deposition.

The Resorption of the New Bone.—As may be seen from Plate XIX., Fig. 5, it is not long before the new-formed bone, in its turn, undergoes destruction; many of the trabeculae show very irregular resorption surfaces with giant cell osteoclasts lying in the indentations. The origin, formation, and significance of the giant cells will be more fully discussed in a later section; meanwhile it may be noted that many of the new-formed trabeculae show osteoclast resorption on one side with layers of osteoblasts laying down apposition bone on the other, so that the trabeculae become very irregularly eroded and often eaten through.

Periosteal New Bone.—Plates XI.-XIV. show dense layers of periosteum over the whole extent of the shaft, and Plate VII., Fig. 4, the formation of new bone within these layers. The process is in principle the same as that already outlined, but in
the periosteum the density of the tissue presents some striking differences. It is not a question of an inner layer of cells becoming osteoblastic, as in normal sub-periosteal growth of bone, but whole layers, running in all directions, have their fibres swollen and homogeneous, as if being transformed in masses into osseo-mucin. Many of these fibres, presenting a very striking picture, run directly through the whole thickness of the periosteum into the subjacent sub-periosteal trabeculae as Sharpey’s fibres.

Giant-Celled Tissue.—It has been already stated that the great mass of the fibrous tissue substitution is of an open type with numerous connective tissue cells, and that there are often wide stretches of this fibrous tissue, which show as yet no new bone formation. But there are numerous scattered areas, especially sub-periosteal, where the tissue is exceedingly cellular with few connective tissue fibres and very numerous multinucleated giant cells. Such areas under low power give the impression of circumscribed areas of giant cell (myeloid) sarcoma, and their significance must be discussed later. Von Recklinghausen looked upon them as multiple areas of “giant cell tumour,” and it is these formations which he looked upon as an end-stage of his disease.

Plate III., Fig. 1, and Plate XVIII., Figs. 1-3, give characteristic pictures of such areas and show a very homogeneous, cellular tissue with the fragmented remains of old or new bone trabeculae. Extravasated blood cells may be heaped up around such bone fragments, or may also extensively infiltrate the interstices of the cellular tissue. The cellular element is a very varied one and is chiefly polymorphous in character and shows, as a rule, a gradual transition into the less cellular fibrous tissue with only a few isolated giant cells. The high power seems to confirm the first impression gathered from the low power view that such giant cell areas are the osteoclasts remaining after their work of bone destruction is over, together with other giant cells which have formed around the extravasated blood cells. The giant cells in these areas are not uniformly distributed, but are often in small groups, around minute bone fragments or around small spaces filled with blood cells.

Formation of the Cysts.—Numerous small cysts were present in all the large sections of the humerus. Plate XVIII., Figs. 4-6, shows the three-fold mode of their formation, which, with their significance, will be discussed in a later section.
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This description of the changes in the humerus may be completed by a reference to three further points: (1) The remains of the medullary cavity; the two marrow areas, indicated in Plate II., Fig. 2, show that the medulla was almost completely replaced by fibrous tissue. The lower of these areas was a cellular marrow, while the upper was still in large part fatty, and in this fatty marrow a striking change was occurring in the connective tissue cells, which may be looked upon as the initial change in its substitution by fibrous tissue. The fat cells were being changed into connective tissue cells and in these and in the connective tissue cell of the reticulum the protoplasm was being transferred into a tuft of fibrils. (2) The head of the bone (Plate XII.) covered by its articular cartilage, was composed of fatty marrow with markedly atrophic old bone spicules, which were directly continuous with the articular cartilage projections. The fibro-osteoid substitution of the shaft could be traced penetrating irregularly into the head of the bone; the method of this transformation of the cancellous tissue of the metaphysis and of its cellular marrow and its penetration through the original epiphyseal line into the head of the bone in no way differed from that already described. The only other bone definitely interpreted as old bone was found in a sub-periosteal zone around the upper metaphyseal end : it can be readily recognised (ob) in Plate XII. in which the white spaces are fatty marrow not yet substituted by fibrous tissue. (3) The lower end (Plate XIV.) shows almost more perfectly than any other the complete substitution by fibro-osteoid tissue. This section is valuable also in showing the substitution of a portion of the articular cartilage (rb) by fibro-osteoid tissue—a transformation which seemed to be taking place in a manner exactly analogous to that of removal of old bone, i.e. a resorption of the cartilage by multinucleated giant cells, and a gradual substitution by fibrous tissue in which new-formed osteoid tissue is laid down.

The Left Femur.—The changes found in the humerus represent an advanced stage in the diseased process we are considering, but the left femur shows an early stage—one which comparatively rarely comes under observation. In contrast to the humerus this bone required a comparatively long time in the decalcifying fluid and in contrast also to the humerus, where the microscopic picture confirmed the macroscopic, there was macroscopically little to note on the longitudinal section,
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while the microscopic picture shows a very definite change throughout the compact and spongy bone. Plate IX. shows the rarefied structure of the middle third of the shaft in longitudinal section, while Plate X. under a very low power represents these changes transversely to the long axis.

These figures indicate how marked a change has occurred in the architecture of the bone: the cortex has its Haversian systems hollowed out into large irregular spaces, which intercommunicate, while the trabeculae of the spongy bone are thinned and the cancellous spaces very greatly widened. The fatty marrow has at one part become a cellular tissue (bm) (lymphoid marrow) but nowhere does it show any evidence of fibrous tissue substitution. The naked eye appearance of the bone gave only the slightest suggestion of this porosity, which is well brought out in a thin unstained section. In the Plates the dark network lines represent the interlacing bone trabeculae, while the pale shading between is the loose, vascular, fibrocellular tissue in the irregularly contoured spaces of varying size.

Under low power the histological picture is extraordinarily striking and is beautifully brought out in the drawings (Plate V.) and photographs (Plate XVI.). (1) The remaining bone present is all old bone, retaining traces of the Haversian systems and the parallel intervening lamellation, the bone cells also retain their uniform distribution, and for the most part their normal outline and canalicular processes. With certain stains, especially Schmorl's thionin blue-picric acid method, there is in this bone a suggestion of the removal of the lime salts by simple solution. The evidences of this are described more fully in the section under Halisteresis and were interpreted as an initial halisteretic atrophy, which preceded any appearances of bone resorption by osteoclasts. (2) The intervening cancellous and Haversian spaces show every transition in size from the minimal enlargement of the Haversian canal to large irregularly contoured spaces, the outline of which against the bone is lined by osteoclasts, each in their own indentation. The contents of these spaces also vary from the small central capillary surrounded by a delicate endosteal layer to masses of central perivascular fibrous tissue and layers of osteoblasts or osteoclasts lining the irregular surface, with a rich network of capillaries and stellate cells in the intervening tissue. This picture of lacunar resorption is very striking in all the sections of the femur (Plate V. and Plate XVI.); it is well brought out in Fig. 1, Plate V., while
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Fig. 2, Plate V., brings out the multiple layers of osteoblasts and the commencing perivascular fibrosis; these Figs. also show the very loose cellular and vascular character of the contents of the spaces, and the mode of formation of the osteoclasts by fusion of the stellate cells.

The whole middle third of the shaft of the bone is undergoing this rarefaction, in the main by lacunar erosion, with possibly a limited amount of initial halisteresis. This comparatively early stage of the disease is of great interest in that it shows no fibrous tissue substitution of the bone marrow which von Recklinghausen considered the primary and essential change—an osteomyelitis fibrosa—while it foreshadows a complete fibrous tissue substitution of the compact and spongy bone—a fibrous tissue which is as yet very vascular and cellular except in the immediate neighbourhood of the blood-vessels in the larger spaces. From the rich network of capillaries in the enlarged spaces there are frequent haemorrhages, but nowhere as yet is there a dense fibrous tissue and nowhere any new bone formation by metaplasia.

Summary.—The femur, therefore, shows changes which are not recognisable as the classical picture of osteitis fibrosa, taking this term in the accepted sense of von Recklinghausen's disease. The picture, however, is one of marked osteoporosis and early fibrous tissue substitution of the destroyed bone. No new-formed metaplastic bone, no giant-celled tumour-like areas, and no cysts could be recognised.

The Vault of the Skull.—The bone was cut readily with a knife and required only a short time in the decalcifying fluid. The microscopic changes here, as in the humerus, confirmed the macroscopic picture, and a comparison of Plate II., Fig. 1, with Plate XV., Fig. 1, a microscopic section taken through one of the thinner portions of the vault shows the intimate correspondence of the two pictures. There is no evidence of a distinction into outer and inner tables with intervening diploe, and the microscopic changes are very analogous to those found in the humerus.

Under low power, the slightly thickened periosteum (pericranium) is composed again of dense layers which show a diffuse change into osseo-mucin; the dura mater is also greatly thickened and shows numerous elongated, oval areas with an almost complete infiltration of calcareous granules. The whole remaining thickness of the skull is transformed into a fibro-
osteoid tissue almost exactly comparable to that of the shaft of the humerus. Here also the new-formed bone, with the possible exception of a few isolated trabeculae that are parallel to the surface pericranium, was interpreted entirely as new-formed osteoid tissue undergoing a minimal degree of calcification. This fibro-osteoid tissue shows numerous pictures of all the structural changes already described; the fibrous tissue transformation into osteoid tissue both by a process of network bone formation and apposition bone, with marked lacunar erosion of the new bone; the cellular giant-celled tissue with hæmorrhagic interstitial infiltration around fragments of unresorbed bone; and the early cyst formation were all present. No trace of bone marrow could be recognised in any of the sections.

In the vault of the skull, therefore, there is a complete fibrous tissue substitution of bone and bone marrow; the formation of osteoid tissue by metaplasia and by apposition; and the presence of giant-celled tumour-like tissue and small cysts—the picture, therefore, of osteitis fibrosa as outlined by von Recklinghausen. Evidence also of calcareous deposits in the tissues was present in the thickened dura mater.

**The Basi-sphenoid.**—This bone was softer than normal and more readily cut; it contained, however, a considerable proportion of calcified bone and the microscopical changes indicate a stage in the evolution of the disease later than that in the femur but less advanced than that in the humerus. The histological picture here is complicated by the presence of the cellular bone marrow—which normally occupies the cancellous spaces. Figs. 3 and 4, Plate XIX., show that these spaces are very greatly changed and that there is a varying degree of substitution of the lymphoid marrow by fibrous tissue. In those spaces in which this substitution is least the fibrous change occurs earliest always near the bone: here the connective tissue fibres form almost concentric layers following the irregular contours of the bone.

The destruction of the bone trabeculae appears to be taking place in two ways: (1) by the usual lacunar resorption by osteoclasts, and (2) by a process of solution of the cement substance by which the original lamellation of the bone is first made evident and then there results its complete fibrillation with the escape of the previously enclosed bone cells. This second picture is so striking, and seemed so convincing and of
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such importance that the three drawings (Plate VII., Figs. 1-3) were made to illustrate it. From the bone substance (old bone) there appear to stream forth, often in a fan-shaped manner, osseo-mucinic Sharpey’s fibres, which end as delicate fibrils in direct continuity with the connective tissue fibrils of the space. Between the Sharpey’s fibres in the zone close to the as yet unchanged bone lie very numerous large uninuclear cells of osteoblast type, which are undergoing active proliferation. The picture of lacunar resorption by osteoclasts is similar to that found in the femur, but there appeared to be as yet no new bone formed in the fibrous tissue, which was gradually replacing not only the destroyed bone but the cellular marrow.

We have, therefore, in relation to von Recklinghausen’s picture of osteitis fibrosa the factors of bone destruction and the substitution of this bone and of a portion of the bone marrow by fibrous tissue. There is as yet no new bone formation by metaplasia, no tumour cell tissue nor cysts; though certain pictures might be interpreted as a possible slight new bone formation by apposition on the trabeculae of old bone.

The Rib.—The costo-chondral junction and the adjoining portion of rib were examined; the bone grated considerably when cut with the knife, but was comparatively readily decalcified. The changes in many ways were comparable to those in the basi-sphenoid, and here also the histological picture was complicated by the presence of a cellular bone marrow. Plate XV., Fig. 2, shows the resorption of the spongy bone, for, over long stretches, the central trabeculae are absent and are replaced by fibrous tissue strands in the midst of and encroaching upon the lymphoid marrow. There is a thin layer of old bone representing the cortex, but at many parts this has been interrupted, and the thickened periosteal strands are in direct continuity with the fibrous tissue which in part or wholly takes the place of the central trabeculae.

The following features bear a striking similarity to those in the basi-sphenoid: (1) the earliest fibrous tissue substitution is always immediately around the bone trabeculae (Plate XIX., Fig. 1); (2) the lacunar resorption of bone is present, but is in the background compared to (3) the gradual defibrillation of the bone with the escape of the bone cells, which appear in multiple layers on the bone contours. It is possible that these bone cells may revert to fibrous tissue cells, and take part in the general fibrous tissue formation, or that they may remain

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active bone cells and lay down bone by apposition; numerous pictures are present in the sections indicating the possibility of both differentiations of those cells. At the costo-chondral junction there is a change analogous to that at the lower end of the humerus, where a substitution of the cartilage by fibrous tissue is taking place by direct metaplasia.

The rib, therefore, shows only certain of the features distinctive of osteitis fibrosa—the destruction of the bone, its substitution by fibrous tissue, and the partial substitution of the lymphoid bone marrow, by fibrous tissue. No bone that could, by any of the staining methods, be interpreted as new bone could be found and no giant cell tumour-like tissue or cysts.

The evolution of the disease as indicated by the changes in the bones would seem, therefore, to be the following: the most advanced transformation of bone elements and structure is found in the humerus and in the vault of the skull, in which bones are present all the characteristic changes of the "osteitis fibrosa with multiple tumours and cysts" of von Recklinghausen; the changes in the ribs and basi-sphenoid are related in time and in degree, for in both there is present the same bone destruction and the same fibrous tissue substitution, and an absence of metaplastic new bone formation; while the changes in the femur are the most recent, and are limited to extensive bone destruction with commencing substitution by a vascular cellular tissue of embryonic type.

(B) THE PARATHYROID GLANDS AND THE PARATHYROID TUMOUR.

Several observations, relating to the presence of a parathyroid hyperplasia or a parathyroid tumour in association with a malacic bone condition, are on record. These observations are of great interest when correlated with the results of experimental work. MacCallum and Voegtlin have shown that after parathyroidectomy there results a deficiency of calcium salts in the blood and tissues, accompanied by an increased output in the urine and stools. The effect of parathyroidectomy in the production of tetany (tetany parathyro-priva) scarcely comes within the scope of this paper. It may, however, briefly be stated that recent experimental work tends to support the view that this function, in the case of the parathyroids, consists in neutralising in some way toxic
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substances formed in the body; if the parathyroids are removed these toxic substances accumulate in the blood and act on the central nervous system, and, peripherally, on the neuro-muscular junctions. According to Noël Paton and his co-workers the most important of these is guanidine, one of the by-products of nitrogen metabolism. The parathyroids thus control the metabolism of guanidine in the body by preventing its development in undue amounts.

Of greater interest in relation to our subject is the view that tetany is determined by a deprivation of calcium, and the production of tetany—a condition of neuro-muscular hyperexcitability—after parathyroidectomy, is related to a decrease in the calcium salts. The parathyroids, according to this calcium theory, as opposed to the toxic theory, regulate the metabolism of calcium just as the pancreas regulates that of glucose; they have, it is supposed, an inhibitory action on the excretion of calcium. The deduction to be drawn from this view, in a malacic case with hyperplasia of the parathyroids, would therefore be that this change indicates an attempt on the part of the parathyroids to prevent the excessive excretion of lime salts which occurs in such conditions as osteomalacia and osteitis fibrosa.

Salvesen’s parathyroidectomy experiments in dogs show that the characteristic feature in the chemistry of parathyroid insufficiency is the drop in blood calcium: they suggest that the parathyroids control the calcium metabolism, and by doing so they influence the functions not only of the muscle and nerve tissue but of all the organs. The importance of calcium in the growth of the tissues is shown by the great demands made by the developing embryo on the mother for a supply of calcium. Widdows found that to a large extent this is met by a regulation of the ordinary metabolic process, but that in the late stages of pregnancy there is a tendency for the calcium content of the blood to decrease—an indication of the importance of a sufficiency of calcium in the diet of the mother, especially during the last months of pregnancy.

In 1891 Gley propounded the theory that the parathyroids were embryonal thyroid tissue, but in 1901 he substituted the view that the relationship is a functional one. In 1904 Vincent and Jolly maintained that the thyro-parathyroid apparatus was one organ, basing this on their observation that after thyroidec-
tomy the parathyroids developed a thyroid gland structure with
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colloid, but many other workers produced dissimilar effects by the removal of these organs, and came to the conclusion that the functional unity of such closely connected tissues as the thyroid and parathyroid, or the medulla and cortex of the suprarenal, is not necessary. Embryological studies show that the parathyroids are genetically independent organs which develop as symmetrical thickenings of the endoderm of the third and fourth branchial clefts in the neighbourhood of origin of the thyroids, and that their multiplicity is due to a secondary constriction of the original epithelial mass. The independent origin and specific function of the parathyroids and thyroids does not exclude, however, the occurrence of a direct or indirect relation in the functions of the two systems.

It must be admitted that it is difficult to formulate any exact deductions regarding the physiological rôle and pathological influence of the parathyroids, and that our knowledge of the significance of the changes in these organs in certain diseases connected with abnormal calcium metabolism is very uncertain. Several writers (Schmorl, Erdheim, Strada, Bauer, Molineus, Hohlbaum and others) have found parathyroid hyperplasia in osteomalacia; others (Erdheim and Ritter) in rickets; others (Maresch, Meyer, Molineus) have found hyperplasia or tumour formation in osteitis fibrosa. Maresch has described a similar enlargement in a case with bone cysts; Ritter in a case of osteogenesis imperfecta; Hohlbaum in a case of Basedow's disease; Askanazy in osteitis deformans; while Todyo has shown the presence of hyperplasia in cases of osteoporosis, senile osteomalacia, and osteitis deformans, but also in four out of twenty-four cases of patients dying with the bones normal.

The association of chronic renal disease with hyperplasia of the parathyroids has been frequently noted; Thomas and Wentworth (Barker) report such an association in a man aged 21, with renal disease of ten years' standing. At the autopsy, in addition to cirrhotic changes and parathyroid hyperplasia, there were present extensive calcium deposits in the tendon sheaths and in all the peripheral vessels, together with bone changes similar to those described in osteitis fibrosa. Barker emphasises the possible relation of the parathyroid hyperplasia to the deposition of calcium salts in the tissues and organs.

The connection between the parathyroid change and the malacia is not clear, but the view of Erdheim has been generally
accepted that the hyperplasia of the parathyroids is not the cause of the bone change but the consequence of hyperfunction owing to an increased calcium metabolism. Cases of parathyroid hyperplasia and tumour have, however, been recorded without skeletal changes.

**Histological Examination.**

**The Parathyroid Glands.**—Four parathyroids of normal or slightly enlarged size were found in their normal relation to the thyroid gland. One of these glands is represented in Plate XXI., Fig. 1, and its structure was found to be composed (1) in large part of sheets of cells separated by strands of a vascular connective tissue; (2) in part of intercommunicating trabeculae of epithelial cells, the reticulum of which was formed by sinusoidal capillaries with a delicate and incomplete connective tissue fibril wall, and in such areas the tissue has a very spongy appearance; (3) small areas were also present with the cells arranged in an acinous manner, with or without a colloid-like secretion in the lumen.

The cells, whether arranged in sheets and masses, or in a network of trabeculae, or in acini, have not a uniform appearance: (1) The type of cell is usually a variation of the chief or principal cells described by Welsh, *i.e.* large, clear, vesicular, polygonal cells, with very distinct cell outline and a scarcely stained protoplasm (Plate XXI., Fig. 3a); the nucleus of these cells is dark, yet shows a definite chromatin network. (2) Amongst these “principal” cells lie small groups of a smaller type of cell, with a small, very dark nucleus, and frequently with fine neutrophile granules; such cells have been looked upon as the forerunners of the “principal” cells, which are the “functioning” cells, and all transitions between the two types could readily be traced. Their abundant appearance in an adult is regarded as an indication of hyperplasia. (3) Lying amongst the “principal” cells, in smaller or larger groups, is found the third type of Welsh—the oxyphil cell with intensely stained oxyphilic granular protoplasm (Fig. 3b); these oxyphilic cells are not so deeply eosinophilic as the corresponding cells in the pituitary. (4) In addition it may be noted that the “principal” cells lining the sinusoids frequently had a definite palisade arrangement—palisade cells.

Syncytial cell masses of the “principal” cell type, without recognisable cell outline were not found. A few large cystic
spaces filled with a granular content were present (Fig. 3c), and two of the glands showed a marked infiltration of the organ with fat cells, and in the areolar tissue separating one of the glands from the thyroid small isolated islets of parathyroid—small cell type—were present, indicating a commencing hyperplasia of the gland. Many of the blood-vessels, both large and small, show deposits of calcareous granules in the media.

The four parathyroids, therefore, may be regarded as normal in structure, both in regard to the arrangement of the cells and the types of cells present.

**The Parathyroid Tumour** (Plate XXI., Fig. 1).—A tumour, at first thought to be an enlarged gland till its outlines were made clear, was found towards the lower pole of the left thyroid lobe. This was the size of a walnut, was smooth in contour, was definitely encapsulated, and distinct from the thyroid gland. On section it was of soft consistence, greyish-white in colour, with minute translucent areas.

Microscopically (Fig. 2), the tumour showed a very uniform structure; it was divided into lobules by a connective tissue stroma, which further penetrated among the cells as a fine fibrillar network, on the strands of which the cells were arranged in one or several layers. The structure was quite definitely papillary, with a core of connective tissue and a delicate capillary. The vascularisation of the tumour is from the capsule, and the blood-vessels and capillaries radiate into the strands and papillary cores. The whole tumour showed little variation from this structure either in arrangement or in type of cell.

The cells of the tumour also were uniform in character, being polyhedral cells with distinct cell outline; they were small in size and showed a neutrophile, almost slightly basic protoplasm; therefore not so clear and vesicular as the principal cells. In size, form, and staining, they had the general characteristics of these cells, with the variations which correspond to a transition between the smaller and the larger "principal" cells of the normal parathyroid. Nowhere could oxyphilic cells be found in the tumour; only in a few areas were the cells arranged in compact masses; and in the connective tissue capsule, especially in the portion in relation to the esophagus, were found small strands of compressed cells which had a network trabecular arrangement. This also was the only point
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at which any evidence could be traced of an apparent infiltration of the capsule. No colloid-containing acini were present, and no fatty tissue between the epithelial lobules.

This structure must be regarded as a papillary adenoma of the parathyroid gland, simple in character, for there were no indications of an atypical cell proliferation. The relation of the cells to the capillaries was not so intimate as that of the palisade cells to the sinusoids of the normal gland. Nuclear groups of what may be regarded as reserve cells of the chief cell type, which were present in small numbers in the normal parathyroids could not be definitely recognised. The origin of the tumour must have been from an aberrant parathyroid, for four normal glands were present—all of which showed normal appearances; one of these glands showed islets of parathyroid tissue in the intervening areolar tissue between it and the thyroid—a suggestion of the possible source of such a tumour.

**Summary.**—A parathyroid mass, composed of modified “principal” cells and built up on a papillary structure, with central capillary core, was found in close relation to the thyroid gland along with four normal parathyroid glands. This mass was interpreted as a simple papillary adenoma, though it must be recognised that adenomata in glandular organs have frequently turned out to be evidences of compensatory hyperplasia.

(C) MULTIPLE CALCAREOUS METASTASES.

**Introduction.**—In all osseous dystrophies, i.e. in all calcification dystrophies in which the anomaly of metabolism occurs in patients whose bones have been presumably at one time normal in their calcium content, it would be natural to find evidence in the excretory organs of the body of an excessive attempt at removal. In several of the papers already referred to there has been noted the presence of calcium in the form of fine granules in the epithelium of the kidney tubules, but the present case seems unique, so far as the writers have been able to examine the literature, in that this calcium deposit occurred so extensively, not only in organs by which it is normally excreted—kidney, intestines, and bronchial mucosa—but occurred also in certain structural tissue elements in all the organs and tissues of the body.

Calcium, after its absorption by the blood, is invisible to
microscopic methods: it occurs in the blood as a colloid solution which penetrates all the tissues and cells, and in the normal body only the bones have calcium in solid form, intimately admixed with the ground substance. Its diminution, therefore, can be microscopically recognised only in bone, and this bone with an absence or diminution of calcium is known as osteoid tissue. In such conditions as osteomalacia an increasing osteoid or decalcified zone surrounding the enlarging Haversian spaces is the most significant feature of the histological picture. An increase of the calcium content in any tissue appears at first in the form of fine granules which become confluent: this may occur in lining epithelial cells, e.g. of the intestine and kidney or in the necrotic epithelium of tumours, and also in elastic and collagen fibres and in any necrotic tissue element. This deposition is stated by Gierke not to be a question of chemical affinity but of physical adsorption through colloid just as in the normal adsorption by osteoid tissue. In addition to this dystrophic process is the combination of calcium with the free fatty acids such as takes place in patches of atheroma.

In extreme resorptive processes in the bone system, e.g. in osteomalacia, osteitis fibrosa, and in bone tumours, calcium deposits occur in the bronchial mucosa, intestinal mucosa and renal tubules, and in these cases the calcium over-deposit from the blood occurs, as far as can be ascertained, in previously unchanged tissue. Askanazy and Hofmeister (quoted by Gierke) hold that the lungs, kidney and portions of the intestine in consequence of acid secretion possess an intense local tissue alkalinity, and therefore a lessened power of solution, e.g. in the stomach the calcium deposit is found especially in the tissue elements of the acid-forming area of the fundus and especially in the parietal cells. The possible function of the parathyroid glands in controlling the acid-base equilibrium, may thus have a bearing on the deposit of calcium in the tissues in cases of insufficient or abnormal parathyroid secretion, for parathyroidectomy in animals causes a temporary alkalosis.

Katase in the attempt to produce experimentally calcification in the tissues of rabbits found that if the excretion of calcium salts by the kidney and intestinal and bronchial mucosa were insufficient, there was a deposit of calcium in the organs and that these organs, which under physiological conditions had a high calcium content, had a high calcium exchange without deposit. He found that the first tissue elements in which
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deposits occurred are the elastic fibres and the fine connective tissue fibrils.

Versé has described two cases of "calcinosis universalis" in which deposits occurred chiefly subcutaneously and in the intermuscular and perimuscular connective tissue layers. He looked upon the condition as a primary disturbance of the whole connective tissue apparatus in a patient with a calcareous dyscrasia. Tilp (Gierke) reports a similar case with excessive calcareous deposits in the subcutaneous tissues of fingers, arms and legs: the examination of the skeleton showed no bone changes.

**Histological Examination.**—Calcium deposits, in the form of fine granules, which in some instances became confluent masses, were present in all the internal organs and in all the tissues of the body. The calcium seemed laid in the minute fibrils, both elastic and connective tissue and muscle and in the lining epithelial cells. According to many observers an overloading of the tissue fluids with calcium is insufficient to determine a deposit, and these writers maintain that a deficient vitality of the structural tissue elements is also necessary: it is obvious that in such a case as the present it is not difficult to postulate such a deficiency and this deposit was in no sense only in necrotic cells and tissue elements. The series of photo-micrographs (Plate XXII., Figs. 1-3) indicates the position of the calcareous deposits and makes a detailed description unnecessary.

**Blood-vessels** (Fig. 1).—In all the medium-sized and smaller arteries the internal elastic lamina was wholly or in part replaced by granules; similar granules were present in the intermuscular connective tissue and elastic fibrils of the media and of the adventitia. The whole media was often an irregular calcareous circular plate, the earliest indication of the change consisting in a swelling of the individual fibrils, both connective tissue and elastic, till the muscle fibres became atrophied and disappeared. The corresponding veins were much less involved.

**Heart Wall.**—Numerous granules were present in the connective tissue fibrils of the endocardium and in some instances these were fused to form patches which encroached on the muscle fibre. The walls of the larger and smaller vessels were involved and the smaller vessels were often outlined for a considerable distance by the granular deposit in the adventitia. In the muscle fibres themselves there seemed to be an imbibition
by the myoplasm, commencing around the nucleus till longer or shorter stretches of the fibre were involved.

**Lungs.**—The lungs showed an early chronic venous congestion and bronchopneumonia. The walls of the vessels and of the bronchi, and the larger septa showed extensive calcareous infiltration, while the whole of the interalveolar elastic and connective tissue content was apparently transformed into a network of swollen calcified fibrils. The mucous membrane of the smaller bronchi showed fused patches of complete replacement and the gradual transition and fusion of the granular epithelium of the less affected area could readily be traced. The cellular and mucoid exudate in the lumen of the bronchi was tinged with dissolved calcareous material.

**Lymph Glands.**—Several glands were examined: all showed a degree of fibrosis with the calcareous granular change. In the sinuses of the root glands of the lung, there was present an inflammatory reaction consisting of polymorphonuclear cells, red blood cells and many phagocytic cells, such as are found in the root glands in bronchopneumonia.

**Liver** (Fig. 3).—The capsule and the larger portal tracts show long streaks of calcareous change, which can be traced into the minutest portal areas. The liver sinusoids show a granular deposit with a swelling of the connective fibrils, which gradually increases and encroaches on the liver cell trabeculae, in a manner exactly analogous to the amyloid change, with complete substitution of the parenchyma in the most affected areas. A few isolated liver cells show an imbibition of the granular material just as in the case of the muscle fibre.

**Spleen.**—The capsule, septa, and blood-vessels are all mapped out by calcareous streaks and portions of the delicate reticulum of the sinuses are transformed into a network of swollen calcareous fibrils.

**Stomach.**—Sections from the fundus (Fig. 2) show an almost complete involvement of the interglandular connective tissue content, so that a network of calcareous tubes seems to surround and compress the glands, the epithelial cells of which are atrophic. Many of the remaining cells, both central and parietal, are full of fine granules. The remaining coats except for the affection of the blood-vessels, especially of the submucosa, are free from involvement.

**Kidneys.**—The course of the interlobular vessels is mapped out under low power by an irregular line of calcareous
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material with off-shoots corresponding to the affected afferent vessels and glomeruli, the intercapillary connective tissue network of which is swollen and granular. Many glomeruli show no lumen of the capillary network, and are compressed and obliterated by the fused granular network. The vessels of the pyramids show a similar change, but the renal arches are unaffected. The epithelium of the collecting tubules and of the convoluted tubules is by no means uniformly involved, but the epithelium of numerous tubules is replaced by fused, globular calcareous granules. The kidney substance shows an early interstitial change, while in this organ almost alone there is a subacute inflammatory cell reaction with foreign body giant cells around the calcareous material that is in the interstitial fibrous tissue. Neither the suprarenal glands nor the thyroids showed any appreciable change except in the blood-vessels.

Voluntary Muscles.—In the intercostal muscle the larger fascial strands show numerous fine granules, but the myoplasm itself is not involved. Many of the dense fascias of the body, e.g. the dura mater, are markedly infiltrated and appear as sheets of calcareous granules.

Pituitary and Pineal Glands.—The larger and smaller connective tissue strands and all the blood-vessels were involved. In the pituitary many of the basophilic cells, especially in the pars intermedia surrounding the colloid-containing spaces, were undergoing calcareous degeneration, and several of the glia cells in the nervous part were completely calcified. The pineal gland shows no definite deviations from its normal structure, except in an apparent increase of the calcareous concretions.

Nervous Tissues.—Portions of the brain cortex, of the pons and medulla, and several peripheral nerves were examined but show no calcareous change either in ganglion cells or nerve fibres and little in the blood-vessels.

IV. CRITICAL DISCUSSION.

Introduction.—The foregoing description corresponds to the classical picture of the generalised type of “Osteitis Fibrosa with multiple giant cell tumours and cysts.” Systemic diseases of the skeleton, such as Rickets, Osteomalacia, Osteitis Fibrosa, and Osteitis Deformans are classified according to their pathology,
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for their pathogenesis is unknown. It is natural to expect a histological distinction between these diseases, but the more intensive the study the more difficult it is found to draw a sharp distinction between them, and von Recklinghausen refused to define a distinction between osteomalacia and rickets.

With the name of Paget we connect a definite clinical and histological picture—Osteitis Deformans: similarly with the name of von Recklinghausen—Osteitis Fibrosa. These two diseased conditions have in common a disturbance of the tissue equilibrium which regulates the relations between normal bone removal and new bone formation: this disturbance leads to bone softening—malacia. Between these two diseases there appear to be all transition stages, so that von Recklinghausen, who included both in the group of "metaplastic malacias" called Paget's form a "hyperostotic metaplastic malacia" and osteitis fibrosa a "simple metaplastic malacia." To one or other type also belong cyst-forming metaplastic and tumour-forming metaplastic malacias: these occur both in the generalised and localised types of osteitis fibrosa. It is obvious, therefore, that the problems that lie before us are very complex: (1) the relation of generalised Osteitis Fibrosa to Osteitis Deformans; (2) the relation of these to other malacic diseases; and (3) the relation of the tumour-like tissue and cysts, arising out of metaplastic malacic conditions, to the benign sarcoma of bone (epulis, myeloid sarcoma) and bone cysts.

In the consideration of these varied relationships it will further be necessary to discuss problems related to the histological details which might interpret such fundamental pathological processes as: (1) the removal of bone by (i.) halisteresis, (ii.) lacunar resorption by osteoclasts, and (iii.) by perforating canals; (2) the origin and mode of formation of the fibrous tissue substitution; (3) the metaplastic new formation of bone: (i.) reticular bone, and (ii.) apposition bone; (4) the formation (i.) of the cellular giant cell tissue, including the origin, mode of formation, and significance of the giant cells, and (ii.) of the gradually-enlarging cysts which, when they coalesce, may form definite bone cysts. This group of, as it were, incidental but fundamental problems will be taken up first, and it will then be possible to note what light they throw on the distinction between the members of this allied group of obscure bone lesions. The unsolved problem of the etiology
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of this group will then be touched upon, together with a note on the possible relation between the parathyroid tumour present in this case and the abnormal calcium metabolism shown by the malacia and the numerous calcareous deposits.

(A) INTERPRETATION OF FUNDAMENTAL HISTOLOGICAL PROCESSES.

(1) Bone Removal.

There is no department of pathology more closely related to surgery than that of the bone. It is necessary, therefore, in order to understand the finer histological processes in bone pathology, to acquire definite ideas regarding the processes which lead to the removal of existing bone tissue, i.e. the mode of bone resorption. Volkmann based his deductions on caries and osteitis on three forms of bone resorption: (i.) Halisteretic atrophy; (ii.) Lacunar erosion; and (iii.) Vascularisation by means of the perforating canals which bear his name.

(i.) Halisteresis.—Halisteresis is one of those pathological terms which, owing to their pregnancy of meaning, and their convenient application, find an assured place in the vocabulary of science. What, then, is the conception underlying this term—a term which it is essential to use when referring to histological changes in Rickets and Osteomalacia, and to a lesser degree in Osteitis Fibrosa and Osteitis Deformans?

The term was at first applied by Kilian (Axhausen) exclusively on clinical and gross anatomical appearances. The bones of the pelvis exhibited increased softness in osteomalacia; it was unthinkable that hard bones should become soft without loss of their calcium content, and Kilian gave the explanation of their decalcification through the agency of the body fluids (halisteresis). The analogous process, clinically and anatomically, recognisable in the rickets of childhood was explained in the same way, and then followed the view of the identity of the two affections—based on the assumption that in both decalcification was the determining factor.

Virchow opposed this view on the grounds of finding non-calcified osteophytes in rickets; he at once recognised that these were newly-formed bone and not decalcified old bone, and came to the conclusion that rickets and osteomalacia were therefore not analogous processes. Virchow claimed that the bones already formed when rickets set in remain calcified; that
those subsequently formed do not become calcified—rickets was therefore not a malacia.

Rindfleisch, by the aid of carmine staining, was the first to observe and describe the non-calcified (osteoid) zones of lamellar bone in osteomalacia; he regarded these zones as arising as a result of the action of the body fluids outwards from the medullary spaces. The whole question of halisteresis centres around the interpretation of these osteoid zones of the lamellar bone. They seemed to harmonise so perfectly with the theory of a slowly-increasing decalcification that Rindfleisch’s view became generally accepted and the question of halisteresis seemed settled in the affirmative.

Cohnheim, however, put forward another interpretation; he claimed that the non-calcified zones were entirely new-formed layers. Pommer's extensive researches supported this new view; he found even in normal growing bone a narrow, non-calcified new-formed zone on all lamellar bone, and claimed that the broad zone found in rickets and osteomalacia had also this origin and was merely a layer of new bone with delayed calcification. In spite of the convincing nature of Pommer's histological data, this view did not find general acceptance. This was in part owing to the fact that Pommer did not altogether repudiate the halisteretic theory that the osteoid layer denoted a regressive modification, and these reservations, in spite of the complete repudiation of the whole halisteretic theory by Axhausen, seemed to leave the nature of the osteoid layer in rickets and osteomalacia still in doubt.

Von Recklinghausen further revived the halisteretic theory, for he claimed that not only had a portion of this osteoid layer in rickets and osteomalacia originated in a decalcification which was the beginning of a destructive degeneration of the existing bone and was the essential feature of the malacic process, but he extended it to the normal growing bone. Thus von Recklinghausen directly opposed Pommer, and the von Recklinghausen-Pommer controversy is the point at which the whole question rests to-day. Pommer's supporters emphasise the fact that his deductions have not been disproved, and that the main weight of von Recklinghausen's process rests on certain appearances (Gitterfigüren) in the transitional zone between calcified and non-calcified tissue, which can be variously interpreted. According to von Recklinghausen, they are signs of a regressive process—halisteretic disintegration—
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while Axhausen, who has exhaustively investigated the same material by means of the same methods, has come to the conclusion that the presence of the "Gitterfigürren" proves only the presence of an osteoid zone in the neighbourhood of the medullary space but throws no light on its mode of origin. The halisteretic theory seemed therefore to Axhausen and numerous subsequent writers (Looser, Ribbert) completely undermined and the significance of these "figures" as a sign of decalcification disproved. Yet Schmidt in the latest edition of Aschoff's Pathology (1923) does not admit the conclusiveness of Axhausen's deductions, and sees no reason for eliminating from pathology so fundamental a conception as halisteresis.

In our specimens, especially those taken from the humerus and the vault of the skull, numerous references have been made to the homogeneous zone bordering the bone trabeculae—a zone which varied greatly in width, and which, with none of the stains used, gave any indication of commencing calcification, such as was evident in the more axial layers (Plate XVII., Fig. 6). These osteoid zones were always in intimate relation to layers of osteoblasts, and their significance will be discussed later under new bone formation by apposition. It is evident that it is not to those new-formed zones that the conception of halisteresis can relate, for the whole impression given by these appearances was that of the most recent layer of not yet calcified bone tissue, applied by apposition to earlier new-formed bone.

It is in the sections taken from the femur, rib and basi-sphenoid that the opportunity arises to discuss appearances suggestive of halisteresis. Even in fully developed bone the normal modification in structure is carried on by alternate resorption by osteoclasts, and bone-formation by apposition in the Haversian canals. In the bone dystrophies we are now considering, and especially in the regressive transformation of the bone indicated in our sections of the femur, there is a marked disturbance of the relation between these two processes, for apposition does not follow resorption to compensate for the destruction which arises, and there result the wide marrow spaces in the compact bone substance, because apposition is too limited. Is it necessary, however, to explain the osteoporosis that has arisen entirely by want of apposition-formed bone?

It has seemed to the writers that several data point in favour of a limited but definite initial degree of halisteresis—
(1) Gradually enlarging Haversian spaces, smoothly contoured, in which as yet there are no osteoclasts apparent, suggest halisteretic atrophy. Such spaces have a definite homogeneous, non-calcified zone (Plate VI., Fig. 2) immediately internal to the concentric lamellæ which are still calcified; the canalicular processes of the bone cells around this zone stop short at the transition line between calcified and non-calcified tissue. (2) In the surrounding lamellæ many of the bone cells, instead of being spindle-shaped with parallel canalici arising uniformly from the sides of the long spindle, have become vesicular and are surrounded by a clear zone which does not take the Schmorl stain; the processes also of such cells are retracted, swollen, and shortened, often completely atrophied (Plate VI., Fig. 2). (3) The appearance of splitting up of the lamellæ, both concentric and parallel, which is so frequently present in all bone sections and which to a certain extent must be regarded as an artefact, is exaggerated in comparison with more normal, non-rarefied portions of the same section. Further, there takes place the gradual fibrillation of the ground structure of the bone by the solution of the cement substance, as in the figures from the basi-sphenoid (Plate VII., Figs. 1-3).

The writers have not had an opportunity of examining sections of true osteomalacic bone in which these osteoid zones, apposed to still calcified bone, reach their maximum development, and in the present case of osteitis fibrosa it has been only in the femur, rib, and basi-sphenoid, and that only in a limited degree, that the possibility of studying this process was presented. But it has seemed natural to assume that in dystrophic processes, where the normal regulation has been lost sight of and where there is such a striking disparity between the processes of resorption and apposition at the stage of the affection we are considering, the appearance of certain osteoid zones, not covered by a layer of osteoclasts, is very suggestive of an initial halisteretic change, which might assume greater proportions did active lacunar erosion not set in rapidly.

(ii.) Lacunar Erosion.—Bone removal, bone resorption, bone destruction, or bone disintegration by the action of giant cells (osteoclasts) lying in Howship's lacunæ is, universally admitted, microscopically so obvious, and the numerous drawings and photographs make it so clear, that
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little need be added to the section in the histological study. Pommer, in opposition to von Recklinghausen, holds that it is the one and only method of bone removal and, however controverted other means may be, this method seems once for all established.

In simple bone atrophy we have a disturbance of the relationships which exist between normal bone resorption and bone apposition so that wide Haversian spaces are found, on the walls of which, however, it is possible to find thin layers of concentric lamellae, which may be interpreted as an expression of a limited apposition—the type character of this is in agreement with the normal. In dystrophic processes, however, in contrast to atrophic processes, normal regulation has been to a considerable extent lost sight of, for apposition does not follow resorption. It may lag far behind, allowing large irregular spaces to be formed, or it may be in excess, as in the new osteophytic formations in rickets and osteitis deformans. Here the apposition is not that of normal lamellar apposition but is altered in type, so that there results a reticular or cancellous bone with lamellae laid down by apposition on the contours of the meshes instead of concentrically on the enlarged Haversian spaces. Apposition is, therefore, altered not only quantitatively but qualitatively: it is not merely retarded apposition as in atrophy, but it is apposition in a wrong direction, i.e. it is a dystrophic process.

All bone not under the control of the living bone cell is slowly dissolved by osteoclasts. These cells digest and erode and remove the intercellular substance of bone, so that a gradually increasing enlargement of the Haversian and cancellous spaces results. The stages in this process can be followed in the figures (Plate V. and Plate XVI.). In the preceding section it has been assumed that the appearances justify the conclusion that the initial stage in this process of enlargement is a degree of halisteresis; and this early solution of the lime salts may possibly be traced to the action of an unknown agent on the bone cell whereby it loses its vital control over a certain area of bone substance. The first recognisable microscopic changes have already been noted as a pale peri-cellular zone around the cells of the inner lamellae, and a similar pale concentric zone of uncalcified bone tissue on the inner wall of the Haversian space (Plate VI., Figs. 1 and 2). The bone cells nearest to this
zone are soon enclosed in this layer of uncalcified tissue, which is dissolved away and the bone cell passes into the space and becomes indistinguishable from the now proliferating cells of the endosteum. The structural elements present in this already slightly enlarged Haversian space are the central capillary with a delicate layer of adventitia and a layer of protoplasmic cells lining the widened space. The further development of this process may be traced in the formation of a delicate network of stellate cells between the central vessel and layer of cells lining the non-calcified zone. These stellate cells are of very great significance in the further process of lacunar erosion which is now to commence: in origin we believe that they are endothelial (Plate V., Fig. 1) and that the central capillary forms a rich meshwork of branching cells such as may be found, e.g., in a fibrinous exudate in pleurisy or pericarditis. This abundant endothelial development may be determined in part by the retrograde process of solution of the bone salts and a primitive type of cell is formed which may undergo a very varied differentiation. The transitional stages between this enlarged space, with its central vessel, its meshwork of branching cells, and its cellular endosteum, to the early irregular giant cell (osteoclast) lined space can be followed in Plate XVI., Fig. 1.

Two modes of formation of the osteoclast can readily be traced in the sections: (1) The cellular lining layer, a derivative in part of the proliferated endosteum, and in part of the escaped bone cell, forms an epithelial-like lining layer, the cells of which may fuse over a considerable surface area to form a narrow syncytial mass directly applied to the bone, and following in its outline the irregularities of the bone surface. (2) The stellate and polymorphous cells of the meshwork fuse together and gradually pass towards the bone surface, where again a syncytial mass is formed. The margin of this syncytial protoplasm applied to the bone shows a regularly striated border, and even may be transformed into fine cilia-like processes which, as it were, interdigitate with the minute bone fibrils, while the free surface of the osteoclast show a series of cytoplasmic processes, which branch in all directions (Plate V., Figs. 1 and 2). Under a high magnification the structure of the early giant cells can be seen to correspond to that of a series of fused, branching cells, for the fibrils of the cytoplasmic
processes can be traced into the substance of the syncytial mass. The further changes in the enlarged space which lead to connective tissue fibril formation will follow later in the section dealing with fibrous tissue substitution.

It is difficult not to recognise in this ciliated fibrillar structure of the osteoclast (Plate VII., Fig. 6) the method by which this cell carries out its work. One gets the impression of an active biological process taking place in the body, the agent used being the fibrillæ of the osteoclasts, and the medium in which they act and which may stimulate them to activity being some unknown agent which causes a physico-chemical change in the body fluids. The giant cells lie in spaces—known as Howship's lacunæ—hollowed out by their own activity, and large, irregularly-contoured spaces result. Such spaces are formed in part by the coalescence of several smaller spaces and in part by the more intense action of the original perforating canals which link up the Haversian systems.

(iii.) By Perforating Vessels.—This represents a third possible mode of bone removal. The resorbing power of penetrating blood-vessels is recognised in endochondral ossification, and the question arises—is there ever present a disintegration of the mature bone by a similar means? Histologically a definite difference may be noted between the structure of the walls of the Haversian canals and that of the so-called Volkmann's perforating canals. The concentric lamellæ of the former stand in genetic relation to the inlaid blood-vessel, but the Volkmann's canals penetrate without relation to concentric or parallel lamellæ and have, on longitudinal section, regular and irregular contours. Volkmann believed that blood-vessels penetrated the mature bone and represented, therefore, an absorption of bone through vascularisation—possibly aided by an active participation of the cells lying in the bone tissue. The study of pathologically changed bone modified this conception, e.g. in callus there is formed a network of new bone, in which the form, number and arrangement of the bone spaces are readily distinguished from those in lamellar bone.

The presence of canals similar to Volkmann's perforating canals, and the presence of halisteresis associated with them, were made a special subject of study in the various sections. In normal bone the Volkmann's canals seem to link up Haversian canals, and must be regarded, therefore, as genetically
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a step in the completion of the Haversian system, and in the pathologically-changed bone, e.g. in the femur, both Haversian canals and the Volkmann canals were found in all stages of lacunar resorption. A careful comparison of numerous pictures led to the conclusion that there was an increased degree of the initial halisteresis around the perforating canals, for frequently an irregular and wide zone of solution of the lime salts appeared to outline such a canal, while around the blood-vessels of these canals the proliferated cells were greater in number than in the adjoining Haversian spaces (Plate XIX., Fig. 3, pbv).

The production of false penetrating canals by the removal of the bone intervening between two enlarging Haversian spaces was frequently followed, and it was in such parts that the appearances seemed to justify the assumption of bone removal by penetrating blood-vessels, for a vessel surrounded by a layer of proliferated endothelial cells was always present at the entrance of such a space—giving the impression of the entering blood-vessel loops in endochondral ossification. On the walls of such canals the osteoid zones suggested a halisteretic process and not apposition bone, and giant cell osteoclasts soon formed lacunæ, with a rapid loss of all the characteristic contours of a perforating canal.

In the examination of sections showing late stages of newly-formed bone, e.g. in the humerus and vault of the skull, where a network-arranged bone with very irregular lamellæ was found, there was only a minimal calcification, and no opportunity, therefore, of tracing the part played by perforating vessels in the rearrangement of the architecture of the bone trabeculae. But it is in such a tissue, which has arisen on a basis of network-arranged bone trabeculae and becomes calcified, that perforating vessels are likely to play a rôle in the reconstruction to compact bone with irregularly formed Haversian systems.

This reconstruction is of great importance in deciding the question whether osteitis deformans may be looked upon as a late stage of osteitis fibrosa. It is possible to conceive of such a bone as the humerus undergoing a reconstruction, if the patient's health improved. In the reconstruction to usefulness of such a bone, it must be remembered that the new bone laid down in the fibrous tissue is an irregular network of trabeculae (Plate XIX., Figs. 5 and 6): the prototype of such a tissue is found in normal callus, and in the reconstruction lamellar bone is laid
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down on the walls of the meshes of the network trabeculae, while simultaneously irregularly coursing blood-vessels are enclosed. In the further reconstruction to a dense bone, the mechanical and physical factors at work exercise their influence on the rearrangement of the trabeculae which now show lamellation, and in this process the enclosed blood-vessels may send out sprouts, which, acting as the original periosteal buds, may help to mould the orientation of the new irregularly arranged Haversian systems. Such new, dense bone, e.g. in osteitis deformans, could be distinguished from normal compact bone by its greater vascularity, its irregular lamellae, and by the presence of numerous trabeculae in which the network grouping could still be recognised. This tissue, composed of lamellar and network-arranged trabeculae, in its still further reconstruction, would become denser and denser by the apposition of new bone on the walls of the new Haversian spaces and of the meshes of the network trabeculae.

In pathological conditions such as osteitis fibrosa there is present a dilatation of pre-existing canals both Haversian and Volkmann, brought about by lacunar erosion, initiated by halisteresis. The old bone is then gradually removed and replaced by fibrous tissue in which a mixed-bone built tissue is formed. In the reconstruction of the new bone, which is thus chiefly a network of trabeculae with apposition lamellae, irregular Haversian systems are formed, in part by enclosure of blood-vessels, and partly by erosion, by penetrating blood-vessels' buds from such vessels. The subsequent calcification would be dependent on the vessel, and the zone of osteoid tissue around the vessel would represent the latest deposited lamella and not in this case a halisteretic zone.

The writers, therefore, conceive of an initial halisteresis, which paves the way for lacunar erosion and in the subsequent reconstruction, before calcification is complete, penetrating blood-vessels may play a rôle—the share depending on the modification in the reconstruction necessitated by the mechanical influences of strain and pressure.

(2) Fibrous Tissue Substitution.

(i.) Its Origin—in which structural tissue element.—The histogenetic study here implied in one of not merely didactic interest. Like the conceptions considered in the last sections,
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this study has a definite practical bearing on our whole view of the nature of this group of diseases and is closely related to the next section, in which the term "metaplasia" will be considered.

Normal and pathological histological appearances point strongly to a distinction between two tissue groups in the bone marrow—an osteopoietic and a hæmopoietic. Reference may be made here to the note given in the "Introduction" on the development of the structural elements in these two tissue groups. Von Recklinghausen regarded the fibrosis of the bone marrow as the essential and primary change in osteitis or osteomyelitis fibrosa, and it seems natural to assume that this osteomyelitis fibrosa has its origin in the reticular stroma of the bone marrow. Nauwerck and Schödel (Oehme) introduced the term "scaffolding marrow" to designate the reticulum in the meshes of which the parenchyma or blood-forming cells lie, and which was continued as a lining zone into all the cancellous and Haversian spaces as an endosteum. The fibrosis of the bone marrow in malacic and other conditions might arise from one or more of several cell elements, amongst which must be named the following: the connective tissue cell of this reticulum; the endothelial cell of the capillary network; the cells of the endosteum lining the spaces; the osteoblast and the bone cell itself—all of these on the side of the osteopoietic tissue. The question further arises: can the hæmopoietic cell participate in the fibro-cellular proliferation which precedes the fibrosis? i.e. can transitions be traced between the blood-forming cell and the scaffolding marrow cell?

(a) Connective tissue cell of the reticulum. The earlier indications of the proliferation of this cell can be recognised in the small areas of the fatty marrow bordering the fibrosed marrow of the humerus. Here all transitions can be traced from the fat cell to its substitution by a protoplasmic cell with tufts of fine fibrillar processes. As the fatty tissue merges into the fibrous tissue, these cells become spindle-shaped and very rapidly give rise to the ordinary fibrils of connective tissue shown by both Mallory's and van Gieson's connective tissue stains. Throughout the stroma of the lymphoid marrow also, the stroma cells in the transition zone between fibrous marrow and lymphoid marrow can be traced, giving rise to fibrils of connective tissue with a gradual replacement of the cell body. The adventitial connective tissue cells of the smaller vessels,
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both in the fatty marrow and in the cancellous and Haversian spaces, must also be regarded as a source of the fibrosis, and very numerous pictures in the sections of the enlarging absorption spaces of the femur indicate this source of origin. (Cf. Figs. 2 and 3, Plate XVI.)

(b) The endothelial cell of the capillary network. If Fig. 1, Plate V., is carefully analysed it will be noted that this enlarged Haversian space contains an extraordinarily intricate network of capillaries. The capillary lumen is lined by a layer or layers of large endothelial cells, cut in various directions and showing numerous mitoses. Such cells, as in organising granulation tissue, soon pass off from the capillary wall and produce interlacing cell channels formed of spindle-shaped or star-shaped cells. The protoplasmic body of these cells gradually darkens as they migrate towards the contours of the eroded bone, but if they remain near the capillary itself the cell becomes elongated and shows very delicate fibrils taking the specific stain for connective tissue fibrils. An increasing zone of such fibrils radiates out in all directions from the near neighbourhood of the capillary, while the immediate neighbourhood of the larger arterioles shows the fibrosis taking place from cells of adventitial type, as indicated in the preceding paragraph.

(c) The cells of the endosteum. The cells and fibrils of the endosteum are in direct continuity with the cells and fibrils of the reticulum. It is natural, therefore, to suppose that they take a considerable share in the fibrous tissue formation. The earliest stage of this participation is found in the smaller Haversian spaces that show as yet no osteoclasts. On the contours of such spaces a single or multiple layer of small cells is found lining the cavity. These cells have a nuclear structure similar to that of a modified fibroblast, and their multiplication is one of the first indications of enlargement of the Haversian space. As this enlargement takes place, two different changes may occur amongst these cells: (1) they may fuse to form osteoclasts, as already noted, or (2) they remain independent, become elongated and parallel to the contour of the space and give origin to fibrils, so that a zone of fibrillar connective tissue is formed immediately adjacent to the bone. In the femur, where osteoclast activity is so pronounced, this phase in the fibrous tissue substitution is not marked, but both in the rib and in the basi-sphenoid it is very obvious (Plate XIX., Figs. 1 and 3).
(d) The osteoblast and the actual bone cell. These two cells may be taken together, for the osteoblast must be regarded as a specifically differentiated cell giving rise to a specific product—osseo-mucin—while the bone cell is an osteoblast embedded in the osseo-mucin it has elaborated, and which may or may not have become calcified.

The osteoblast is simply a further differentiation of the cells of the endosteum. These are, in process of repair, regarded as osteoblasts when they have become more polygonal and protoplastic and have arranged themselves in an epithelial-like layer on the contour of the bone. This change in their specific structure results in the formation of the specific osseo-mucin and soon they are themselves embedded in the osseo-mucin secreted by them—thus being transformed into bone cells. In pathological processes such cells proliferate rapidly and are arranged in one or several layers (Plate XIX., Fig. 2), and complete transitions can be traced between the cell immediately adjoining the bone, with its very characteristic nucleus and one or two nucleoli and the dark cytoplasm to cells in the outer layers which are laying down fibrils of connective tissue. The question to be decided here is a basic one, and meets us again in the section on metaplasia: are these osteogenic cells, which are reverting to an earlier stage of differentiation and then becoming fibril-forming cells, or are they proliferated cells of the reticulum, which as they approach the bone are becoming osteogenic?

Numerous pictures can be found, especially in the sections from the rib and basi-sphenoid in which the only connective tissue fibrils present in the enlarging Haversian space or in the marrow-containing cancellous space, were those in this zone between the layers of proliferated osteoblasts and the marrow cells. The picture was usually interpreted as a reversion of the proliferated osteoblast to a connective tissue fibril-forming cell.

In regard to the actual bone cell, it is extremely difficult to decide the question whether the bone cells which escape, through halisteresis or lacunar erosion, into the Haversian space and take a share in the lining of such a space can similarly revert to fibril-forming cells. Modern conceptions of pathology regard the bone cell as so specifically differentiated a cell that having given rise to osseo-mucin, as an end-product, it lives only to carry out its specific function of controlling the calcium content of the bone area under its influence, but that it is...
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too differentiated to carry out its vegetative function of proliferation—in this being comparable to the nerve cell.

This question is of great significance in relation to bone transplants, where it is generally assumed that the actual bone cells die. Very numerous sections have been examined by the writers with this point in view with the increasing conviction that the bone cells are living, vitally active, specific cells regulating the calcium content of the area controlled by them. But while this is so, bone is a tissue in constant change and its cells, as in other tissue, except nervous tissue, if not too greatly damaged by an injurious agent, bacterial or toxic, can become active proliferating cells. As such, they would become cells of the osteoblast layer again and with them might revert to fibril-forming cells. In a living bone transplant, therefore, it is possible that the bone cells might pour out from the opened spaces in which they lie, and, together with the cells of the endosteum, take a share in forming the osteogenic fibro-cellular tissue, which is later to lay down bone trabeculae, which will bridge the gap. In this way the end-product or differentiated product of cell activity dies, just as in muscle and possibly in the peripheral nerve, but the cell itself retains its vegetative function and gives rise to its specific product again.

(e) The haemopoietic cell. It is still more difficult to be dogmatic as to the possibility of the haemopoietic cell taking a share in the fibrous tissue formation. In the cellular marrow ("lymphoid marrow") of the rib and of the basi-sphenoid it has already been stated that a zone of fibrillar tissue immediately lines the enlarging spaces. The origin of this tissue has been admitted to be in great part from the endosteum, but, as the transition zone is traced into the cellular lymphoid tissue, the scaffolding marrow becomes distinctly more recognisable. The becoming evident of this reticulum near the fibrous tissue zone may be due to a proliferation of the cells of the reticulum with an atrophy of the parenchymatous element—the haemopoietic cell—but there are very numerous pictures which seem to point to a reversion of the haemopoietic cell to a primitive undifferentiated cell and then to the differentiation of this primitive cell to a fibril-forming cell. Such a reversion in all probability takes place in the fibrosis of the bone marrow accompanying some forms of leukæmia.
(ii.) Its Primary Site: Medulla or Haversian Spaces?—
Von Recklinghausen regarded the essential and primary change in osteitis fibrosa as a fibrous substitution of the bone marrow: this change then passed from the medulla and cancellous spaces into the Haversian systems. He further regarded this fibrous tissue as in some way responsible for the osteoporosis. Plate X., taken from a cross-section of the shaft of the femur, shows that there is neither a fibrous nor a cellular substitution of the fatty marrow, while there is a very marked osteoporosis of the cortex and a very extensive substitution of the compact bone by a loose fibro-cellular and very vascular tissue. The changes in the femur have been regarded as an earlier stage of those shown in the humerus, where a fibrous tissue substitution had taken place not only in the compact bone but in the cancellous bone and medulla. It is obvious, therefore, that in this case, showing osteitis fibrosa in its earlier manifestations, the primary change has not been a fibrosis of the bone marrow. The fibrosis in the femur occurs first in the gradually enlarging Haversian systems of the compact bone. The numerous drawings and photographs from this bone, showing the gradual enlargement of the Haversian spaces of the cortex, the gradually increasing lacunar erosion, and the gradual substitution by fibrous tissue, compel one to the conclusion that the primary and essential change lies not in the fibrous tissue formation but in a loss in the specific activity of the bone cell whereby the control of the lime content is lost, and an initial halisteresis results with all the train of structural changes which then follows.

(3) New Bone Formation.

Metaplasia.—By this term is understood the conversion of one tissue into another of similar morphological origin and functional character, e.g. the supporting tissues of the body, and it has already been noted that this is distinct from the change that occurs in the differentiation or transformation of embryonal tissues.

The metaplastic process can take place in two ways: (1) Directly, i.e., the slow substitution of one tissue for another, e.g. cartilage into bone, with or without new cell formation; this is probably a very rare occurrence. (2) Indirect metaplasia which takes place in two phases: (α) a
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neoplastic, with a new formation of cells of a less differentiated type, and (b) a true metaplastic phase—the differentiation of these cells in a new direction. The new mode of differentiation can bring about a higher development—a progressive metaplasia—e.g. the differentiation of gall duct epithelium to liver cells; or bring about a regressive differentiation (anaplasia) as in the change of glial cells to ependymal cells.

By this indirect metaplasia, therefore, cartilage and bone can arise, the latter without any connection with preformed osteogenic tissue out of fibrillar connective tissue or in muscular callus, as in injury. The new bone thus produced is at first network or reticular bone and later shows a lamellation by bone apposition, through the medium of a layer of cells—osteoblasts—applying themselves to the surfaces or meshes of the reticular bone. These layers of osteoblast cells are, however, descendants of the connective tissue cells, and so this apposition bone is also metaplastic. Bone cells in metaplasia arise in this way from fibroblasts, either directly or through an intermediate form—osteoblasts.

It has just been stated that a direct metaplasia of cartilage into bone may possibly occur, but true normal bone does not arise out of cartilage in this direct way but only through a new formation of cells and blood-vessels, which in part erode the calcified cartilage and, on the remains of the calcified cartilage ground substance, bone is deposited by osteoblasts by apposition.

It is perhaps necessary at least to refer to forms of so-called metaplasia which are not true examples of the above transformation, e.g. (a) a false bone tissue can arise out of connective tissue directly—the fibrillar substance becoming hyaline and calcified and the connective tissue cells coming to lie in this calcified mass; but even in this calcified substance, by a new formation of cells and blood-vessels, marrow spaces can be formed and on the walls of the marrow spaces the young cells can form true bone on the surfaces of the calcified tissue. Nicholson has similarly described the formation of bone in a calcified epithelioma of the skin as a secondary process following necrosis and calcification. This writer looks upon the fibroblasts of the marrow spaces as taking on the function of osteoblasts, whenever stimulated to this process by the presence of lime salts, which had been dissolved out of the calcified material by giant cells. Pearse has described the occurrence of bone formation in the scar tissue of the kidney in rabbits after
various forms of injury, e.g. after the ligation of the renal artery. The first result of this was a necrosis of the kidney tissue, followed by a widespread deposition of lime salts. He ascribes the formation of bone in unusual locations to two causes—(1) the conversion of the connective tissue into a callus or osteoid tissue; or (2) the resorption of calcified material by blood-vessels and giant cells: the formation of a marrow space and the deposit of bone in its periphery by an osteoblastic membrane derived by metaplasia from the connective tissue accompanying the vessels. (b) Another form of false metaplasia is merely a change of form not of structure or function of the cell, e.g. in cirrhotic lung conditions the flattened lining cell of the alveolus can become cubical and cylindrical, or, in an inflamed bursa, the lining cells can become arranged like epithelium. (c) A type of aberrant metaplasia may be seen locally in disturbances of development, e.g., cartilage can arise in the tonsils from the second branchial cleft.

Instances of true metaplasia of the supporting tissues may be found, for example, in the development of bone or cartilage in the sclera or choroid or brain membranes or scars of the skin, or in tumours, e.g. fibroma, where the fibrillar tissue may become homogeneous and changed into bone. In all these cases a reticular tissue is formed, later a lamellar bone often with well-formed marrow spaces and cellular marrow: it is not a question of bone-forming osteogenic cells brought by blood-vessels, as in periosteal budding, but bone and bone marrow arising in loco from the connective tissue.

In the origin of bone out of connective tissue without relation to periosteum, chronic inflammatory processes often play a rôle—the inflammatory processes frequently develop in relation to injury or other mechanical influences and the young tissue develops to cartilage or to bone and calcium is then deposited from the plasma. In the degenerative and chronic inflammatory changes in muscle which may arise as a result of excessive exercise, e.g. riding, circumscribed cartilage or bone formations may occur: similar bone may form elsewhere in injured muscle but in considering this as metaplasia an inclusion of periosteum must be excluded.

In callus—the prototype of the new bone tissue we are considering in osteitis fibrosa—very numerous cell forms and fibrils are present on the borders of the blood-clot and fibrin network; as the fibrillar tissue becomes denser, among the
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delicate connective tissue fibrils are found some with a more homogeneous character which pass directly at their ends into the more delicately stained fibrils. This is the first beginning of a specifically differentiated substance—osseo-mucin—which increases in density till the cells are enclosed in its mass, at the periphery of which the fibres radiate in every direction. Between these radiating fibres we find cells larger than the surrounding connective tissue spindle-shaped cells, yet with all their morphological characters, and their shape and position correspond to the type of osteoblasts. A definite distinction between the connective tissue cell and these cell forms cannot be made, and it is probable that the individual elements of both types, being closely related, pass over into each other.

It is very important here to remember that in callus-formation the resultant granulation tissue contains very numerous proliferated osteoblasts, both from the periosteal and endosteal layers, and that so long as the histological forms can be traced back by simple genetic processes, it is unnecessary to bring in metaplasia. The origin of bone in callus and in osteogenic tumours requires no metaplastic explanation. Nicholson claims that the term metaplasia should be reserved for a metamorphosis and not extended to a simple differentiation; he regards the fibroblast as an indifferent cell, whose line of differentiation is dependent on its site—in the soft parts it becomes a connective tissue cell, but in bone a bone corpuscle. But the modern conception of the term metaplasia relates it to the differentiation of tissues genetically related and it is thus we use it. The question is still therefore to be answered: is there a justification for the use of the term “metaplastic” in relation to the new bone formation in osteitis fibrosa? The other alternative: can this new bone be explained entirely by the presence of osteogenic cells from the periosteum and endosteum? relates the process to its prototype-callus. The answer may seem to many one of mere academic interest, but it goes deeper than that, for, according to the view taken, it is possible to look upon developmental factors as having a share in the etiology.

The cell content of one of the larger Haversian spaces in the femur, where the earliest stage of the fibrous tissue substitution is taking place, reveals a picture which presents many similarities to that seen in osteogenic development. Maximow has shown that the early undifferentiated mesenchyme
cells, which surround the capillary periosteal buds, have a structure which can be recognised in its essentials, through various stages of cell differentiation to endothelial cell, connective tissue cell of the reticulum, osteoblast and osteoclast. The writers have had the privilege of examining with Dr Stump some of his slides bearing on this osteogenesis, and have had his criticism and help in the interpretation of the developing cellular content of the enlarging Haversian spaces. The large polymorphous-shaped and stellate cells seen in Figs. 1 and 2, Plate V., bear a very striking resemblance to the differentiating mesenchyme cells in his sections, and the staining reactions of these cells and the further steps in their evolution increased the conviction that it was here not a question simply of cellular granulation tissue with numerous capillaries but a question of a return to early embryonic development, with numerous capillaries surrounded by cells, indistinguishable from the almost undifferentiated mesenchyme cell. Many of these cells formed osteoblasts, and many fused to form osteoclasts in embryonic development, but the great mass of the cells were set apart to form the fibrous tissue, which later completely replaced the resorbed bone. Other cells, as has been seen in a previous section, shared in building up this fibrous tissue but only in a minor degree, and many of these also had their origin in this intense capillary endothelial development. This view of this cellular tissue relates its development, therefore, not to an actively proliferating connective tissue cell forming a very embryonic-looking tissue, whose further development might be inherent in the ubiquitousness of the fibroblast, but relates it to a reversion to a cell not far removed from the early mesenchyme cell. This early cell differentiation in this enlarging Haversian space takes place in part to form osteoclasts by fusion, in a minimal degree to form osteoblasts, for new bone by apposition is scarcely evident at this stage, and in great part to form the fibrous tissue substitution—in this fibrous tissue new bone is laid down. The transformation to bone occurs, therefore through the two phases indicated as essential to true metaplasia—that of a neoplastic stage and a stage of differentiation. The differentiation results in two forms of bone formation—reticular and apposition. The mode of development of these respective types has already been indicated, but may be briefly recapitulated.
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(i.) **Reticular or Network Bone.**—Plates VIII. and XVII. will help to make this development clear. In the loose fibrillar connective tissue the first indications of change are shown by the fibrils becoming denser and more homogeneous and staining more vividly: soon there comes a fusion of these strands and a small irregularly contoured focus, an almost homogeneous substance—osseo-mucin—results, from the periphery of which radiate out thick, dense fibres continuous with the more delicate fibrils of the unchanged connective tissue. Such radiating fibres can be traced sometimes directly through the homogeneous mass, and are analogous to the Sharpey's fibres of membranous bone. In the fibrous tissue, e.g. of the medulla of the humerus, such formations are present in all stages of development and in all shapes; they all ultimately assume a more or less elongated trabecular form, from the ends of which pass the radiating fibres. In these radiating fibres further fusion is taking place, till the original isolated strands are linked together by connecting strands in an earlier stage of development, so that a wide-meshed network of strands or trabeculae is formed. This reticular bone formation is analogous to that in the first stage of bone laid down in membrane.

(ii.) **Apposition Bone—Lamellar Bone.**—In endochondral ossification the calcified cartilages of the foetus are covered with a layer of specifically differentiated mesenchyme cells; these cells have acquired the power of laying down a granular intercellular matrix, in which they become buried—a substance which in time becomes homogeneous and later calcified. This new osteoid tissue is laid down in successive layers—lamellae—as successive layers of cells deposit the osseo-mucin, and this deposition on a given substance, such as the calcified cartilage columns, is called "aposition."

In the new formation of bone in osteitis fibrosa, the first deposit of osteoid tissue is a reticular bone, but soon the strands of this network become modelled, possibly as a result of mechanical influences, and on their more flattened contours a layer or layers of cells are being aligned (Plate VIII., Fig. 5, and Plate XVII., Fig. 5). These lining cell layers are a further differentiation of the cells of the connective tissue; their essential nuclear characters are the same, but they have now assumed a darker, more abundant protoplasm and are now differentiated as osteoblasts, which are to lay down on the
surface of the bone trabeculae osseo-mucin and themselves become embedded in it—forming lamellae of osteoid tissue by apposition, both on the outer surface of the strands and on the inner surface that outlines the meshes. In the centre of the trabeculae the axial cells are irregularly grouped and often vesicular, while on the margins the distribution is more uniform and the cells more spindle-shaped as in lamellar bone. By Schmorl's stain (Plate VI., Fig. 3) the cells can be shown to have very delicate processes in the canaliculi. The osteoblasts are descendants of the connective tissue cells which formed the reticular bone, and according to the view indicated of the origin of this fibrous tissue, this apposition bone must also be regarded as metaplastic.

In this manner bone is formed both after the type of that laid down early in membrane and by apposition as in later membranous and in endochondral ossification. There is no fundamental difference in the way in which the two varieties are produced, the difference being more apparent than real; in the one the fibrils, i.e. the intercellular product of the cell, become dense and homogeneous, forming a ground substance in which the former connective tissue cell becomes embedded and transformed into a bone corpuscle; in the other type, the cells (osteoblasts) secrete a ground substance (osseo-mucin) in which they themselves become embedded.

(4) The Formation of Giant-Celled Tissue and Cysts.

The purpose of this section is to indicate the origin and structure, the formation and significance of the giant cells and giant-celled areas and cysts as revealed in the case of osteitis fibrosa. In a later section (B)(3) it will be supplemented by a discussion of the significance of giant cells and cysts in bone tumours and bone lesions generally; and of the relation of this polymorphous-celled tissue with giant cells to giant cell sarcoma, both of benign type and of malignant type.

(i) The Giant Cells—their Origin, Function and Significance.—The early and later stages in the development of the changes in osteitis fibrosa are associated with giant cell formation. The one (a) is represented in the femur (Plates V. and XVI.) where lacunar erosion by giant cells of osteoclast type is so dominant a feature of the histological picture; the
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other (6) is represented in the polymorphous and giant-celled areas of the humerus (Plate XVIII., Figs. 1-3).

(a) The origin of the early osteoclast giant cell. Plate V., Fig. 1, shows one of these enlarging Haversian spaces with its rich capillary network, from which pass off uninucleated cells which rapidly differentiate into rounded or spindle-shaped and more especially stellate-shaped cells. The capillary proliferation is so intricate that it seems a network in the meshes of which lie cells, the nuclei of which have the same characteristics as those of the endothelium of the capillary. All transitions can be traced between the uninucleated cell and the fully formed giant cell by fusion, and individual examples are readily found where two, three, or more cells have been fixed in the process of fusion. At first the cell processes of the stellate cells seem to link together till the whole cell body is incorporated, and the cell outline is ultimately lost, though an indication of the fusion may be recognised for a long time under high power as a network of fine fibrils. As these cells fuse, they form large syncytial masses which border the contour of the bone; the surface applied to the bone develops a fringed fibrillar border, while the free surfaces have branching processes, which are often in intimate union with the processes of other cells (Plate VII., Fig. 6). These syncytial osteoclasts engaged in lacunar resorption are larger than the osteoclasts of normal physiological bone development, but their morphological characteristics are the same: these have been already outlined, and can be readily seen from the drawings. Numerous mitoses are present in the free cells, but we have been unable to recognise any mitoses after fusion, and the individual nuclei remain independent in the syncytial protoplasm.

While a fusion of endothelial cells from the capillary network is the most usual mode of formation of the osteoclast giant cells, there are very numerous appearances which indicate that they may also arise by fusion of a proliferated layer of osteoblast cells lining the cancellous space; such cells lie in palisade rows, and a fusion of adjoining cells to form narrow elongated syncytial osteoclasts can frequently be traced.

The function and significance of these early osteoclast giant cells are so obvious, that the further portion of this section will be devoted to the origin, function and significance of the giant cells found in the later stages.

(b) The origin of the later giant cell of the giant-celled areas.

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A study of Plate III., Fig. 1, shows a striking general agreement with that of Plate VII., Fig. 5, in a totally different type of tissue. Both sections are taken from the fibro-osteoid tissue of the humerus, and, as large sections, such as Plate XIII., are examined, varying pictures come into view. In some there are long stretches of fibrous tissue without any osteoid tissue: this is, as a rule, a loose fibrous tissue, but sometimes it is dense, with the fibres in strands, recalling the structure of a fibroma. In other fields there is a fibro-cellular vascular structure which suggests granulation tissue and which gradually merges into a very polymorphous-celled tissue in which large giant cells lie isolated and in groups throughout the area. Two almost constant features of such areas remain to be noted: the one, that this is a very haemorrhagic tissue with red blood cells in small masses, and also scattered throughout the interstices of the tissue; the other, that on the borders of such areas the remains of bone fragments, often small and almost entirely eaten away, are often present, and that the giant cells are grouped around these and around the small haemorrhages. These multiple giant-celled areas which are often subperiosteal, are quite definitely related to haemorrhagic areas, and especially where such haemorrhage is in close relation to spicules of unabsorbed old bone or partially calcified new bone. The giant cells, while often very numerous, have not a uniform distribution in the cellular vascular tissue.

The cell forms seen in the drawing (Plate VII., Fig. 5) are all uninucleated cells in the process of fusion to form giant cells, and cells representing two and more fused forms, rounded and spindle-shaped, can again be readily traced. Here also the origin is, in the main, from the endothelium of capillaries, which are very abundant in this cellular tissue, and numerous mitoses are present both in the capillary endothelium and in the individual cells before fusion. The giant cells that result from such a fusion are morphologically similar to the osteoclast giant cell, varying only in size and in number of nuclei. The nuclei remain independent and are uniform in size and staining—unless closely arranged they show the essential characters of the cell of origin; and they may be scattered through the cytoplasm or grouped in the centre, where they often show a whorled arrangement, but they are never only peripheral. The cytoplasm, if the nuclei are central, is abundant, and stains darkly, is homogeneous or granular or vacuolated with red.
blood cells in the vacuoles; they may contain much granular hæmosiderin pigment, which gives the Prussian blue reaction, or the cytoplasm may be diffusely tinged blue. The forms grouped around any bone fragments often show all stages of degeneration, extensive vacuolation of the protoplasm and nucleo- and cyto-lysis, till only shreds of the cytoplasm remain in the fibro-cellular tissue.

The remaining structural elements of these areas are polymorphous cells and young blood-vessels, and, if the spindle cell prevails, a certain amount of fine fibrillar tissue, while large numbers of phagocytic mononucleated cells are present containing hæmosiderin pigment.

*Function and significance of the giant cell.* The giant cells that are applied to remnants of bone are still engaged in bone destruction, and such cells may attain a very large size with a nuclear content in a single section of more than a hundred independent nuclei. The other giant cells present are more recently formed, and often contain vacuoles with red blood cells or hæmosiderin pigment. It is a natural deduction that they have arisen in part as a result of the haemorrhages, which might so readily be determined in a vascular tissue by the mechanical influences to which such a diseased bone would be subjected.

Our view, therefore, of the significance of the giant cells in the giant-celled areas in osteitis fibrosa is that many are the remains of osteoclast giant cells left in the fibrous tissue after their work of resorption is completed or almost completed, and that their numbers are increased by a new development—from fused endothelial and other cells, determined by the presence of numerous capillary hæmorrhages around which they form. They may become phagocytic to the red blood cells, with the later development of hæmosiderin granules. Very numerous degenerative forms may be found, from an early vacuolation to complete nucleo- and cyto-lysis, and as they disintegrate, their place is either left empty and forms an early stage in the formation of cysts, or it is replaced by granulation and fibrous tissue. In the latter case no trace would be left of its presence, and a more or less dense fibro-cellular or fibrous tissue might in time be substituted for the entire giant-celled area.

Such areas cannot be regarded, therefore, as the early writers assumed, as multiple giant cell sarcoma. In spite of
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the many similarities to the structure of myeloid sarcoma, the writers look upon these dark red areas scattered in the naked-eye section, which show microscopically a vascular, polymorphous and giant-celled structure, as part of a reactionary inflammatory process of a mild type, which has occurred in a metaplastic tissue, around the fragments of unresorbed bone. They have been determined in large part by haemorrhage into a tissue which has retained many of its embryonic characteristics, including an abundant development of endothelial cells which fuse to form the giant cells: their presence is an attempt at repair and reconstruction—a reconstruction which may lead to fibrous tissue replacement.

(ii.) Cyst Formation: its Mode of Origin. — Von Recklinghausen regarded the formation of cysts as an end-result of osteitis fibrosa, more especially in the localised type but rarer in the generalised type as definite gross cysts. A study of the literature on osseous dystrophies shows much confusion as to the relative frequency of cysts in these conditions, for the true nature of osteitis fibrosa was only slowly grasped, but it may be said that cysts are the rule in osteitis fibrosa, less frequent in osteitis deformans, and are rare in true osteomalacia. Their presence seems to be determined by the cellular character of the proliferative change, and this may be so active as to prevent their formation. In the case under review the formation of cysts was quite a secondary process, but numerous pictures were found both in the humerus and in the vault of the skull comparable to those described by other writers as cyst formation. The relation of true cysts, the walls of which contain a giant cell tissue, to these solitary and multiple bone cysts, will be considered in a later section (B)(3).

Three modes of origin are present in our sections, all of which were advanced sufficiently to indicate the possibility of the formation of the true multiple cysts associated with the osseous dystrophies. The present patient suffered from very extensive calcareous deposits in all the organs and tissues, and the examination of sections of the heart and lungs and stomach and kidneys made it difficult to understand how the essential functions of the body could be carried out. He finally died with a commencing bronchopneumonia, possibly at a stage of the dystrophic disease when the later developments had not definitely set in.
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The three modes of origin of the small cysts (Plate XVIII., Figs. 4-6) are related the one (a) to degeneration, the second (b) to productive proliferation, while the third (c) is determined by haemorrhage. (a) The degenerative process is first evident in a myxomatous change in the loose fibrillar stroma, e.g. in the medulla of the humerus; multiple small loculi result, the septa of which are formed by denser tissue. These ultimately give way (Fig. 4) with a rupture of their capillary vessels, and the space thus formed is filled with a blood-stained mucoid content round which giant cells may form. The myxomatous softening may extend till the nearest new-formed bone trabeculae are reached and they, together with the osteoclasts eroding them and the new-formed osteoclasts, may form the first wall of this small cyst, a wall in the formation of which fibrous tissue, new-formed bone and a giant-celled tissue may share. The onset of the myxomatous softening must be related to unknown circulatory conditions determining lymph stasis. (b) The proliferative process may lead to cyst formation by a dense fibrous tissue causing retraction of the looser tissue. Several such retraction areas are seen in Fig. 6, and the breaking down of the intervening septa would lead to a cystic space lined by the fibrous tissue and bone trabeculae with their osteoclasts. (c) The third mode of origin is definitely related to the giant cell areas, and the initiation of such a cyst is seen in Fig. 5, where the space occupied by degenerated portions of osteoclasts is filled by red blood cells and the surrounding giant cells are all in process of disintegration. Such a small cyst would have an almost complete lining zone of giant-celled tissue.

Summary.—Multiple minute cysts are present in the sections. These have commenced as spaces in the meshes of oedematous fibrous tissue and become enlarged through haemorrhages, or as retraction spaces in a fibrous tissue of varying density, or finally as haemorrhagic spaces in giant-celled areas owing to the lysis of numerous large giant cells. The cysts, therefore, have arisen secondarily as in many pathological conditions. The relation of such cysts to “Bone Cysts” and the question of the identity of the underlying process — osteitis fibrosa — must be discussed in the next section (B) (3).
(B) NATURE OF THE PROCESS UNDERLYING OSTEITIS FIBROSA.

Turning now from the consideration of the conceptions underlying the histological changes, it is necessary to ask: do these throw any light upon the nature and origin of the process underlying osteitis fibrosa? In 1891 von Recklinghausen, as we have seen, regarded the condition as a chronic productive inflammation, thus bringing it into line with Paget's view of the nature of osteitis deformans, but in 1910 von Recklinghausen modified his standpoint, and, while not altogether giving up the view of its inflammatory nature, related it rather to a metaplastic malacia. In the further differentiation of the disease osteitis fibrosa into generalised and localised types, the consideration of the latter form necessitates a discussion as to its relation to neoplasms. Is the process, then, inflammatory, metaplastic or neoplastic?

(1) Inflammatory.

(i.) Introduction.—In the attempt to answer this question it is necessary to refer briefly to the significance of the term "inflammation," for the conception of the inflammatory process varies from that of those to whom the term implies all the phenomena associated with exudation of fluid and cell infiltration of the blood-vessel walls, to that of those to whom it is merely a reaction process, which may express itself by increase in the vital activity of any of the tissue elements. According to the latter comprehensive view, all changes which reveal any kind of progressive phenomena in any of the structural elements are included in the term inflammation.

The earliest histological changes that can be recognised in a case of osteitis deformans are the enlargement of the Haversian and cancellous spaces; an intense cellular proliferation around their periphery, and in the spaces, the development of a rich network of delicate capillaries with an embryonic cell content in the meshes. Although this cellular, vascular tissue does not correspond to that of an acute or chronic inflammation, it must be admitted that it is a reaction process—the earliest phase of which in a possible degeneration may be overlooked, while later stages show the presence of osteoclasts in Howship's lacunae—an appearance very characteristic of rarefying osteitis, and still later stages show a reparative process in the fibrous tissue substitution.
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(ii.) Relation of Osteitis Fibrosa to allied conditions.—

(a) Fibrous Osteitis.—It is necessary to distinguish between the fibrous osteitis which is a pathological process that may result from a variety of stimuli, and the localised osteitis fibrosa which is a recognised clinical entity. The former may appear as an extension of inflammatory conditions, e.g.: the bone underlying an inflamed bunion may be transformed into a tissue indistinguishable from that of the reticular fibro-osteoid tissue in osteitis fibrosa; a similar process may be seen in the bone around the cavity of a septic tooth; and Zeigler, in investigating the subchondral changes in arthritis deformans, compared the bony changes to a chronic inflammation with a transformation of the bone trabeculae into connective tissue and fibro-cartilage. A fibrous osteitis of this secondary character may thus be definitely associated with inflammatory lesions, but this is not the primary disease distinguished by the name “Osteitis Fibrosa,” although it seems not unreasonable to believe that there may be transitions to the circumscribed or diffuse affections of individual bones found in localised osteitis fibrosa.

(b) Chronic Hyperplasia of the Superior Maxilla and Otosclerosis.—Westmacott has recorded cases of unilateral enlargement of the upper jaw in which the antral cavity is filled with a vascular cancellous tissue. Microscopically the laminae of bone are surrounded by osteoblasts; numerous osteoclasts are also present and the spaces are filled with a fibro-cellular and vascular tissue. Westmacott considers the process a reversion of the bone to an embryonic type and notes the absence of any inflammatory or suppurative change which might indicate septic infection. He admits, however, that such a condition must exist around the carious roots found in most of the cases, and that it may be the origin of the irritation which apparently causes the change in the bones. In sections of two cases of this rare condition, reported by Douglas Guthrie and examined by the writers, the tissue from the alveolus consisted of numerous trabeculae of new bone with a reticular arrangement; the meshes of this reticulum were irregular in size and form and were occupied by a loose fibrous tissue. The process has its origin in a fibro-osteoid tissue and has resulted in the formation of a network of osseous tissue, which has become almost completely ossified; there was present only a slight inflammatory reaction, evidenced by the presence of a few scattered lymphocytic cells.
In otosclerosis the early changes, found in the labyrinth capsule, are related to a resorption of the bone with the formation of spaces filled with a central blood-vessel and a fibro-cellular tissue. In the later stages the bones become sclerosed by the deposit of new bone on the walls of the spaces. Various views have been put forward as to the pathogenesis of this disease. Gray suggests that otosclerosis is the manifestation of a tendency to biological variation; he believes that general constitutional conditions may evoke the variation and, further, that the tendency to otosclerosis may be influenced by local conditions of an acute or chronic inflammatory nature in the middle ear. Fraser and Muir strongly support the view of the chronic inflammatory nature of the process; they believe that following attacks of catarrhal or suppurative otitis media, a chronic infective condition invades the labyrinth capsule from the deep layer of the mucosa. This view does not exclude the hereditary transmission of a tendency to the disease, for it is thought possible that in certain families the mucosa of the middle ear, and the bony capsule of the labyrinth are congenitally weak and, therefore, unable to resist infection from the surface. The region of the oval window, the site of predilection in otosclerosis, might thus be regarded as a “locus minoris resistentiae.” Other writers refer to a loss of nerve influence, but all emphasise the hereditary factor, while some see in the occasional association of otosclerosis with fragilitas ossium and blue sclerotics the possibility of a congenital weakness of mesenchymatous tissues. The changes in the affected region are often very limited in extent; the osteoporosis in the early stages is the essential characteristic, while later stages show a varying degree of deposition of new bone and fibro-cellular replacement. Jenkins, in a comparison of cases of osteitis deformans and otosclerosis, finds a similarity in the histological changes in the affected bones. The osteoporosis—more sharply defined in extent in otosclerosis—is the important point of contact, but the fibrous tissue substitution, very characteristic in osteitis deformans, is not so constant in otosclerosis.

In the two conditions outlined above, changes are present in localised areas of bone which bear a striking resemblance to those described in osteitis fibrosa. In both conditions there is a close relation to a mucous membrane, frequently the site of septic infection, and the histological changes are related to those just described as “fibrous osteitis,” the result of local
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infection, e.g. from an inflamed bunion. But the reference by
Westmacott to a reversion, to an embryonic type, of the
cancellous tissue of the antrum and the acknowledged pre-
disposition in certain individuals of the bony capsule of the
labyrinth to resorptive processes with osteoporosis; and, further,
the histological similarities of these conditions to aspects not
only of the osteomalacic process, but more especially to those
of osteitis fibrosa and, when “repair” takes place, to those
of osteitis deformans, raises the question of their relation to
localised types of osseous dystrophies. In the section on
“Etiology,” reference will be made to the importance of the
rôle of toxii-infective factors in localised types of osteitis fibrosa,
and it may be possible to look upon chronic hyperplasia of
the antrum and otosclerosis as transitions between a fibrosa
osteitis and a localised osseous dystrophic process.

(c) Osteitis Deformans.—Paget and Butlin emphasised the
inflammatory character of the bone resorption, the cellular
and vascular tissue in the enlarged spaces, and the gradual
process of repair at first by fibrous and later by fibro-osteoid
tissue. The duration of the disease, Paget thought, accounted
for the simple type of the chronic inflammatory reaction, while
the combination of the resorptive and regenerative processes
resulted in thickened and asymmetrical bones which, because
the new bone remained long uncalcified, permitted of great
deformity.

In osteitis fibrosa, however, von Recklinghausen traced the
development of the process as starting in a productive inflamma-
tion in the bone marrow; this initial change was continued
into the cancellous spaces, leading to bone resorption and a
later reparative substitution. According to this view there
was no question of a possible initial degeneration in the bone
substance but a proliferative inflammation, which was designated
at first as “chronic osteomyelitis fibrosa”; this hyperplastic
inflammation gave place to an osteoplastic substitution. Von
Recklinghausen recognised a further proof of the inflammatory
character of the disease in the relation of the changes to
mechanical and thermic factors, and, further, in the vague pains
often associated with its onset. He believed that long-standing
stimuli brought about the slow hyperplastic inflammation, which
he compared to elephantiasis, and the indurating skin changes
associated with chronic eczema and chronic ulcers in which
venous congestion and stasis are present. In the walls of the
arterioles in the fibrous areas he found abundant granular pigment and other evidences of hæmorrhage, and he thought that the changes in the blood channel furnished the stimuli to fibrous tissue formation, bone resorption, and fibrous tissue substitution.

Paget regarded the bone resorption, the vascular and cellular reaction in the enlarged spaces, and the reparative fibro-osteoid tissue substitution as evidences of a "low" inflammation—a mild rarefying osteitis. Von Recklinghausen, on the other hand, accepted the changes as related to a primary productive inflammation in the bone marrow due to circulatory changes; the fibrous tissue formation leading to bone resorption by budding of new vessels and by osteoclasts, and ending in a complete fibro-osteoid tissue substitution.

What, then, is the relation of osteitis fibrosa to osteitis deformans—a condition which in its earlier stages at least is histologically the same? Osteitis deformans is a disease of late adult life; it runs a chronic course with bending and thickening of the bones; spontaneous fracture is rare, and, probably because of this the condition progresses to healing of the bones; and, also related to the comparative absence of fractures, there is no tendency to the hæmorrhages which determine the formation of the tumour-like areas and cysts. Von Recklinghausen and Sternberg and many others regarded the two conditions as essentially the same disease occurring respectively in adult life and old age, and histologically indistinguishable in the early phases. Jefferson points out the necessity of having a clear idea of what is understood by the term "Paget's Disease"—"Osteitis Deformans"—and asks the question: "Do we mean a definite, constant and characteristic microscopic, macroscopic and X-ray picture; or do we mean rather a disease of the bones whose only constant features are the attitude of the sufferer and certain bowings and thickenings of the various bones?"

The bone changes in Paget's disease are far from uniform, and numerous cases are described in which the cortex and cancellous bone are both porous and sclerosed and the bone marrow fibrous or fibro-osteoid. The softening due to bone resorption and fibro-osteoid tissue substitution is constant, but in the subsequent stages the picture varies; the softening leads to bending of the long bones due to static factors and to analogous changes in the bones of the skull due possibly
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to thermic factors. If the patient should die at this stage the microscopic changes point to bone resorption and fibro-osteoid tissue formation, with little calcification of the osteoid tissue. The process has been a slow one, unaccompanied, as a rule, by fractures, or even minimal fractures of new calcified trabeculae; in the fibrous tissue the cellular reaction related to secondary inflammatory changes due to hæmorrhage is therefore absent, and we do not find the tendency to the formation of tumour-like tissue and cysts. The bones at this stage, both the long bones and those of the skull, though thickened, would cut readily with a knife. If, on the other hand, the patient should live, and healing, as it were, take place, (1) the new osteoid tissue becomes calcified and the bones become hardened in their bent position; (2) new bone continues to be laid down by apposition on both the old and new trabeculae, while (3) subperiosteal new bone formation takes place leading to further thickening.

The bones at this late stage thus become sclerosed, hyperplastic and eburnated; the normal distinction between compact and cancellous bone is lost; and the medulla is replaced by a reticular fibro-osteoid tissue which has become calcified. The whole internal architecture of the bones, therefore, is altered, but as bone remains an active vital tissue with processes of resorption and apposition going on simultaneously it is probable that irregular Haversian systems and intervening lamellæ become arranged to meet the new conditions of strain and stress.

It must further be noted that the progressive calcification and sclerosis may take place very irregularly, so that in the skull, for example, it is possible to find side by side areas in which the bone is fairly porous, soft and vascular, and other areas in which the sclerosis has already taken place. The varying pictures described correspond, therefore, to those varying phases of the disease—the degree of porosis or sclerosis being dependent on whether the bone apposition prevails over bone resorption as in normal bone, and also to what degree the new bone becomes calcified.

Summary.—Osteitis deformans has been regarded as essentially a chronic inflammatory process which begins as a rarefying osteitis with production of a fibro-cellular tissue, which, through a fibro-osteoid tissue stage, leads to repair; the softening permits of great deformity, but owing to the
elastici ty of the fibro-osteoid tissue fractures are rare; in late stages of the disease the bone apposition from within and from the periosteum results in a hyperplastic and sclerotic bone, which, when calcification sets in, retains its bent shape. The sclerotic changes, especially in the skull, may be focal, giving a focal osteo-sclerosis. The writers have not had an opportunity of examining tissues from a case of osteitis deformans, but as a result of the critical examination of the available literature, they believe in the essential similarity of the two processes with the modification indicated in the preceding paragraph.

(d) Leontiasis Ossea.—Sections of the vault of the skull which we have examined from a case of leontiasis ossea show a hyperplastic, sclerosed bone structure with narrow and irregular Haversian spaces. The changes are consistent with those that might occur in a bone where the resorption had not led to complete removal of the old trabeculae, where fibro-osteoid tissue had been laid down and continuous bone apposition had taken place on the old and new trabeculae till sclerosis had resulted: the changes are consistent also with those outlined as the late stage of osteitis deformans. Schmidt, in the last edition of Aschoff's Pathology (1923) gives a description of osteitis fibrosa under the heading "Osteitis Deformans," and further adds that if osteitis deformans affects the bones of the head and face it is called "Leontiasis Ossea." Bockenheimer looks upon leontiasis ossea as a diffuse hyperostosis of the skull and face bones, the pathology of which is identical with osteitis fibrosa. If the thickening is irregular, tumour-like excrescences may result.

(2) Metaplastic Malacia.

In our specimens the first recognisable change is a resorption of bone and the later stage is the reparative fibrous tissue substitution. It is this later reactive stage that some writers have regarded as alone inflammatory and it is the early resorption—a change that may be interpreted as purely degenerative—that throws doubt on the essential inflammatory nature of the process. The bone resorption results in a slow osteoporosis, and Wilks (Jefferson) has suggested the term "Osteoporosis Deformans," and there is no doubt that opinion is changing, since Paget and von Recklinghausen used the term "Osteitis," to the view that in both conditions the initial phase is related to calcium metabolism, i.e. that the bone softening—the malacia
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—and not the inflammatory stimulus is the primary and essential factor.

In 1910 von Recklinghausen modified his standpoint of 1891, which had been based on the early inflammatory changes observed in the reticulum of the bone marrow. He recognised in the bone resorption the essential change, and brought osteitis fibrosa into relation to the malacic diseases, rickets, and osteomalacia, including both osteitis fibrosa and osteitis deformans, under the designation "metaplastic malacias," the former being a simple metaplastic malacia and the latter a hyperplastic form. In discussing the term "metaplasia" in an earlier section it was noted that metaplastic changes frequently occur on the basis of inflammatory processes, so that von Recklinghausen was only modifying his standpoint. The term "malacia" has to a great extent an anatomical conception—weakness or softness—while the term "metaplastic" conveys the idea of a complete metamorphosis of bone architecture. It was at first in this sense, rather than in the strict sense metaplasia that it was used, though the conception of a complete transformation of bone structure and the means by which it was effected were included in the term.

(i.) Classification of Malacias.—The work of von Recklinghausen is so little known in this country that it seems advisable to give a brief account of his classification of the malacias. The writers have attempted to simplify this classification as follows:

(a) Porotic malacia with subgroup porotic hypoplastic malacia.
(b) Hyperplastic malacia with subgroup plegmatoplastic malacia.
(c) Metaplastic malacia:

Simple metaplastic—osteitis fibrosa.
Hyperplastic metaplastic—osteitis deformans.
Tumour-forming metaplastic malacia.
Cyst-forming metaplastic malacia.
Metaplastic new growths—benign sarcoma of bone.
(d) Myeloplastic malacia.

(a) The porotic malacias include many of the more usual types of rickets. The medullary cavity is widened and the cortex thinned, with marked resorption of the bone trabeculae, mainly through halisteresis, for there is little osteoclast formation.
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and therefore little lacunar erosion—except in callus formation. The Möller-Barlow type is included in the porotic hypoplastic malacias, in which there is an exaggeration of the porosity and a corresponding fineness of bone trabecular structure. Because this disease is hypoplastic, there is a relative shortness and thinness of the diaphysis and the porosity of the epiphysis is related to deficiency in development of their centres of ossification. The postural deformities of bone, e.g. coxa vara and coxa valga, genu valgum and genu varum may occur in this group.

(b) The hyperplastic malacias show a relative excess of bone formation with thickened cortex and diaphyseal ends through osteoid tissue. There may result, therefore, osteophytes in relation to the periosteum and an over-production of osteoid tissue in the medullary cavity of the metaphysis. This group includes the hyperplastic varieties of rickets, in which both periosteal and medullary bone formation is present. The subgroup—plegmatoplastic malacia (plegma = a network) differs in that the periosteal formation is slight and the over-production is limited to the bone elements of endochondral origin, so that a network of osteoid tissue is formed in the medullary cavity of the metaphysis. The essential characteristic of this plegmatoplastic type, therefore, is the almost complete limitation of the immature bone to the metaphyseal bone marrow.

All degrees of porotic and hyperplastic malacia may appear in the course of rickets.

(c) Metaplastic malacia. This group includes not only osteitis fibrosa and osteitis deformans but the tumour-like areas and cysts formed in osteitis fibrosa—their separate subgrouping being a recognition that such formations are not an essential part of the osteitis fibrosa process; the final subgroup is termed metaplastic new growths—the benign sarcoma of bone.

We have noted that the amplification “metaplastic” carries the inference that the underlying process involves a complete reconstruction. It therefore implies also that the bone has at one time possessed its normal structure. This group, therefore, should also include osteomalacia, both puerperal and non-puerperal, since this disease appears in bones already developed, but because the fibro-osteoid reconstruction, which gives the group its designation, metaplastic, is minimal, osteomalacia has come to be included in the porotic malacias.

(d) Myeloplastic malacia (Osteogenesis imperfecta; Fragilitas
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ossium; Idiopathic Osteopsathyrosis). Von Recklinghausen prefers the term myeloplastic malacia, because it indicates the nature of the most prominent lesion, and it includes the conceptions underlying other terms, e.g. congenital osteomalacia, foetal osteoporosis and foetal rickets, as well as the general conception of bone atrophy, hypoplasia, aplasia, and dysplasia. Osteogenesis imperfecta is an affection existing in the foetal and even in the embryonal period, and is therefore a disturbance in the first development of the body tissues. The affected bones show the following changes: (1) Bone marrow cells replace the normal ossifying centres in the epiphysis, and it is the overproduction of the marrow cell that gives the name "myeloplastic." (2) The formation of apposition bone on the calcified cartilage columns is extremely deficient, and this is replaced by a network of well calcified bone trabeculae—a very brittle material. (3) The cortex of the long and of the flat bones shows deficient apposition also, and is therefore very thin and porous. (4) The callus is formed of a network bone which is well calcified, and again, therefore, very brittle.

The essential changes are the abundant lymphoid marrow and the brittleness of the bone trabeculae. The reconstruction in the cartilage transition zone and its calcification are not materially changed, so the condition is not a form of rickets. The hypoplasia of the bone is regarded as secondary to the hyperplasia of the bone marrow (myeloplasia) and, once established, these two factors interact on each other.

This account of the types of the malacias and their significant changes gives little idea of the wealth of material and of illustration in von Recklinghausen's monograph. In spite of the extensive works of Pommer and Axhausen which call in question the interpretation of certain histological appearances, e.g. the "Gitterfigüren" and the "Onkosis" of the cells, on which many of the deductions are based, the work, carried out during a period of over twenty years with unwearied patience, is fundamental, and no worker on bone dystrophies can afford to ignore it.

(ii.) Relation of Osteitis Fibrosa to other Malacic Diseases.

—(a) Rickets.—Although the changes that dominate the microscopic picture of rickets are the exaggerated cartilage proliferation zone and the defective or absent calcification zone with its sequel, the penetration of the periosteal buds into the proliferated car-
tilage zone, yet many writers do not recognise these changes as the fundamental characteristics of rickets. Schmorl, Lesser, Fromme, and many others, believe that the essential change is an aberrant proliferation of the endosteum through which an inferior tissue (osteoid) deficient in calcium is formed; while together with this there is also present a change in the bone marrow, which is hyperæmic, cellular, and hyperplastic, with an increase in the connective tissue elements of the reticulum. The histological changes, therefore, include: (1) an irregular and exaggerated cartilage formation with deficient calcification; (2) an exaggerated endosteal formation in the metaphyses of osteoid reticular bone with deficient calcification both of this and of the apposition bone; (3) a fibro-cellular reaction in the bone marrow, which may lead to varying degrees of fibrous or fibro-osteoid tissue formation; (4) an aberrant proliferation of the periosteum, leading to osteophyte formation, may also be present.

It has been previously noted that bone apposition and bone resorption go on all through life, especially in the growing bone. There is, therefore, a constant reconstruction, and in the normal adult these two processes are so proportioned that a tissue equilibrium results. In rickets there are not only the above-mentioned factors, but a gradual destruction and melting away of bone—a process designated by von Recklinghausen as "thrypsis"; if thrypsis prevails over apposition, a porotic type of malacia results; if, however, apposition prevails, a hyperplastic type is brought about. In rickets all degrees of, and transitions between, these two types may be present. Almost all the deformities that appear during the growing period of life have their basis in a rachitic condition of the skeleton; accidental mechanical factors may produce the special type of deformity, but a purely mechanical interpretation of postural deformities is insufficient.

Such a comprehensive picture of the anatomical characteristics underlying rickets removes many of the difficulties met with in explaining the close relationship between rickets and osteomalacia. The difference between rickets, late rickets, and osteomalacia are quantitative, are related to the age of the patient, and show all transitions, while the conception of the process underlying both is mainly the same. The relation between rickets and other malacic diseases, including osteitis fibrosa, thus becomes more intelligible, for in the anatomical
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conception "malacia" and in the histological picture there can be traced a relative yet not a specific distinction and there are all gradations.

Summary.—The distinctive relation between osteitis fibrosa and rickets lies in the factors of the pathological process that are common to both: the disturbance of the endochondral ossification present in rickets does not, therefore, fall to be considered, but osteoporosis through thrypsis and osteoclast resorption and the new formation of osteoid tissue enter into the conception of the pathology of both diseases. In rickets it is a question of the substitution of a part of the normal neoplastic ossification of cartilage from the bone marrow by an abnormal metaplastic ossification of cartilage marrow and of perichondrium—that is, osteoid tissue in rickets is to be traced more to the fibrosis of the bone marrow than to the osteoblast formation. Oehme, in a very extensive series of observations, found the fibrous tissue was constant in rickets in a narrow zone around the blood-vessels in the deep cartilage, and sometimes completely filled the subchondral bone marrow.

(b) Relation of Osteitis Fibrosa to Osteomalacia.—Early writers used the terms synonymously, and Hirschberg in 1886 described a case of "osteoalacia with multiple brown tumours and cysts," but since von Recklinghausen's classical account of osteitis fibrosa, the presence of multiple tumour-like areas and cysts has been sufficient to classify the condition as osteitis fibrosa.

The constant and characteristic lesion in osteomalacia is the presence of osteoid (non-calcified) zones in the periphery of the trabeculae, while few osteoclasts are present. The marrow changes are inconstant, and may vary from a gelatinous or fatty type to a cellular and vascular tissue, but there is very rarely any true fibrosis; the periosteum is thickened and forms a fibrous sheath for the partially decalcified bone.

It will be convenient to discuss briefly the relation between osteomalacia and rickets before attempting to define the distinction between osteomalacia and osteitis fibrosa. Recent writers on rickets, late rickets, the hunger osteopathies, war osteomalacias, and puerperal and senile osteomalacias, believe all these conditions to be morphologically identical. In accepting this view it is necessary to bear in mind the comprehensive picture outlined above of the anatomical characteristics of rickets, and further, to remember that varying degrees of the
process may come into consideration in any one case, while, further, in rickets and late rickets, which can appear so long as the X-ray picture shows a space between epiphysis and diaphysis, i.e. so long as endochondral ossification is not completed, the irregular cartilaginous change and the malacia of the ossification zone may dominate the picture. In all these conditions, thrypsis (a conception which seems almost synonymous with halisteresis, but does not necessarily exclude a participation of osteoclasts) osteoporosis, hypoplasia, and hyperplasia, enter in varying proportions into the pathological process. In rickets the bones of the extremities are usually the most affected, while in osteomalacia it is chiefly the pelvis and vertebræ; in rickets the reticular bone formation may be very abundant with marked atrophy of lamellar bone, while in osteomalacia the reticular new formation of bone is almost absent, and the lamellar bone shows a gradually increasing osteoid zone of decalcification—a zone, however, which is attributed by Pommer and Axhausen to apposition formation.

The important distinction between the two conditions is the existence of endochondral disturbance in rickets, its absence in osteomalacia. In late rickets this change is less apparent, and the decalcification of the diaphysis, of the cancellous bone and of the endosteal bone is more evident—thus relating it more closely to osteomalacia. Hanau (Fromme) has shown that in the gravid condition there is a degree of osteomalacia with an osteoid zone on the trabeculae, and Wieland has demonstrated a similar change in the bones of rapidly growing children: these observations indicate that in these physiological conditions the bones normally assume a dystrophic character. It is easy to conceive that in a tissue which, like bone, shows such extremely active formative and resorptive processes, transition from physiological to pathological variations may occur endemically, as they did in certain countries during the war.

Fujii regards osteomalacia and osteitis fibrosa as two quite distinct pathological processes. In osteomalacia he states that the characteristic changes are: (1) that the osteoid zone is broad and smooth and shows no osteoclasts—Molineus and others have also pointed to the absence of osteoclast resorption in osteomalacia; (2) that the bone corpuscles are few and irregularly distributed; and (3) that the bone marrow shows no connective tissue change. In osteitis fibrosa, as we have indicated, however, (1) the osteoid zone is narrow and irregularly
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contoured with numerous osteoclasts; (2) the bone corpuscles remain uniformly distributed and show no marked change except at the periphery of the lamellæ; and (3) the bone marrow is fibrous or fibro-osteoid. The changes, though so different, result in a diminution of the stability of the bone, and in the same deformities and the differential diagnosis, therefore, is often difficult during life.

Summary.—The essential distinction between osteomalacia and osteitis fibrosa lies in the activity of the resorptive processes in the latter, together with the productive processes which end in a fibro-osteoid tissue substitution, and the formation of multiple tumour-like areas and cysts—all changes which point to the progressive character of the process. In osteomalacia, on the other hand, the bone resorption takes place by a gradual halisteretic atrophy; the reactive conditions are slight, and the active resorption by osteoclasts is almost absent; and, as a corollary of the absence of osteoclast resorption, the giant cell areas, for which we must presuppose a stimulation of the osteoclasts, rarely form; the bone removal by halisteresis is followed by apposition of bone which remains osteoid during the period of the disease.

(c) Möller-Barlow Disease (Osteotabes infantum: Infantile scurvy).—Von Recklinghausen included this condition in the hypoplastic subgroup of porotic malacias. The chief change must be looked for, therefore, in a rarefaction of the growing bone, i.e. bone resorption prevailing over bone formation. Together with this there are: (1) the presence of an oedematous fibrous tissue in the cancellous spaces, with few osteoblasts and few blood-vessels; (2) an irregular epiphyseal cartilage zone and an absence of bone apposition on the calcified cartilage columns—leading often to fracture at the epiphysis; and (3) hæmorrhages in the medulla in the cartilage proliferation zone, and in the subperiosteal layers. Indications of the hæmorrhagic diathesis may be present in the skin and mucous membranes.

The essential characteristics are the resorption of the bone and the imperfect ossification on the calcified cartilage columns. Ziegler contrasted the Möller-Barlow disease—a marrow and bone atrophy—with rickets, the essence of which he claimed to be a fibro-cellular proliferation of bone-forming tissue, both endosteum and periosteum. The changes thus differ from rickets, but rickets is present in about half of the cases. Little need be added in regard to the relation of the disease to osteitis
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fibrosa: the reconstruction of the bone in the latter condition is entirely absent in infantile scurvy.

(d) The Hunger Osteopathies.—These are accompanied by marked bone destruction and rarefaction; the bone marrow shows an oedematous fibrous tissue with little or no new bone formation, and haemorrhages may be present. The changes are not constant, but they approximate to those found in scurvy, rickets, late rickets and osteomalacia.

Osteolysis.—Schlagenhaufer has reported several cases of complete disappearance of the body of one vertebra. The histological examination of the remains of the vertebrae led to the conclusion that a resorption of bone had taken place, as if the bone had been dissolved by some chemical agent. The author suggests that a spontaneous decalcification had occurred, followed by resorption and complete osteolysis. In one patient the osteolytic process had affected several vertebrae and other bones. No cause is suggested, but the writer considers the changes differ from the hunger osteopathies, and may be related to a tropho-neurosis.

(e) Osteogenesis Imperfecta (Fragilitas Ossium; Fœtal Rickets; Osteopsathyrosis).—The most complete account of this condition known to us is that given by von Recklinghausen, which we have already noted. It may be summarised briefly thus: (1) the proliferative processes in the cartilage take place normally, so that the bones grow in length; (2) there is a deficient endosteal and periosteal bone formation due to deficient activity of the osteoblasts, so that the bone is reticular and porous, and, as calcification takes place, the bone is brittle and numerous fractures occur—these intrauterine fractures healing with abundant callus formation; (3) there is an over-production of the marrow which gives it the name “myelo-plastic” malacia.

Schmidt has described an “Osteogenesis imperfecta tarda” which arises in extra-uterine life and forms the anatomical basis of so-called “idiopathic osteopsathyrosis,” i.e. a tendency to fracture with little cause.

Bronson, discussing the association of fragilitas ossium with blue sclerotics, states that the only known factor is heredity, and that fragilitas ossium, whether prenatal or postnatal in the onset of its symptoms, shows a deficient functioning of the osteoblasts. Metaplasia is said to be frequent, but is probably compensatory in character, not primary. The association of
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fragilitas ossium, with blue sclerotics and otosclerosis, in possible relation to a congenital weakness of the mesenchymatous tissues, has already been noted.

Summary.—The important symptom is the bone brittleness—the osteopsathyrosis—the essential anatomical feature of the disease is a deficient capacity to form bone on the part of the osteoblasts so that the affection involves bone laid down both in cartilage and in membrane, and not only endochondral formed bone as in chondro-dystrophy.

(f) Chondro-dystrophia Fœtalis. (Achondroplasia; Micromelia; Chondro-malacia; Fœtal Rickets.)—Chondro-dystrophy is an intrauterine disease of the growing cartilage, and so the growth in the length of the bone is deficient or absent (contrast osteogenesis imperfecta). The essential features of the histological changes are the following: (1) an absence of the proliferating cartilage with short cell columns; (2) if present, the cartilage columns may get a provisional calcification; (3) the periosteal growth is undisturbed, so that the long bones become thick and compact. The disease may set in early or late in intrauterine life; if the child survives birth it becomes a short-legged dwarf owing to the failure of growth in the cartilage columns. Symington and Alexis Thomson, in the examination of a case of "Defective Endochondral Ossification in a Human Fœtus," regard the essential lesion as "an absence or an arrest or perversion of the normal process of endochondral ossification." The change is limited to the group of bones, which, formed in cartilage, are largely dependent for their growth during foetal life upon endochondral ossification; the bones belonging to this group are the long bones of the extremities, the ribs, the posterior portion of the base of the skull, and the innominate bones. They regard the condition as a simple arrest of a normal process.

Ollier has described under the term "Dyschondro-plasia" a rare affection of the growing skeleton, which consists in irregular and delayed endochondral ossification, with the formation of numerous cartilaginous masses in unusual sites—both subperiosteal and medullary. These form tumour-like swellings, specially involving the phalanges, and may give a one-sided shortening and thickening of the limbs.

(g) Relation of Osteitis Fibrosa to Osteitis Deformans.—This has been considered in the former section in which osteitis deformans was included because of its place in the historical
development of this group of diseases. In this later section it is included in the "malacias" as a hyperplastic metaplastic malacia in contrast to osteitis fibrosa a simple metaplastic malacia.

In the group of malacic affections there remain to be considered only the subgroups of the metaplastic malacias, namely, the tumour-like formations and cyst-formations in Osteitis Fibrosa and the metaplastic new growths. It has already been pointed out that a study of these conditions raises the possibility of the neoplastic nature of the process underlying localised osteitis fibrosa.

(3) Neoplastic.

This, the most important section of this paper, has such a far-reaching, practical bearing, that it is necessary to give in outline the progressive development of the ideas relating to the pathological processes which fall to be considered. These include the sub-groups of von Recklinghausen’s metaplastic malacias; (a) the tumour-like areas in osteitis fibrosa; (b) the cyst formations, solitary and multiple, found in osteitis fibrosa and other conditions; and (c) the metaplastic new growths of bone—the so-called "benign sarcoma of bone."

It is necessary again to recall the distinction already noted between the osteopoietic and haemopoietic tissues of bone in order to indicate the histogenesis of the tumours to which reference will be made. The osteopoietic tissue includes the stroma reticulum of the bone marrow and its continuation into the cancellous spaces as endeosteum, also the osteoblast and osteoclast cells. The haemopoietic tissue consists of the series of blood-forming cells, including the erythroblasts, myeloblasts and lymphoblasts. It also includes the giant cells of the marrow, which Adami, recognising their myelogenous origin, called myeloplaxases—a term which has largely given place to that of megakaryocyte. Adami, believing that the numerous multi-nucleated giant cells present in the comparatively benign tumour found in the medulla at the ends of the long bones were myeloplaxases, and therefore of myelogenous origin, named these tumours "myeloma." Such tumours, fairly circumscribed, not markedly infiltrative, very vascular and friable and resembling granulation tissue with mottled areas, have long been recognised naked eye under the term "myeloma" or
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“myeloid-sarcoma.” Microscopically the structure is that of a polymorphous-celled tissue, containing very numerous uniformly distributed giant cells, numerous blood-vessels, and a varying degree of fibrous tissue. The giant cells have a characteristic structure, resembling the normal osteoclast, and the view of their myelogenous origin, as myeloplaxes, has been largely given up. A tumour with similar structure grows subperiosteally usually from the bones of the jaw, and in contrast to the central medullary type, this subperiosteal growth is more fibrous and areas may be found in it containing no giant cells (Plate XX., Fig. 2).

It is obvious that the term “myeloma,” indicating an origin from the myelogenous cell, is unsuitable, and a further argument against its use is the fact that the structure of the “multiple myeloma,” to which reference will immediately be made, is in no way similar to the so-called “myeloma.” There are many arguments also against the use of the term “myeloid sarcoma” for this type of structure: the term “sarcoma” does not recognise its relatively benign character, and the epithet “myeloid”—implying central or medullary—does not recognise the existence of the subperiosteal varieties with a similar structure. Bloodgood has suggested the use of the term “medullary giant-cell tumour”; this equally ignores the periosteal group, and in the epithet “giant-celled” suggests that the giant cell is the distinctive structural element of the growth—a claim which few workers would be willing to admit, while it also fails to bring out the distinction between this tumour and the malignant giant cell sarcoma about to be described. In the following discussion the term “myeloid sarcoma” is in the meantime retained for this class of tumour including those originating in the medulla, usually at the diaphyseal ends of the long bones, and those arising from the periosteum (the giant-celled epulis). Microscopically they show two types of cells (cf. Plate XX., Fig. 1; Plate III., Fig. 1), the one forming a polymorphous-celled stroma of connective-tissue type; the other, giant cells of osteoclast type, scattered fairly uniformly in the cellular, and often vascular stroma. Both macroscopically and microscopically these relatively benign growths have a characteristic appearance and their cystic degenerative changes are equally well recognised.

The tumour to which the term “myeloma” is applicable
arises from certain primitive cells of the hæmopoietic series. They are usually multiple in bones, possibly primarily multiple, for they appear simultaneously in many bones, and as they grow they cause resorption often with spontaneous fracture, especially of the ribs. They are very malignant and their metastases in the internal organs occur first in those organs that are related to a blood-forming function in embryonic life. Both in the liver and in the spleen, and in other organs, if present, they take the form of diffuse infiltrations, of the primitive cell type, such as are found in the leukæmias. The myelomata may arise from any of the cells of the blood-forming series, but the majority are of lymphoblastic or of myeloblastic type and are usually accompanied by the presence of Bence-Jones protein in the urine.

It is necessary to emphasise that the term “myeloma” applied to such a tumour carries the inference of its origin from a myelogenous, i.e. a hæmopoietic cell: such a tumour microscopically bears no resemblance to the “myeloid sarcoma” (so-called “myeloma”) described above. If giant cells are present in the myelomata they are of the myeloplaxe (mega-karyocyte) type (Plate IV., Fig. 2 c) and they carry the same significance as the similar findings in the sinuses of the spleen and liver in leukæmic conditions.

Another important group of tumours, occurring most frequently at the diaphyseal ends of the long bones, must be carefully distinguished from the “myeloid sarcoma.” This group, which includes the round- and spindle- and mixed-celled sarcoma of endosteal and periosteal origin, has been given the name “osteogenic sarcoma” owing to their capacity to form new bone trabeculae. These sarcomata may be said to resemble similar round- and spindle- and mixed-cell sarcomata elsewhere, and their distinctive feature lies in the osteogenic function which they possess in virtue of the cell of origin being the endosteal or periosteal osteoblast. Their histological structure consists of the usual sarcoma tissue with thin-walled capillaries, and also shows irregular strands of osteoid and osseous trabeculae or a very delicate network of osteoid tissue, in the meshes of which the tumour cells lie. Extensive areas may be found with no new bone formation, and only evidence of bone resorption—those of periosteal origin invading the cortex, and finally the medulla from without and those of endosteal origin destroying the can-
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cellous tissue and the cortex from within, more or less covered by a thin expanded shell of bone.

Histologically such a tumour bears no resemblance to a myeloid sarcoma, but two different processes may occur simultaneously which lead to the gradual development in this tissue of structural elements that need to be differentiated. The one process is the result of a rapid multiplication of the tumour cells with the occurrence of mono- and multi-nucleated giant cells (Plate IV., Fig. 1, and Plate XX., Fig. 3) such as may be found in all rapidly growing sarcomata. The presence of areas where many such large cells are present, scattered individually or in groups amongst the rapidly dividing tumour cells, gives the name "giant-celled sarcoma." Such a designation is a correct one, for it signifies the intense proliferative activity of a malignant cell, with irregular and multipolar mitoses which result in giant cells of mono- and multi-nucleated types. The second process referred to is the possibility of the development, in this malignant giant-celled tissue, of other giant cells—the osteoclast type of giant cell—such as are found in large numbers in the "myeloid sarcoma": these arise in relation to bone resorption both of the old and new trabeculae, and in relation to the multiple minute haemorrhages that so frequently occur around spicules of bone.

(i.) Characteristics of the Types of Giant Cells.—The histological characteristics of the three types of giant cells mentioned will now be indicated (Plate IV., Fig. 2): (a) The osteoclast giant cell of "myeloid sarcoma," the polykaryocyte; (b) the malignant mono- or multi-nucleated giant cell of an endosteal or periosteal sarcoma; and (c) the bone marrow giant cell—the myeloplex (megakaryocyte). It is obvious that in the pathological report on a small portion of tumour tissue removed at a preliminary operation there lie the possibilities of grave errors of diagnosis, especially if the tissue is badly fixed—the possibility of mistaking the osteoclast giant cell for the malignant multi-nucleated giant cell with a report which leads to amputation of the limb, where conservative surgery would be sufficient; or, on the other hand, of mistaking the malignant giant cell for an osteoclast cell with fatal consequences to the patient.

In the following description we are largely indebted to...
Mallory's careful account of these cells, and more especially to Stewart's valuable recent papers.

(a) The Osteoclast Giant Cell of Myeloid Sarcoma.—The distinctive features of the "myeloid sarcoma" are the following (Plate XX., Figs. 1 and 2): the giant cells (Plate IV., Fig. 2a) vary greatly in size and in number in different cases and in different parts of the same tumour, but their morphological characters remain remarkably constant; the intervening tissue may be cellular or fibrous, but is usually of a polymorphous-celled type; the more rapidly growing have many giant cells and are very vascular—a feature which explains the softness and proneness to degeneration and haemorrhage in the central myeloids of the long bones; the cytoplasm of the giant cells is abundant and may be homogeneous or vacuolated, especially at the periphery; the nuclei are very numerous, are isolated and uniform in size, and may be grouped with a whorled arrangement in the centre of the cell.

(b) The Malignant Giant Cell—mono- and multi-nucleated.—The malignant sarcomata of bone have the following features (Plate IV., Fig. 1; Plate XX., Fig. 3): the stroma may be round- or spindle- or mixed-celled, and the giant cells vary greatly in number; it is always possible to find transitions between the cells of the tumour and the giant cells. The striking feature (Plate IV., Fig. 2b) is the large and irregular size of the nuclei, which may be linked together with lobings and indentations; the nuclei rarely exceed six or eight in number, and are often so clumped together that it is difficult to determine how many are present; cells with single enormous sized nuclei are present, and mitotic figures, often irregular and multipolar, are numerous both in the cells of the matrix and in the giant cells. Such cells are never found in the "myeloid sarcoma," while the osteoclast type of giant cell may also be present in the malignant tumour in virtue of the presence of bone undergoing resorption.

Stewart agrees with Adami in looking upon the osteoclast giant cell as a specific constituent of the tumour tissue, and therefore a tumour cell. Mallory, however, claims that they are an accidental feature, depending on the situation of the growth in bone; that is, they are of the nature of foreign body giant cells. But Stewart and others ask: if they are foreign body giant cells, how are we to account for their presence in such large numbers in the case of myeloid sarcoma, and
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their fewness or actual absence in other sarcomata of bone, where bone is also undergoing resorption? In answer to this point the writers would put forward the view that osteoclast giant cells are present in the slowly-growing fibroblast tumours of bone (the myeloid sarcoma), because the bone is being slowly replaced—in part by stroma tumour cells and in part by osteoclasts, which have formed by fusion of endothelial cells to carry out this function. The slow growth of the tumour gives time for the maturity of both tissue elements—the fibroblast to form fibrillar tissue, and the osteoclast to realise its mature type. The tumour, therefore, has reached a tissue type and is a histioid growth composed of fibrous tissue (it is only when haemorrhages occur into this tissue that it becomes of the polymorphous-celled character) and mature cells—osteoclasts. In the malignant tumour, on the other hand, although this also involves bone resorption, the activity of the malignant cell occasions bone destruction, probably by osteolysis, so rapidly that the osteoclast is not called into play, and there is no time for the maturity of the structural element, the osteoclast, as in the benign growth.

In the writers' view the myeloid sarcoma has originated as a cellular fibroblast growth which may be central or periosteal. The latter are usually related to the jaw and form a large proportion of the myeloid growths: in virtue of their origin in bone and their local slow destruction of bone, osteoclast giant cells are called out in such large numbers as to dominate the histological picture. The tumour may go on to fibrosis but, as it is liable to secondary changes through haemorrhages, the basis of the tissue becomes more cellular and vascular and assumes the histological character of a fibro-sarcoma, and, as in other cellular fibromas, there is the possibility of its assuming a more malignant and infiltrative character. We believe, however, that in the metastases if present, the type of cell will be that of the groundwork of the primary tumour without the osteoclast giant cells. The cell from which the tumour cells arise is not yet definitely settled, but it is of connective tissue type, and probably not osteoblastic, for the osteogenic capacity of such tumours is slight. We retain the name “myeloid sarcoma” as an accepted and understood term until its true histogenesis is determined.

Analogous to the formation of benign cellular fibroma of periosteal and central origin with osteoclast giant cells which
give the tumour, the "myeloid sarcoma," its characteristic appearance, there may arise periosteal and central malignant tumours of connective tissue type—round- and spindle- and mixed-celled sarcomata. These tumours arise not from the connective tissue framework of the bone but from its more differentiated cell, the osteoblast. They are rapidly growing, and the tumour cells retain their osteogenic function, and at the same time may act as bone resorbing cells; while the true osteoclast is not called out in large numbers, and has not time to grow to its mature type. Where such tumours become intensely proliferative they produce, as in all rapidly growing tumours, large mono- and multi-nucleated cells of tumour origin. These cells may be isolated through the tissue, or occur in groups sufficient to dominate the microscopic picture, and, in spite of their very characteristic appearances, if the tissue is badly fixed, may lead to errors in diagnosis. The examination of sections from a malignant giant cell sarcoma, where osteoclast giant cells have also formed, e.g. around haemorrhages, provides examples of very numerous pseudo-transition forms—the explanation of which lies in the plane in which the nuclei of these large cells have been sectioned. The metastases from the malignant tumours contain all the cell types of the primary growth, including the large mono- and multi-nucleated types, but not the osteoclast giant cell. There is no essential difference between the endosteal and the subperiosteal varieties: both ultimately break through the periosteum and invade the soft tissues, in which new bone is being laid down ahead of the growing tumour, partly by the migration of periosteal osteoblasts, partly by metaplasia from fibrous tissue, which has replaced the destroyed muscle and later, partly by the extension of the osteogenic tumour cells.

(c) The Bone Marrow Giant Cell—the mega-karyocyte or myeloplaxe.—These cells are clearly differentiated from both the preceding types (Plate IV., Fig. 2c), by the fact that they possess a single, much convoluted, or even basket-shaped nucleus. The nucleus is comparable to that of its smaller prototype, the neutrophile polymorpho-nuclear leucocyte. The numerous variations in the structure, related to the plane of the section and the portion—periphery or centre—of the nucleus sectioned, correspond to the similar variations found in the granular leucocyte: the commonest forms are circular and horse-shoe shaped, and the lobing is always distinctly indicated.
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Such cells have no points of contact with the osteoclast giant cells of the myeloid sarcoma ("myeloma"): they occur only rarely in the multiple myelomata, both in the primary growths and in the secondary infiltrations. The illustration (Plate IV., cf. a and c) brings out the unreasonableness of the terminology which ascribes to tumours containing osteoclast giant cells, a name "myeloma" suggesting the identity of their origin with the bone marrow giant cell.

(ii.) Relation of Osteitis Fibrosa to the Metaplastic Sub-Groups—(a) The Giant-celled Areas—"Tumour-forming Metaplastic Malacia."—We are now in a position to discuss the nature of the giant-celled areas (Plate XVIII., Figs. 1-3) found in osteitis fibrosa, and their relation to myeloid sarcoma. The origin, structure, and significance of these areas have been given in an earlier section, where it was pointed out that all transitions may be traced between loose fibrous tissue, dense fibrous tissue, fibro-cellular and vascular tissue to the polymorphous-celled areas which showed much haemorrhage, and contained numerous giant cells in all stages of development. The cellular character of the tissue was related in large measure to a reaction in the connective tissue cells, following minute haemorrhages: such interstitial haemorrhage would be a stimulus to a proliferative cell reaction, while larger hemorrhages would result in a granulation tissue, resulting later in an attempt at organisation. In this cellular tissue lie very numerous giant cells, distributed in parts uniformly, or grouped in small clusters around bone spicules or fused red blood cells. Figures 1-3 (Plate XVIII.) sufficiently indicate the structure of such areas, which were often immediately subperiosteal.

The writers have had an opportunity of examining sections from two recent cases of localised osteitis fibrosa: the appearances presented differ in no essential, morphologically, from those in the generalised type. In both cases the expansion of the bone outline was caused by the presence of subperiosteal bone formation on a thin layer of compact cortex (Plate VII., Fig. 4): the whole of the cancellous tissue being replaced by fibro-osteoid tissue, in which small groups of giant cells were found. In the sections in our case of generalised type, very large numbers of the giant-celled areas were subperiosteal, and one small area in this position was found in the first portion of bone removed from the humerus for diagnosis in 1921. It would be easy, therefore,
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if such an area as is represented in Fig. 2 (Plate XVIII.) were present in the section to give the diagnosis “myeloid sarcoma” to the condition. The true nature, however, lies not in a neoplastic formation but in a cellular reaction in a potentially metaplastic tissue. The cell proliferation is an indication of the progressive character of the change which leads through phases of loose fibrous tissue with few cells to this very cellular tissue in which numerous giant cells lie, almost incidental to the process and yet as evidence of an attempt at repair. Throughout such areas all stages of vacuolation and degeneration of the giant cells could be found to a complete nucleo- and cyto-lysis, and a reversion again to a fibrous tissue without giant cells. The giant cell areas were very numerous in the humerus: in Plate XIII., which represents the lower shaft, fourteen areas of varying size were present in one section. The nature and origin of this cellular reaction scarcely justifies the title of von Recklinghausen’s sub-group “tumour-forming metaplastic malacias,” nor the title “osteitis fibrosa with multiple tumours.” The cyst-forming metaplastic malacias would naturally fall to be considered now in their relation to the tumour-forming areas, but it will be convenient to continue this section with the localised giant cell areas, which are large enough to fall under von Recklinghausen’s designation of “metaplastic new growths”—the myeloid sarcomata.

(b) The Myeloid Sarcomata—“Metaplastic New Growths”

(von Recklinghausen).—In the present section all myeloid sarcomata, periosteal and endosteal (Plate XX., Figs. 1 and 2) are included: the differences of structure are quantitative only, for the former are more fibrous and may show areas of fibrosis with no giant cells, while the latter are more cellular and vascular, but may also show areas of fibrosis. Von Recklinghausen, we have seen, looked upon osteitis fibrosa as a specific, metaplastic, malacic disease, combined in its later stages with giant-celled tumour-like areas—the formations we have discussed in the previous section—but he extended this conception to include the so-called benign sarcomas of bone—the myeloid sarcoma. Multiple tumours of this variety are, however, rare, so that it is in relation to the localised type of osteitis fibrosa that this tumour comes into consideration. Myeloid sarcomata both medullary and subperiosteal (epulis) were therefore to von Recklinghausen not tumours but metaplastic new formations. The naked eye recognition in such growths of mottled areas—
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white strands in the maroon-coloured tissue—was confirmatory proof to him of the essential identity of the process to localised osteitis fibrosa, for the white areas were fibrous or fibro-osteoid tissue in the midst of a vascular, giant-celled tissue. He believed that the whole affected area, e.g. at the diaphyseal end of a long bone, had its origin in a fibro-osteoid tissue, which showed transitions to a cellular, haemorrhagic tissue with many giant cells. If the osteoplastic process was in the background, the whole medulla might be occupied by this vascular, giant-celled tissue, which might penetrate into the epiphyseal ends and extend along the shaft, yet usually remained fairly circumscribed. Successive haemorrhages in this vascular tissue would lead to increased giant cell formation and increased cellular reaction, with the resulting formation of a vascular, polymorphous-celled and giant-celled tissue—the "brown tumours."

Numerous writers (Gaugele, Platou, and others), while agreeing with von Recklinghausen that giant-celled areas occur in osteitis fibrosa, cannot find any ground for regarding the neoplastic proliferations (myeloid sarcomata) as identical formations, and point to certain differences in the structure and distribution of the giant cells. In osteitis fibrosa the giant cells are said to be scattered in nests, and they usually contain red blood cells or haemosiderin pigment; in myeloid sarcoma, on the other hand, the giant cells are uniformly distributed throughout the tissue. The intervening cells may show numerous mitoses; and although haemorrhages are frequent, the giant cells rarely contain blood pigment. We have examined very many sections of myeloid sarcoma in order to confirm these observations, but except for the more uniform distribution of the cells in myeloid sarcoma, the giant cells in the two processes have identical characters; phagocyted blood pigment is present in the giant cells in both, and mitosis in the intervening cells is occasionally found in both conditions. The areas of fibrous tissue transformation, especially in the epulis, is a further point of approach to the fibrosis occurring in the tumour-like areas in osteitis fibrosa.

In spite of these morphological considerations which point to the identity of the two conditions, and which are justification of von Recklinghausen's grouping of the benign sarcomata of bone under metaplastic malacias, there are other considerations which make it difficult to relate all myeloid sarcomata to a localised osteitis fibrosa. The tumour-like areas in the latter
condition arise in definite relation to a given cause—the osteoclastic resorption of the fragments of bone and the hæmorrhages around these fragments. The cellular proliferation has therefore a definite limit, and passes by imperceptible gradations to a non-cellular fibrous tissue. The mass of its proliferative activity is therefore determined by the strength of the factors that initiated it and, as it were, require it: it is surrounded on all sides by fibro-osteoid tissue, which shows no deviation from a tissue that is almost quiescent, and which has the appearance of undergoing gradual reconstruction to a mature tissue.

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the benign character of the growth. When the fibrous tissue or fibro-osteoid tissue is present to any considerable extent, it is possible to find in the neighbouring bone, areas with fibrous tissue in widened cancellous spaces—this fibrous tissue being in direct continuity with the fibrous strands of the tumour. The central tumours may expand the shaft, encroaching on and breaking through the thinned cortex, and they may infiltrate the periosteum and soft tissue. Ewing thinks that when this takes place osteoblasts may participate and endow the process with more aggressive qualities. Clinically the tumour may remain simple for a long time, and numerous instances are recorded of local recurrence after several successive operations for removal. No thoroughly established case of metastases has been recorded with the presence of the osteoclast giant cells in the secondary growths.

(c) Relation of Cyst-Formation in Osteitis Fibrosa to Solitary and Multiple Bone Cysts.—The structure and mode of formation of multiple cystic areas of varying size, distributed throughout the fibro-osteoid tissue of the humerus and skull, have been indicated in the histological study (Plate XVIII., Figs. 4-6). The small size of these areas in our case is in keeping with the observations of many other writers in cases of generalised osteitis fibrosa, and it has been suggested that where proliferative processes are in the ascendant, as in the production of giant cell areas, the cystic changes are less marked. Their commencement as spaces in the meshes of the edematous fibrous tissue; their enlargement through haemorrhages; the absence of a definite lining membrane, except the compressed fibrous tissue; and the presence of giant cells and bone trabeculae in the immediate neighbourhood are appearances that justify the assumption that larger cysts, with blood-stained contents and a more definite pseudo-membrane, might arise through confluence of such small cysts. In the edematous fibrous tissue were present numerous transitions showing the pre-cystic stage that might end in multilocular areas, the giant cells present in some of the septa being found in the haemorrhagic contents of others undergoing complete degenerative changes. The explanation of the nature and origin of these multiple cystic areas thus occasions no difficulty, and they are recognised by all writers as end stages in the process of osteitis fibrosa.
Their occurrence in osteomalacia and in osteitis deformans has been frequently reported; but it is probable that most of the cases have been true osteitis fibrosa, for one of the accepted criteria in the differential diagnosis of these conditions is their rare occurrence in osteomalacia and their comparative rarity in osteitis deformans.

It is in the attempt to relate solitary bone cysts to localised osteitis fibrosa that difficulty arises. In 1877 Virchow described a solitary cyst of the humerus, the wall of which was composed of fibrillar cartilage. Virchow interpreted the cyst as the result of a disintegration of a chondroma, and, generalising, he enunciated the view of the neoplastic origin of bone cysts. Such a cyst, however, had nothing to do with the fibro-cystic bone dystrophies. Von Recklinghausen, as already noted had, in 1891 and in 1910, related the solitary bone cyst to degenerative changes occurring in localised osteitis fibrosa; the tissue of this localised osteitis fibrosa, being badly nourished and oedematous, gradually softened and gave rise to multilocular cysts which became confluent. The contents of the cysts were serous and blood-stained, and in the wall of the cyst a giant-celled tissue might develop; by a process of gradual disintegration and encroachment on the cortex a thin shell of bone would be left with or without a thickened periosteum.

Miculicz (1904) was the first to give a precise description of solitary bone cysts under the term “fibro-cystic juvenile dystrophy.” He stated that it was an affection of the growing bone which attacked usually the metaphyseal ends of the long bones, and that it often started with an initial trauma—possibly overlooked. He noted its benign character, with absence of recurrence and metastases, and also the possibility of healing by consolidation after spontaneous fracture. The pre-cystic stage was one of a localised fibro-osteoid tissue with numerous giant-celled areas. Numerous French observers about the same time, especially Tixier (1902) and Delanglade (1903) (Cornil et Caudray) had reported the finding of solitary cysts in the long bones—a scraping from the wall of the cyst showing the structure of myeloid sarcoma. Kummer (1906) included all non-parasitic bone cysts under the term “fibro-cystic bone dystrophy”; he thought that they were usually of traumatic origin, and began in an abnormal reaction in the injured bone, with the production of fibro-osteoid tissue and its subsequent vacuolation and degeneration. Mauclaire and Bernini (1911)
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described cases of "ostéite vacuolaire meta-traumatique"—
osseous dystrophies related to trauma which formed pseudo-
neoplasms and cysts.

Amongst recent writers who have studied fibro-cystic disease
of bone and solitary bone cysts are Stumpf (1912), Bérald
and Alamartine (1914), Loudon (1914), Lobell (1916), Elmslie
(1917), Morton (1922), Young and Cooperman (1922), and
Paterson Brown (1922). All of these writers are in agreement
in looking upon one group of bone cysts as related to an
osseus dystrophy, but most of them also agree that there
is not sufficient ground for accepting this as the sole origin
of all non-parasitic bone cysts.

Structure of solitary bone cysts. These occur usually in the
metaphysis, and are limited by the epiphysis but are also
found diaphyso-epiphyseal. The cavity has seldom a membrane
but a fibrous tissue pseudo-membrane which can be curetted
and examined histologically. The wall of the cyst may show
several layers, the inner of which is the vascular and pigmented
fibrous tissue membrane; outside this, the thinned cortical bone
trabeculae are separated by enlarged medullary spaces filled
with a vascular connective tissue, or the cortex may be completely
replaced by a vascular fibro-osteoid tissue with numerous osteo-
clast giant cells, and the outer layer of the cyst wall may
correspond to the periosteum. The contents are never quite
haemorrhagic, but are blood-stained masses with numerous giant
cells, especially near the lamellar bony shell; these giant cells
are seldom sufficient in number to characterise the condition
as myeloid sarcoma.

It is obvious that in the preceding description of a cyst
with a pseudo-membrane continuous with the fibrous tissue
between the bone trabeculae we are dealing with cystic changes
in a localised osteitis fibrosa, and von Recklinghausen’s claim
is that all solitary, non-parasitic bone cysts have this origin
and form, therefore a sub-group of the metaplastic malacias—
"cyst-forming metaplastic malacia."

Excluding the rare cysts in enchondromata and myxomata
and cysts in callus formation, the only other cyst that comes
into serious consideration is that due to cystic degeneration
of a myeloid sarcoma—those due to a degenerative change
in a malignant sarcoma may be ruled out, as the solitary benign
cysts of bone are of a chronic nature. In the cystic degeneration
of a myeloid sarcoma there is present on one side or all

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round a thin shell of expanded bone with a varying degree of subperiosteal new formation. The currant-jelly contents can be shelled out from the eroded bony wall, and microscopically these show a very vascular, cellular structure with numerous osteoclast giant cells and little or no supporting stroma. Sometimes the contents have become more fluid, and only the thin bony shell shows a lining layer of giant-celled tissue which may encroach upon and infiltrate the surrounding soft tissue.

There is, therefore, a very close similarity in structure between a solitary bone cyst due to a dystrophic process and that due to a cystic degeneration of a myeloid sarcoma, especially if the latter should show a secondary fibro-osteoid change in the neighbouring bone. We have admitted that the histological difference between the multiple brown areas in generalised osteitis fibrosa and the localised myeloid sarcoma is only one of degree; so here also it would not be difficult to trace histological transitions between solitary bone cysts that are definitely related to localised osteitis fibrosa, and the cysts that seem to be definite degenerations of a myeloid sarcoma. But just as the question arose: are all myeloid sarcomata the late stage of a localised osteitis fibrosa? so the same problem arises: are all solitary non-parasitic bone cysts the late degenerative stages of a localised osteitis fibrosa, or may some not be cystic degenerations of true myeloid sarcoma?

The solitary bone cyst, if not too large, may become filled with a loose fibrillar connective tissue, and in this fibrous tissue, by metaplasia, new osteoid tissue may be formed, which later undergoes ossification. The cavity is therefore replaced by a cancellous bone, and healing occurs: spontaneous fractures in such cavities have also been reported with healing by consolidation of the callus. The possibility of spontaneous healing by fibrosis in a myeloid sarcoma of the long bones is at least conceivable and has been described by Ribbert; and it is recognised that a giant-celled epulis may be thus replaced by a fibrous epulis, but the spontaneous healing of a cystic degeneration of a myeloid sarcoma is less probable. Is the difference between the cystic dystrophy and the cystic tumour only one of degree, or are there cysts due to dystrophic processes and cysts due to neoplastic processes?

Summary.—We have endeavoured to trace the development of the views held as to the relation between localised osteitis fibrosa and myeloid sarcoma, i.e. to relate the tumour-forming
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and cyst-forming metaplastic malacias to the metaplastic “neubildungen” of von Recklinghausen—the benign sarcomata of bone. We agree with the view that the tumour-forming areas and multiple and solitary cysts in generalised and localised osteitis fibrosa pass by insensible histological transitions into the structure of myeloid sarcoma and cystic degeneration of a myeloid sarcoma, but believe that there are no sufficient grounds for including the two latter conditions under the term metaplastic malacias in preference to neoplastic formations.

(d) Relation of Localised Osteitis Fibrosa and Myeloid Sarcoma to Chronic Haemorrhagic Osteomyelitis.—There is a further historical development that it is necessary to trace in order to complete the picture of the relations of osteitis fibrosa and of myeloid sarcoma. We have seen that Adami classified myeloid sarcomata as “myelomas,” because of the supposed identity of the giant cell in these tumours with the myeloplaxe—the tumour must be, therefore, he claimed, of myelogenous or haemopoietic origin. The osteopoietic origin, however, of this giant cell is now almost universally admitted, and with this admission the term “myeloma” is inapplicable; further, Bloodgood (1912) in a critical study of this group of tumours, recognising that they were relatively benign, that they never formed metastases—although they might recur locally—gave them the name “medullary giant cell tumour” instead of the term “sarcoma.”

But an entirely different standpoint is presented in Mallory’s (1911) and Barrie’s (1913) papers; these writers claimed that the osteoclast giant cells found in these benign processes arising in bone were foreign body giant cells. Barrie, therefore, put forward the view that these tumour-like formations are masses of proliferated granulation tissue, and that the presence of the giant cell is due to its environment in cancellous tissue. They were not to be regarded, therefore, as a neoplasm but as haemorrhagic granulation tissue formed in response to inflammatory stimuli; the initial cancellous destruction might be due to trauma, or to a mild non-suppurative chronic infection, or to some metabolic disturbance. The stages in the process of this change Barrie described as follows: (1) An embryonal vascular granulation tissue, which caused (2) pressure and destruction of the delicate cancellous trabeculae from nutritional inhibition; (3) during this period numerous osteoclast giant cells form; (4) increased stimulation by certain chemiotactic
substances brought about a fibrous transformation of the granulation tissue; (5) fibrosis means contraction and retraction, and therefore no more destruction but cyst formation, and the hæmorrhagic tissue is converted into a fibro-cystic stroma. The first stage is a chronic proliferative hæmorrhagic osteomyelitis; the final stage is a fibro-cystic osteomyelitis. Stewart has described recently a case of myeloid sarcoma of the lower end of the radius, which was white throughout its whole mass and microscopically consisted of cellular giant-celled tissue. He believes that the white areas of the mottled granulation tissue so characteristic of the usual myeloid sarcoma consist not of fibrous tissue but of cellular non-hæmorrhagic tissue; that the dark maroon colour is therefore an accidental characteristic due to increased vascularity and hæmorrhage; and that this case is a striking commentary on the view advanced by Barrie that myeloid sarcoma is neither more nor less than a chronic hæmorrhagic osteomyelitis.

Barrie carried out a series of experiments in rabbits which consisted (1) in the aseptic insertion of minute strands of gauze subcutaneously. Six weeks later the gauze was found embedded in a hæmorrhagic granulation tissue with giant cells of osteoclast type in the meshes of the gauze fibres—a structure indistinguishable from the giant-celled tissue of myeloid sarcoma; (2) in the removal of a portion of cancellous bone from the lower end of the femur to admit of the insertion of a few threads of gauze. Several weeks later a giant-celled tissue had developed, again indistinguishable from "myeloid sarcoma." Mallory has carried out analogous experiments in which he drilled a hole in the femur of rabbits and studied the process of repair around the bone dust; he found in six days a cellular tissue. The proliferated endothelial cells had fused to form osteoclast-like giant cells.

Mallory points out many analogous instances of the attraction of endothelial cells into a cellular tissue by substances which arise as a result of retrograde processes, e.g. free fat, cholesterin, cornified epithelium, and the subcutaneous injection of agar-agar—the proliferated endothelial cells subsequently fusing to form osteoclast-like giant cells. Both Mallory and Barrie claim that the presence of such giant cells in a tumour involving bone signifies only erosion or disintegration of bone substance; and that though the giant cells may not be in actual contact with bone the tissue has contained disintegrating...
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particles of bone which stimulate the endothelial reaction. The presence of the giant cells is therefore an index of a mild and chronic inflammatory process. Hæmorrhages may occur in this vascular granulation tissue, and with the onset of hæmorrhages the number of the foreign body giant cells may greatly increase. Subsequent organisation of the granulation tissue results in areas of fibrosis, with contraction and retraction and cyst formation, and the chronic hæmorrhagic osteomyelitis may be converted into a fibro-cystic osteomyelitis. (Synonyms: benign bone cysts; chronic osteomyelitis fibrosa cystica.)

Summary.—The presence of this granulation tissue is in Barrie's view the reaction to a chronic mild inflammatory stimulus. The giant cells are factors in the attempt at repair and reconstruction—a reconstruction which may end in a fibrous or fibro-cystic osteomyelitis. Cysts occurring in this process should be grouped with fibro-cystic lesions, not with neoplasms. The cysts are not degenerations, but related to contraction and retraction of the fibrous tissue.

The three standpoints we have considered of the nature of myeloid sarcoma and its cystic degeneration are related to a metaplastic, inflammatory, and neoplastic basis. According to von Recklinghausen, these formations are not primarily tumours nor inflammatory processes but "metaplastic neubildungen": according to Barrie they are neither neoplastic nor metaplastic processes but chronic inflammatory processes—chronic hæmorrhagic osteomyelitis and fibro-cystic osteomyelitis; and according to the view prevailing in this country, they are neoplastic and not primarily inflammatory nor metaplastic.

It is necessary, however, to modify this clear distinction between the three views, for Barrie separates the bone cysts due to so-called myeloid sarcoma, which we have seen he designated "chronic fibro-cystic osteomyelitis," from the fibro-cystic lesions of metaplastic malacia. "The latter," he states, "give an entirely different picture from the lesions due to trauma or to isolated pathological processes caused by infection: in these inflammatory processes the fibrous stroma becomes firm, dense, and avascular, and the lesion represents the terminal stage of a primary process that had its origin in a localised hæmorrhagic osteomyelitis, which in its turn was preceded by mechanical influences, by the spirochaeta pallida, the tubercle bacillus, or some other infecting organism—all of which might end in the same effort at reconstruction."
In this attempt to show the relations between the tumour-like structures and cysts in localised osteitis fibrosa; the myeloid sarcoma and its cystic degenerations; and the chronic haemorrhagic and chronic fibro-cystic osteomyelitis, we have thus outlined the three contrasting views of the nature of these lesions which, according to the standpoint of individual writers, are called "myeloid sarcoma" (neoplastic), localised osteitis fibrosa (metaplastic new formations), and chronic haemorrhagic osteomyelitis (chronic inflammatory). We have also outlined the views regarding non-parasitic solitary bone cysts with a fibro-osteoid and giant-celled tissue in the wall—to von Recklinghausen they all represent a stage in the metaplastic malacias. Barrie and English writers, in general, agree in admitting this origin for many solitary bone cysts, but Barrie looks upon the solitary cysts which English writers claim as cystic degenerations of true myeloid tumours as the fibro-cystic stage of a chronic haemorrhagic osteomyelitis which may have been determined by one or more etiological factors.

(iii.) Relation of Myeloid Sarcoma to the Malignant Giant-Celled Sarcoma.—It does not come quite within the scope of this paper to include a consideration of the malignant giant-celled sarcoma, as they cannot be regarded as "metaplastic," but in view of the great importance of the differential diagnosis between a localised osteitis fibrosa solida or cystica, a myeloid sarcoma, and a malignant endosteal or periosteal giant-celled sarcoma, occurring for example at the end of a long bone, an attempt must be made to make clear their histological characteristics (cf. Plates III., IV., and XX., Figs. 1-4). Those of the two former have already been sufficiently indicated, and it has been noted that the writers can find in sections from very numerous myeloid sarcomata none of the histological features indicated by Lubarsch that distinguished the giant cell areas in osteitis fibrosa from similar areas in the myeloid sarcoma, except that in general the distribution of the giant cells is less uniform in osteitis fibrosa. The morphological character of the cells, however, their phagocytic activity to red blood corpuscles and, therefore, their haemosiderin content, and their degenerative appearances are identical, while the intercellular stroma tissue varies so greatly in individual tumours that it is possible to find all the transitions, noted in osteitis fibrosa, present also in myeloid sarcoma. In cystic
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degeneration of the myeloid sarcoma, however, we have not
found as a constant feature the fibro-osteoid character of the
adjoining tissue which merges into normal bone, although
areas of fibrosis and fibro-osteoid tissue may be present in the
tumour itself, and a degree of subperiosteal new bone
formation may exist to account in part, with the expansion of
the medulla, for the swelling.

The diagnosis between localised osteitis fibrosa and a
myeloid sarcoma must come into consideration at a stage
before infiltration of the periosteum and of the soft tissues
by the myeloid growth has occurred; when this has taken
place, and new bone is being laid down in the infiltrated
periosteal and parosteal tissue, the diagnosis can rest only
between the benign central giant cell tumour (the myeloid
sarcoma), which has become infiltrative, and the malignant
giant cell tumour (the osteogenic sarcoma).

Both tumours usually begin in the metaphysis near the
epiphyseal line, where the cancellous tissue is resorbed and
the shaft expanded but still covered by a thin layer of bone,
or, in the case of the periosteal malignant variety, the shaft
is ultimately replaced and surrounded by a globular mass
covered by a thin shell of new bone. The structure of the
myeloid sarcoma with its polymorphous-celled vascular stroma
and its osteoclast type of giant cell has already been noted.
The medullary and periosteal malignant sarcomata ultimately
involve marrow, shaft, and subperiosteal tissue of the meta-
physis, and may cross the epiphyseal line; they may extend
up the shaft and also surround it, and the separated periosteum
may remain as a capsule for a time but is later invaded, as
well as the surrounding soft tissues, in which a delicate network
of new bone is laid down, both in the infiltrated tumour tissue
and in advance of it. The structure of such a tumour (Plate IV.,
Fig. 1, Plate XX., Fig. 3) is very cellular; it may be round
or spindle- or mixed-celled, with an intricate network of osteoid
tissue, in the meshes of which the cells lie; the strands of new
bone may be osseous and form coarser trabeculae, or the new
bone formation may not be a marked feature, especially in
the periosteal variety. The tumour cells, however, are osteo-
blastic in origin and retain their functioning capacity in spite
of their intense vegetative capacity, while osteoclasts in small
numbers are present, engaged in bone resorption.

Such a tumour microscopically has few points of contact
with the picture of the myeloid sarcoma, dominated as it is by the osteoclast giant cell. But this malignant sarcoma may take on so active a vegetative proliferation that very large mono- and multi-nucleated giant cells are formed (Plate IV., Fig. 2b). The character of these cells has already been given; they occur usually isolated or in small groups, but numerous fields may be found where, under high power, they stand out in sufficient numbers also to dominate the picture and justify the term "Giant Cell Sarcoma." Numerous mitoses can be found in the intervening cells, while the giant cells themselves show very irregular and multipolar mitoses, and all stages of transition in size and in the characters of the nuclei can be found between the cells of the tumour and the giant cells, which therefore do not differ except in size from the true tumour cells. There is no difficulty in distinguishing them from the isolated osteoclast giant cells adjoining them engaged in bone resorption or grouped around small haemorrhages. Plate IV. brings out the essential characteristics of this malignant giant cell, and Fig. 2 the contrasting characters of the three types of giant cells.

The relatively benign character of the one, the myeloid sarcoma, is related (1) to the presence of the bone resorbing cell—the osteoclast—which melts or erodes the bone but has no other activity, and (2) the fibroblast character of its main cell mass; both cells differentiate to an almost mature type of tissue cell. Such tumours, Ribbert claims, may become fibrosed, the giant cells may disappear, and new bone be laid down in the fibrous tissue. Eve describes a case of a central myeloid sarcoma which he regarded as a fibro-sarcoma with extensive areas of fibrosis. We therefore agree with Mallory and Ewing's view that tumours containing osteoclast giant cells should be classified according to the nature of the other cells present in the tumour, e.g. fibroma or fibro-sarcoma, "with osteoclast giant cells."

Stewart has made a critical analysis of fifty cases of myeloid sarcoma, and five cases of malignant giant cell sarcoma. He looks upon the myeloid sarcoma as originating from the fibrous tissue framework of the bone periosteum or endosteum, and considers the osteoclasts as integral and essential cells of the tumour, just as they are essential constituents of normal bone. He further thinks that it is unnecessary to assume that some foreign substance, endogenous or exogenous, must be present
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to account for them, and he has found similar cells in myeloid tumours of tendon sheaths in which cholesterin or other stimulant to their production was absent. His recent papers indicate the histological criteria by which the true myeloid sarcoma may be distinguished from the malignant giant-celled sarcoma. It is the absence of this distinction that is the cause of many errors in diagnosis, and one of the explanations of the marked discrepancy in the data dealing with results of treatment and prognosis of sarcoma, when both types are simply called "medullary or central giant-celled sarcoma." All writers are in agreement in regard to the relatively benign character of the myeloid sarcoma and to the absence of metastases—"save in the infrequent cases in which it undergoes sarcomatous modification" (Adami), in which case osteoclast giant cells would not be found in the metastases. Conservative surgery is justifiable in the case of myeloid sarcoma—if the locally infiltrative character and possibility of recurrence and of sarcomatous modification are kept in mind. In contrast to the favourable result of local treatment in these tumours is the gravity of the prognosis, in spite of radical treatment in many of the malignant giant-celled sarcomata.

(iv.) Note on Metaplastic Carcinomatosis.—Two types of changes have been described in secondary carcinomatous processes in bones: (1) the one, osteoclastic, in which the bone is resorbed in large part by lacunar erosion, and a tumour tissue takes its place; the gradually increasing osteoporosis may lead to fracture before complete substitution has taken place; (2) the other, osteoplastic, in which, in the tumour tissue new bone is laid down (a) in the fibrous stroma of the tumour as new network trabeculae, and (b) as a deposit on the resorbed surfaces of the old trabeculae. The tumour cells may pass through the vessels of the cortex to the surface and lead to periosteal thickenings. In this second type the bone, at first osteoporotic, may become more and more dense, and, if calcification of the new bone takes place, no fractures occur. Schmidt and Klemperer both refer to the predominance of osteoclastic changes in thyroid and mammary cancer metastases, and of osteoplastic changes in prostatic cancer.

Von Recklinghausen thought that the cancer cells, which develop first within the channels of the small veins of the medulla of the long bones, initiate a diffuse and extensive resorption of the calcium salts of the cancer-free bone tissue—a
true halisteresis—and this resorbed bone is replaced by fibrous tissue in which new osteoid reticular bone is laid down. The process could thus be called a carcinomatous fibrous osteitis. A second possibility presented itself if this new bone remained uncalcified (osteoid), that the softening of the bones might be due to a special type of osteo-malacia, "carcinomatous osteo-malacia." In this latter condition the resorption was initiated and completed by halisteretic atrophy, in the former initiated by halisteresis and completed by lacunar resorption.

In sections from a case of mammary cancer, with extreme secondary deposits in the ribs, the writers found an extensive replacement of the centre of the affected ribs by fibro-osteoid tissue, while the periphery of the bone showed extreme osteoporosis and substitution of the resorbed bone by tumour cells. The fibro-osteoid tissue had completely replaced the central trabeculae and bone marrow and had been laid down by metaplasia, in a reticular manner, with later apposition—exactly comparable to the new bone in osteitis fibrosa. In this central area were groups of necrotic tumour cells undergoing fibrous substitution. At the periphery the tumour cells were closely applied to the atrophic trabeculae (Plate XX., Fig. 5), which showed an osteoid zone, no osteoclastic resorption could be traced, and the appearances suggested an osteolytic action of the tumour cells (Plate XX., Fig. 6, tc), such as has been postulated in previous sections for the proliferated endosteal cells. Both the new fibro-osteoid tissue and the osteoporotic bone were easily cut by the knife, showing that the new bone was not calcified, and that the remains of the old bone were decalcified, so that the anatomical conception of malacia could be applied clinically—"osteomalacic carcinomatosis." The fibro-osteoid transformation of the interior of the rib was very striking; in secondary carcinoma in bone it is a well-recognised feature that if a small area of bone becomes isolated and surrounded by tumour cells, the medullary spaces in the interior of the isolated bone undergo fibrosis, but in this case, though the periphery of the rib and the parosteal tissue showed tumour deposit, yet the central fibrosis had undoubtedly occurred in tumour tissue, and it was in this fibrous tissue that the osteoid reticulum was laid down. The whole series of changes indicated in Plates VIII. and XVII., from the shaft of the humerus, could have been taken from the interior of the rib in this case of metaplastic carcinomatosis.
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Reference may be made to the frequency of the occurrence of malignant growths as the end-stage in the cases of osteitis deformans recorded by Paget: this proportion has not been supported in recent observations, and there is no reason to believe that a malignant change, carcinomatous or sarcomatous, has any definite relation to an osseous dystrophy.

(c) ETIOLOGY.

The nature and origin of the changes underlying osteitis fibrosa have now been discussed, together with their relation to diseases which have certain clinical or anatomical characteristics in common. We have no definite knowledge, however, of the determining cause of this obscure bone lesion, but the unity of conception regarding the nature of the processes that underlie this group of allied diseases and the recognition of their morphological similarities, raises the question of their genetic relationship.

With the use of the term “dystrophy” the group of muscular dystrophies naturally suggests itself. These, however, represent types of one disease and not separate morbid entities, and in them, in contrast to bone dystrophies, hereditary and family factors are very prominent, though they resemble bone dystrophies in showing: the existence of transitional forms, the tendency of one type of the disease to pass into another, the possibility of atrophies being mistaken for dystrophies, and the fact that little is known of the final cause of the disease. In regard to the etiology of the muscular dystrophies and certain diseases of the central nervous system, developmental factors have been postulated, in the sense that “they lay the foundation of the constitutional tendency which renders the individual more susceptible to the injurious influences of later life”—that they, therefore, indicate a diminished resistance or a diminished vitality. The assumption of a developmental genesis of disease as distinct from predisposition, however, would appear in the light of recent pathological knowledge to be untenable. Modern conceptions of disease again do not admit of primary importance being attached to the influence of cold and trauma, except in the sense that they may be the exciting factors, which lower the resistance of the organism and allow the final determining factor or factors to operate.

Although the special stimulus which originates the processes
involved in osteitis fibrosa is quite unknown, it is necessary to pass briefly in review the evidence on which various views regarding it are based. The possible etiological factors may be grouped under (1) toxi-infective agents; (2) the endogenous hormones of the endocrine glandular system and the exogenous hormones—the vitamins; (3) developmental factors; while, more especially in relation to the localised form, the additional and subsidiary factors of trauma and circulatory changes must come into consideration.

(1) Generalised Osteitis Fibrosa.

(i) Toxi-infective Agents.—The early view of the inflammatory nature of the process, that is, of a primary proliferative change in the connective tissue stroma of the bone marrow, by which the parenchyma, the haemopoietic cells, became crowded out, gave the justification for the conception of a chronic productive inflammation which might be due to an attenuated form of infection, in some way comparable to tubercle or syphilis, without their specific effects. The change was looked upon as a chronic "osteomyelitis fibrosa interstitialis productiva," occurring with intermissions, during which a certain degree of healing might occur, and exacerbations, during which both the new-formed bone and the other bones became involved. The disease might occur in this way in circumscribed areas in several bones, or become diffuse through the whole skeleton.

We have seen that the assumption of a chronic inflammatory stimulus leading to bone marrow fibrosis in osteitis fibrosa finds no support in recent literature, and with the relinquishment of this view of the nature of the process, the toxi-infective genesis of the generalised form has also been abandoned. The experimental work of Morpurgo points to the possibility of the production of rickets in growing rats and of osteomalacia in adult white rats by the injection of bacterial cultures of a diplococcus; similar changes have been produced by Koch in dogs by the injection of streptococci intravenously, and a possible relation has been traced between these findings and the osteomalacic phenomena of epidemic character found by veterinary surgeons among goats and other animals, and the endemic appearance of late rickets in the child. The examination of the blood, however, has been invariably negative, and
there are no sufficient grounds for assuming the existence of a filterable virus.

Later it will be seen that several data support the view of the association of some localised types of osteitis fibrosa with toxi-infective processes, without necessarily implying any genetic relationship.

(ii.) **Hormones — Endogenous and Exogenous.** — Bone retains throughout life its formative activity, and bone apposition prevails over bone resorption until advanced age, when the latter process is more in evidence and a degree of senile osteoporosis sets in. A comparison of this normal balance with the processes of bone destruction and bone formation in the malacias, points to a disturbance of the tissue equilibrium as the important underlying principle. Recent writers have laid emphasis on the conception of the animal organism as an “integration of activities” (Johnstone), and in the consideration of the means by which the various activities are linked together and co-ordinated it is recognised that two systems work together—the sympathetic nervous system and the endocrine glandular system.

Modern conceptions of the pathogenesis of many obscure forms of disease are related to the functions of the various endocrine glands, and it is in the close relation of the sympathetic system to the endocrine system that a completer view of the co-ordination of bodily activities may be found. Garrod, in a recent illuminating address, has indicated the mechanism by which the efficient control of the processes in the living body is effected by the hormones produced by the endocrine glands; these are themselves under the control of the sympathetic system, a control which is to some extent automatic, for the supply of a hormone is regulated by the demand, as is the gas-supply of an incubator. Garrod further notes the evidence which points to a balance of the endocrine glands, some of which co-operate while others secrete antagonistic hormones. Myxœdema is given as an instance of the effect of inactivity of a gland; here the thyroid is thrown out of action and the changes in the body are due to the uncontrolled action of other endocrine glands which the normal thyroid holds in check. The evidence that some of the endocrine syndromes are due to over-activity of a gland is considered to be less conclusive—a view of great significance in relation to the hyperplasias and tumours of the parathyroid often found
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in malacic conditions—and acromegaly and exophthalmic goitre are given as instances of diseases related possibly to a perverted rather than an exalted functional activity, *i.e.* that not merely an excess of the pituitary and thyroid hormones are produced, but a wrong kind of hormone. As an instance of true hyperactivity of a gland, Garrod instances the example of endocrine antagonism related to the thyroido-Langerhans syndrome, where there is good reason to believe that over-activity of the thyroid inhibits the islands of Langerhans, and allows of the production of glycosuria, while the high glucose tolerance of patients with myxedema points to over-activity of the islands of Langerhans when the control of the thyroid is removed.

In addition to the endogenous hormones, there are present in the body the exogenous hormones—the vitamins—and the study of deficiency diseases, believed to be due to deficiency of vitamins, raises the question of their mode of action. Cramer, Drew, and Mottram, have helped to place the conditions present in deficiency diseases on a pathological basis, by correlating the general conditions produced with definite pathological lesions in specific tissues. Their results show that the general marasmus, due to the withholding of water-soluble vitamin B, is due to atrophy of the lymphoid tissues, in the absence of which the food is not assimilated in the intestine. Again, the increased susceptibility to certain types of a virulent infection, which is the characteristic of animals fed on a diet deficient in fat-soluble vitamin A, is found to be associated with atrophy of the intestinal mucosa and a diminution in the number of blood platelets, which are active agents in the agglutination of bacteria. In vitamin A deficiency, therefore, the atrophy of the intestinal mucous membrane leads to a continued and increasing invasion of the blood stream by intestinal bacteria; these are agglutinated by the blood platelets until the number of blood platelets is diminished to such a low level that the defence against bacteria becomes ineffective.

These observations led Cramer and his co-workers to the conception that these food accessory substances called "vitamins" are "food hormones," *i.e.* that the different articles of food contain in varying amount substances having a drug-like stimulating action on the digestive tract. The full functional activity of the digestive tract is thus dependent on an abundant supply of these substances in the food, in the same way as the
full functional activity of the uterus is dependent on a continued supply of the ovarian hormones. The digestive tract is, therefore, the key to the problem of the mode of action of these food accessory substances, and M'Carrison's words may here be quoted—"Persons receiving too little vitamins are living in a state of potential morbidity, which may be converted into one of actual disease by a variety of factors which further exhaust metabolism." Amongst such factors are enumerated cold, damp, mental depression, overcrowding, and infective agents.

These résumés of recent papers by Garrod and by Cramer have been given to show how complex may be the factors involved in the causation of obscure diseases, and that amongst these factors, the endogenous hormones from the endocrine glands and the exogenous hormones—the vitamins—play a rôle that cannot be easily exaggerated. The finding of a parathyroid tumour of considerable dimensions, in our case, is therefore of great interest. In an earlier section we have noted briefly the more important cases recorded, of the presence of parathyroid hyperplasia or a parathyroid tumour in association with malacic conditions, and correlated these observations with the results of experimental work. The two views of the function of the parathyroids were seen to be related; the one to the neutralisation of toxic substances formed in the body, especially those related to nitrogen metabolism; the other to the regulation of calcium metabolism by exerting an inhibitory action on the excretion of calcium. A legitimate inference from the latter view would be that the parathyroid hyperplasia found in certain cases of rickets, osteomalacia and osteitis fibrosa, is an attempt on the part of the parathyroid glands to prevent the excessive excretion of lime salts, analogous to the view that acromegaly is related to hyperpituitarism. This view involves the assumption, as Garrod has pointed out, that a hyperplasia or an adenoma of a gland increases the output of its secretory products. It is recognised, however, that acromegaly may be absent, even with a lesion destroying the pituitary, that diabetes may be present without any recognisable change in the islands of Langerhans and that many malacic conditions have been observed in which no changes were found in the parathyroids, while cases of parathyroid tumour have been recorded with no skeletal changes. In our case the parathyroid increase had passed beyond the bounds of a simple hyperplasia, and gives the picture of a benign papillary adenoma. There comes, therefore,
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the question: in what relation does the parathyroid tumour stand to the bone disease?

The conception that the bone disease is a consequence of the parathyroid tumour cannot be entertained, for malacic conditions, as has just been noted, may arise independently of any change in the parathyroids. On the other hand, a possible connection between the parathyroid hyperplasia and the bone disease cannot be denied, for recent experimental work has established a close relation between the parathyroids and calcium metabolism, and many bone lesions are obviously associated with anomalies of calcium metabolism, yet these data do not give a clear impression of the actual relationship. The final determining cause of osteitis fibrosa is unknown, but the recognition of the relation of the parathyroids to calcium metabolism gives the key to the elucidation of the problem of the etiology of malacic disease. The causal factor does not stimulate the bone marrow to fibrosis, but its action is to be sought in the primary and essential change in the bone cell, the activity of which may be controlled by the parathyroids.

It has been previously emphasised that the bone cell is a very specifically differentiated structure; that in its high degree of differentiation it has given up its vegetative powers and carries out, by means of its processes in the bone canaliculi, the specific function of retaining control over the metabolic activities of the area of bone, as it were, assigned to it. As long as the nutrition of the bone cell is sufficient, its specific function of controlling the metabolic exchange of lime salts to be adsorbed will be retained. The bone cell may be looked upon as exercising this function in virtue of the supply of the hormone of the parathyroids, and if any injurious substances are circulating in the blood, whatever their origin, this highly sensitive cell is damaged and loses its control over the adsorbed lime salts. This we believe is the essential and primary change in osteitis fibrosa—a loss of the control that the bone cell exercises over the exchange of lime salts in its own area; the histological evidence of this is shown in Plate VI., Figs. 1 and 2. In an endeavour to enable the bone cells to retain their power, the parathyroids may in some cases yield an increased supply of hormone products—the possibility of this automatic regulation has already been noted—and the attempt to meet this need results in a hyperplasia analogous to the hyperplasia found in the lobules of the renal cortex when an interstitial change
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throws an increased effort on the unaffected lobules. In some cases this hyperplasia may pass over, as in the present case, into a true adenomatous formation. This view of the relation of the parathyroids to malacic conditions justifies the conclusion that such lesions are due to whatever may cause a loss of the hormone control normally exercised by the parathyroid, but does not explain the initial factor responsible for the damage to the bone cell and for the disturbance, therefore, of the protective mechanism, which, in spite of its hyperplasia, was insufficient.

The view here submitted relates the changes found in osteitis fibrosa to the action of the unknown causal factor primarily and essentially on the bone cell, which therefore loses the control which the hormone from the parathyroid gives it over calcium metabolism. The possibility, however, cannot be excluded that the causal factor acts primarily on the parathyroid or that the adenomatous formation of the parathyroid is primary; in either case the parathyroid, by giving a perverted hormone, would itself lose the power to control the bone cell. In diabetes mellitus, a disease due to defective function of the islets of Langerhans, the hyaline changes found in the islets or the disintegration of the $\beta$-cells, point to such an analogous primary change in an organ producing a hormone, that of the islets of Langerhans, which acts on the liver cell. Diabetes, it is true, may have been present without recognisable histological appearances in the islets of Langerhans, but when one remembers the rapid post-mortem changes that take place in the pancreas and the specific staining methods required for indicating changes in the $\beta$-cells, it is not unreasonable to assume that the delicate structural degenerations could not be recognised. In the case under consideration, however, the existence of four histologically normal parathyroids would point rather to an equilibrium between the parathyroid hormone supply and the bone cell activity, until some further factor, by damaging the bone cell, called for an increased supply, which was responded to, but insufficiently, by the hyperplasia of an islet of aberrant parathyroid tissue. The completely differentiated cells of the four normal parathyroids did not respond by hyperplasia, but the incompletely differentiated cells, of which aberrant parathyroid tissue is usually composed, proliferated, giving an adenomatous hyperplasia of small transitional cells, rather than of the mature, clear, vesicular cells of the normal parathyroid. Such a hyper-
plasia of islets of incompletely differentiated cells would be comparable to the hyperplasia of islets of lymphoid tissue that occurs under certain circumstances, in susceptible individuals to meet infection. The lesions present in localised osteitis fibrosa also point to a primary change in the activity of the bone cells in localised areas, determined, as will be seen, by toxi-infective, traumatic and circulatory factors.

The brief account of the mode of action of the endogenous and exogenous hormones as outlined by Garrod and by Cramer has prepared the reader (1) for the view there propounded, that the orderly sequence of metabolic changes which is at work in the normal organism is profoundly disturbed by the incursion of the agents of disease; (2) for the multiplicity in the variety of these agents, especially those elaborated in the intestinal tract, when exogenous hormones are deficient; and (3) for the recognition that the interrelation of the glands of internal secretion enables us to postulate the reaction on this endocrine balance of the hyperactivity or the perversion of the parathyroid gland secretion.

It is important to remember that the disease is not uniform and progressive; the causal factor, therefore, must be in operation over a long time, allowing of remissions of the disease, when the calcium content of the bones, as indicated by the X-ray photographs in our case, shows an increase. The mode of action may be directly on the bone cell, or indirectly, by setting up changes in the ultimate vascular supply of the parts affected, lowering its vitality. This latter mode of action may be supplementary to the former and be responsible for the site of the early changes in the long bones, which are usually in the metaphyses—an area where two sets of vessels have their terminations, practically as end-arteries, an area also in the growing bone requiring an abundant blood supply. It would be natural, therefore, for toxic substances to act more readily in parts more sensitive to trophic disturbances, the metaphyses. It is necessary, further, to bear in mind that the toxic substances wherever elaborated, may not act thus directly or indirectly on the bone cell, but may produce a definite metabolic disturbance, which in its turn is specific to bone, and from this point of view it may be justifiable to give the name “meta-infectious diseases” to rickets and osteomalacia, for these conditions may follow acute infections.

(iii.) Developmental Factors.—In the proportional allocation
to any agent of a place in the causation of disease, its effects must be determined not only by its own activities but also by factors inherent in the patient which assist its action. The possible etiological factors discussed in the previous sections may be latent, or even potential, in many individuals without giving rise to disease, and to explain this circumstance, the further possibilities of diminished resistance and diminished vitality must be considered. In relation to the muscular dystrophies, it is natural to assume that in these the muscles are endowed with a restricted vitality and, therefore, with a shorter term of life than normal muscles. In such dystrophies it is conceivable that pathological, metabolic and other toxic products exist which are the final determining factors, but the actual disease is the direct expression of an inferiority of the tissue laid down in embryonic life. This conception can legitimately be extended to other tissues of the body than the muscles, and it is further possible that the selective action of toxins shown in so many conditions, especially of the central nervous system, may be related to their action on a tissue that has less power of resistance. The occurrence of two malacic diseases in the foetus—osteogenesis imperfecta and chondro-dystrophia foetalis—might argue in favour of this view, but it must be remembered that the factors which come into operation in producing malacic conditions in extra-uterine life may act through the mother in foetal life.

This brief note may be closed by quoting again from Garrod, who, after pointing to the need of taking into account factors inherent in the individual, admits the truth in a limited sense of the doctrine of diathesis as defined in the New English Dictionary—"a permanent (hereditary or acquired) condition of the body which renders it liable to certain specific diseases or affections—a constitutional predisposition or tendency." Garrod believes that such predispositions exist, and that they have their origin in deviations from the normal metabolic scheme of the species.

(2) Localised Osteitis Fibrosa Solida and Cystica.

Among the more immediate factors that "further exhaust metabolism," and that must be considered in relation to the etiology of the localised type of osteitis, are trauma, circulatory changes and toxi-infective agents, all of which possibly play a
The recognition of the changes that lead to cyst formation in the areas of fibrous tissue substitution makes it impossible to separate the etiology of osteitis fibrosa solida from its cystic form. In both solida and cystica the lesions are usually diaphyso-epiphyseal and there are numerous transitions showing pre-cystic stages. In both again the tissue presents many features in common with the myeloid sarcoma and its cystic degeneration forms; the histological data have already been given that led the writers to the view that the giant-celled areas are not true tumour formations and it is unnecessary to discuss the lesions from the standpoint of the etiology of a neoplastic process. The influence of the endocrine glandular system, of the exogenous hormones, the vitamins, and of the factors inherent in the individual which have been discussed in relation to the generalised form must all here also play a part, though probably a lesser one. It may, however, be added that organotherapeutic measures are said to influence the consolidation of bone lesions, and in regard to the so-called developmental factor, it may be noted that numerous observations point to the occurrence of localised dystrophic lesions in patients with a predisposition to rickets.

(i.) Toxi-infective Agents.—The possibility of a transition between secondary forms of fibrous osteitis, some of which are definitely related to adjacent septic irritation and the existence of certain similarities between the late stages of tuberculous granulation tissue and the late stages of osteitis fibrosa, have made the organismal origin of the latter suspected. Further, Rehn has described, regarding pigs, an affection of the facial and skull bones which he has related to an inflammatory septic process starting from the teeth. The affected bones exhibit all the characteristics of bone removal, fibro-osteoid tissue substitution, and cyst and giant-celled tissue formation that are found in osteitis fibrosa, and Rehn concludes that the reaction to infection initiates the nutritional and proliferative changes which are the essentials of all malacic diseases. Tixier, Braun, and others, have isolated organisms from the fluid contained in the bone cysts, but they admit the possibility of contamination, and it is generally admitted, in spite of Rehn's work, that the view of the infective basis of these conditions has little to support it.
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(ii.) **Circulatory Changes.**—To circulatory conditions peculiar to the long bones must be assigned, on the other hand, a considerable rôle. At the metaphysis—the seat of predilection—the arterial branches are almost end-arteries, and it is at the metaphysis that both the periosteal and endochondral bone growth is most active, and that here also the bone is exposed to the greatest effects of strain and pressure. The localised forms of the disease occur as a rule during the growing period of the bones, when any interference with the circulation in the metaphysis would be of critical significance. In the mid-diaphysis, the second most frequent site of the disease, the vitality of the tissue is also endangered owing to the large dimensions of the medullary cavity.

The mode of action of the circulatory changes may be twofold: on the one hand, diminished blood supply may bring about a deficient vitality and, on the other hand, local circulatory disturbances can result in venous stasis with a retention of carbonic acid in the tissues. From the time of Boerhave, the view has been held in some form that an acid working in the blood dissolved out the lime salts; various acids have been suggested as acting in this way, *e.g.* lactic, butyric, oxalic, phosphoric, or carbonic acid. The histological evidence of halisteresis or thrypsis lent support to such a view, a view which in its cruder form has long been abandoned. Yet it is not unreasonable to conceive of the possibility of the bone cell, which receives its material from the blood, stores it up, and exchanges it, being hindered in its metabolism by the presence of carbonic acid, and therefore being unable to bind to itself or adsorb the lime salts present in the body, for chemical analysis often shows that there is an excess of lime in the tissue fluids.

The functions of the tissue therefore take a wrong direction and this wrong direction is indicated in the prefix dys-, dystrophy, dyscrasia.

(iii.) **Trauma.**—The name “ostéite vacuolaire métatraumatique” bears evidence to the rôle assigned to trauma. French writers especially have emphasised this causal connection; they believed that the injured bone, instead of showing progressive regenerative processes that led to repair, exhibited an excessive central rarefaction, which ultimately resulted in cavity formation. Of the same nature are the fibro-osteoid tissue reactions in the bone marrow, which are stated to arise from primary...
hæmorrhages, and there give place to degenerative cystic changes.

The initial trauma in localised osteitis fibrosa is, however, not constant; it varies much in its intensity and may be overlooked, and it is doubtful if it is not in most cases the fracture, due to a slight injury, that reveals a prior lesion in the bone. There are, however, many observations which lead to the view that a circumscribed osteitis fibrosa, later becoming cystic, may arise in the region of a badly united fracture. Von Recklinghausen denied that the trauma and hæmorrhage in osteitis fibrosa are primary; he thought it improbable that in a normal bone traumatic hæmorrhages could originate a metaplastic malacic process, but he conceded that in an unhealthy bone multiple minute hæmorrhages could extend the process. Lexer attempted, in dogs, to produce changes similar to those of osteitis fibrosa; his results are also against the view of a true traumatic genesis, for either fibrous tissue or cystic changes. Lotsch introduced into the medullary cavity of dogs foreign bodies and fluids of various kinds, including silk threads, iodine, adrenalin, and fibrolysin; he found that there was an intense connective tissue proliferation and organisation of the hæmorrhage, but no marked bone destruction, bone new-formation, or cyst formation; he, therefore, as Lexer did, excluded the possibility of a true traumatic origin for osteitis fibrosa or its cystic type.

The rôle assigned to traumatic hæmorrhage must therefore be secondary; it may reveal the existence of a localised dystrophic process, and accelerate it by altering circulatory conditions, and by setting up a proliferative activity in the structural tissue elements.

**Summary.**—The view here put forward relates osteitis fibrosa to an initial disturbance of the controlling activity of the bone cell over its calcium metabolism—an activity which is normally regulated by a hormone from the parathyroid glands. The process of decalcification is thus reduced to a defective functioning of the bone cell, following damage by an agent circulating in the blood or deranged hormone control. The damage to the bone cell may be caused by any one of the factors outlined above, especially toxins resulting from faulty tissue metabolism, and those elaborated in the intestinal tract. The automatic regulation of the supply of hormones, or in other
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words, the call of the damaged bone cell for an increased supply of hormone, leads to a hyperactivity of the parathyroid gland—a hyperactivity which results in hyperplasia, and in a possible perversion of the hormone, for in spite of its hyperplasia, the protective regulation of the activity of the bone cell is insufficient. The individuals affected and the bones affected may be related to factors inherent in the individual.

V. CONCLUSION AND SUMMARY.

An endeavour has been made to describe the essential histological features in a case of Generalised Osteitis Fibrosa, and to indicate the conceptions underlying the pathological process involved in Bone Dystrophies. The writers have but touched upon or outlined matters which, to be grasped in all their bearings, require a fuller presentation. It has been felt that observations, however detailed, based on one case of an osseous dystrophy, are insufficient to justify any generalisations; for these could only be largely hypothetical and liable to be modified by further observations. It may be thought that in the sections on the nature of the process and on the etiology, the writers have already gone a long way, via inferences, from actual observation, yet the main object of the critical discussion is to give the reader an attitude or an indication of direction in his attempt to understand this obscure group of bone diseases. No further conclusions, therefore, than those already tentatively offered, will be formulated, but a brief summary of the more important sections of the foregoing study is here presented.

(1) Histological Study.

(A) The Bones.—The sequence of the histological development has appeared to us as follows:—

The initial change is a disturbance of the functioning activity of the bone cell, by which its vitality is lowered, and it loses the power of fixing the calcium. This is indicated by the peri-cellular loss of calcium, by the osteoid zone at the periphery of the Haversian system, and by the splitting up of the constituent fibres of the ground substance of the bone.

The same stimulus which damages the specifically differentiated bone cell acts as a proliferative stimulus to the cells of the endosteum, which multiply rapidly. These proliferated cells, instead of acting as functioning osteoblasts, act in
osteolysis and bring about the further solution of the bone substance. Should remission of the disease occur, these proliferated cells give up their osteolytic activity and resume their osteoblast function and lay down bone by apposition.

The irregular erosion of the spaces of the Haversian system by halisteresis and osteolysis leads to a diffusion of the lime salts into the space and a rapid multiplication of the endothelial cells of the capillaries, so that a rich network of large branching cells is formed.

The proliferated cells of the endosteum may fuse to form syncytial giant cells, osteoclast in type, and the proliferated endothelial cells form similar giant osteoclasts, both syncytial types having a fibrillated border next to the bone, which, by physico-chemical action, now actively aids in the resorption of the bone (lacunar erosion).

In this way the compact and cancellous bone is resorbed, leaving large irregular spaces, the centre of which is occupied by a narrow meshed capillary and cellular network, and its periphery by syncytial osteoclasts.

The centre of these irregular spaces now shows a development of fibrils of connective tissue around the vessels, and at the periphery of the space, loops of new blood-vessels, surrounded by cells of embryonic type, penetrate through the thin bridge of bone left between two enlarged Haversian spaces, or the bridge may be eaten through by osteoclast resorption.

A stage is now reached when thin irregular strands of old bone are left, bordered by osteoclasts and separated by fibrocellular and vascular tissue, which is becoming more and more fibrous; finally the whole old bone, with the exception of small fragments encircled on all sides by osteoclasts, is removed and a complete fibrous tissue substitution of the bone has taken place.

In the bone marrow of the long bones no change has been noted until very extensive resorption has already taken place. The first indication of a fibrous tissue substitution is seen in an enlargement and proliferation of the connective tissue cells of the reticulum with the development of tuft-like processes and fibrils, and finally the fatty marrow is replaced by a loose fibrillar tissue with numerous thin-walled capillaries. In the cellular (lymphoid) marrow of the short bones the fibrosis always begins around the periphery of the bone trabeculae and generally extends into the cellular tissue. The bone trabeculae
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themselves are resorbed, in part by the halisteretic atrophy, in part by the osteolysis of the osteoblasts, and in part by lacunar erosion by osteoclasts.

The bone removal having been completed and a fibrous tissue substitution effected, new bone is laid down in this fibrous tissue by metaplasia. This takes place at first as a reticular formation, and its earliest stages can be traced in a transformation of the finest fibrils of the connective tissue into osseo-mucinic tissue, in which the original connective tissue cells are enclosed as bone corpuscles. The osseo-mucinic tissue gradually becomes more homogeneous, but for a long time the continuity of the fibres which run through its substance with those outside can be recognised; such fibres are analogous to the Sharpey's fibres of membrane bone. The islands of osseo-mucinic tissue are gradually linked up by intervening strands and soon a wide-meshed network is formed, in the meshes of which lies the original vascular connective tissue. Both within the meshes and on the outer surface of the isolated strands, the cells of this connective tissue become more protoplasmic, and are arranged after the manner of an epithelial lining layer to form one or more layers of osteoblasts. These now on the surface of the strands of osseo-mucinic tissue, lay down osseo-mucin in regular layers, so that a lamellar bone, by apposition, is deposited on the network strands, leading to a narrowing of the meshes, with a new and irregular Haversian system.

The osteoid (osseo-mucinic) strands gradually become partially calcified, and by osteoclast resorption and osteoblast apposition, a new architecture is laid down according to the mechanical and circulatory factors brought into play. Should complete remission of the disease and healing occur, it seems possible that the new bone, e.g. that of the cranial vault, may become dense in irregular focal areas. Remission of the disease leads to a degree of calcification of the reticular osteoid tissue, while an exacerbation leads to a resorption of the new bone and of the remaining old bone.

Areas of the fibrous tissue substitution, where fragments of old bone may still remain, surrounded by osteoclasts, may be looked upon as specially liable to rupture of capillaries through minimal injuries to the malacic bone. Around these haemorrhages further giant-cell formation and cellular proliferation occur, so that very polymorphous-celled areas are formed, containing numerous giant cells with or without minute 541
fragments of bone. Such giant-celled and polymorphous-celled areas, with interstitial haemorrhage, present a histological picture almost indistinguishable from that of the "myeloid sarcoma." Numerous areas of this type, small and large, may fuse to form a giant-celled tumour-like tissue occupying the medullary cavity or infiltrating the periosteum.

Further, in the fibrillar connective tissue which has replaced the resorbed bone and the bone marrow, numerous small cysts may be found. These arise (1) as a result of circulatory changes which lead to stasis and oedema; the myxomatous tissue then gives place to multiple loculi which merge into each other, and in the septa and wall of the cyst giant cells may be found. Similar cysts may arise (2) in an area of haemorrhage around a fragment of bone encircled by osteoclasts; or (3) by the retraction of the fibrous or osseo-mucinic tissue.

In the early stages, when a thin layer of compact bone is still left, especially at the ends of the long bones, a considerable periosteal new formation may take place—accounting in part for the thickening of the bone outline.

The early stages of the above sequence of changes may be traced in the femur; later stages in the rib and basi-sphenoid; while the final stages are present in the humerus and vault of the skull. In these latter bones is found the complete picture of the disease first described by von Recklinghausen as "Osteitis Fibrosa or Deformans," and later as "Osteitis Fibrosa with Multiple Tumours and Cysts."

(B) The Parathyroid Glands and Tumour.—Four parathyroid glands, normal in size, were present. Both in regard to the arrangement of the cells and the types of cell present, these glands were all regarded as normal in structure. Small isolated islets of parathyroid tissue were found in the areolar tissue between the parathyroid glands and the thyroid; these consisted of small cells of the type which is generally regarded as the forerunner of the "principal" (functioning) cells; their abundant appearance in an adult is taken as an indication of hyperplasia.

The parathyroid tumour was, microscopically, very uniform in structure and in the type of its cells. These were modified "principal" cells and were built up on a fine papillary structure with central capillary core. The tumour mass was interpreted as a hyperplasia of incompletely differentiated cells, which had
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arisen from aberrant parathyroid tissue of undifferentiated type and had passed over into the structure of a simple papillary adenoma.

(C) Calcareous Deposits.—These have been regarded as an instance of "metastatic calcification." This is found chiefly in cases associated with destructive lesions in bone, and has also been produced in rabbits by the experimental injection of soluble calcium salts; the calcium salts are deposited in what seems to be normal tissues, especially in the lungs, gastric mucosa and kidneys. In these three tissues we have the three chief places where acid is excreted—in the lungs CO₂ is given up by the bicarbonate, in the stomach HCl is excreted, and in the kidneys acid phosphate, by a reaction which leaves basic phosphates and carbonates in the blood and tissues. Wells has pointed out that the coincidence of the location of the calcium deposits and the acid excretory function of the tissues leaves little or no room for doubt that the precipitation of calcium in metastatic calcification occurs, because calcium salts are slightly less soluble in the more alkaline fluids present in these tissues. In such areas, a local alkalinity of the tissues is left behind, and in this more alkaline fluid the calcium salts are less soluble and are precipitated from the blood. Metastatic calcification is said to occur whenever, from any cause, the proportion of calcium present in the blood is so great that it requires the efforts of both the colloids and the CO₂ in maximum concentration to keep it in solution—then the calcium salts are deposited where the CO₂ of the fluids is least.

The more usual pathological calcification is the deposit of calcium in tissues with lowered vitality or in necrotic tissues. This deposition is not related to the activity of living cells, and this is the essential point of difference between calcification and ossification—processes which morphologically have many points of resemblance.

Areas of calcification may undergo a transformation into true bone by a process analogous to normal endochondral ossification. The calcified material simply takes the place of the calcified cartilage, and vascular granulation tissue may erode it—the cells of the granulation tissue undergoing a differentiation into osteoblasts under the specific osteo-genetic influence of the calcium salts.
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(2) Interpretation of Fundamental Histological Changes.

(A) Bone Removal.—The writers recognise (a) an initial halisteresis. This is followed by (b) a lacunar resorption, in which two cell types take part; the one, the proliferated cells of the endosteum which, giving up their osteoblast function, take on a vegetative function and then become osteolytic; the other, the giant syncytial osteoclasts, which, possibly by means of their ciliated fibrillar structure, act in a physico-chemical manner in eroding bone. A third possible mode of resorption is represented by (c) vascularisation; capillary loops surrounded by embryonic cells are present in large numbers in the enlarging Haversian spaces, and give the impression of the periosteal capillary buds in endochondral ossification.

(B) Fibrous Tissue Substitution.—The cells of the Haversian spaces, including those of the endosteum and of the capillary and of any intervening tissue, in their reversion to an embryonic type, have come to resemble the early undifferentiated mesenchyme cell. We suggest that it is possible that any of these “indifferent” cells may, if necessary, become fibril-forming cells and lay down fibrous tissue. In this reversion to an embryonic tissue the bone cell itself, if not too greatly damaged, and even the hemoblast, may participate. The primary site of this fibrous tissue substitution is not in the bone marrow, but in the gradually enlarging Haversian systems of the compact bone.

(C) New Bone Formation.—This takes place in the fibrous tissue, (1) first as a wide-meshed network of osteoid strands; this reticular bone formation is analogous to that in the first stage of bone laid down in membrane. Later, when these osteoid strands have become modelled and a layer of connective tissue cells has become differentiated as osteoblasts, new bone is laid down (2) by apposition; this new osteoid tissue is thus deposited as lamellæ on the contours of the strands, both on their outer surface and on the inner surface that outlines the meshes. There is no fundamental difference in the way in which the two varieties of bone, reticular and apposition, are produced; in the one, the fibrils, the inter-cellular product of the cell, become dense and homogeneous, forming a ground substance in which the former connective tissue cell becomes embedded and transformed into a bone corpuscle; in the other type, the cells (osteoblasts) secrete a ground substance (osseomucin) in which they themselves become embedded.
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Osteitis Fibrosa has been regarded by the writers as a distinct pathological entity. It is characterised by (a) bone resorption; (b) fibrous tissue substitution; and (c) new formation of bone—both reticular bone and apposition bone. Variations in the histological picture may be related to the fact that the process is observed at different stages, and to modifications in its development due to the fact that the course of the disease is not uniform and progressive, and to the further fact that remissions may occur. If remissions and healing do occur, a new architectural reconstruction of the bone takes place, under the influence of osteoblasts and osteoclasts, to meet the mechanical and circulatory influences to which the new bone is subjected.

(3) Pathogenesis—Metaplastic Malacia.

It is maintained by the writers that the initial change is in the activity of the bone cell and not in the stroma elements of the bone marrow. This degenerative change in the bone cell is followed secondarily by a reaction in the cell and blood-vessel content of the Haversian system, which, while inflammatory in character, appears to have a deeper significance, for it results in a reversion to an embryonic cellular tissue that is potentially metaplastic.

The anatomical conception underlying the term "malacia" is confirmed by the histological picture, for there is a progressive decalcification and resorption of the old bone and its replacement by an osteoid, i.e. non-calcified, tissue. The epithet "metaplastic" is justified, because the functioning cells of the Haversian system have assumed the character of an early mesenchyme cell and subsequently differentiate along several lines. This preliminary reversion and later differentiation are implied in the term "metaplasia." Metaplasia signifies the transformation of one tissue into another of similar morphological origin and functional character; it takes place in two phases: the one, a neoplastic, in the sense of being a new formation of cells of a less differentiated type; the other, a true metaplastic phase—the differentiation of these cells in a new direction, i.e. into a tissue genetically related. In osteitis fibrosa these two phases are represented by the reversion of the cell content of the Haversian system to embryonic cells, the great majority of which differentiate into fibroblasts and lay down fibrous tissue.
New bone arises in this fibrous tissue by metaplasia from these fibroblasts, either directly (reticular bone) or through an intermediate form of osteoblasts, which are also of fibroblast descent (apposition bone). In this connection it is important to remember the specific osteogenic influence exerted on connective tissue cells by calcium salts, which may be derived from the resorbed bone.

(4) Relation to other Malacic Diseases.

There is good reason for believing that the pathogenesis of rickets, osteomalacia, osteitis fibrosa, and osteitis deformans is allied, and it is recognised that the pathological conceptions of these diseases pass over into one another. All the diseases in this group have in common a disturbance in the relation between bone resorption and bone apposition, which leads to softening. An understanding of the appearances which characterise regressive transformations of the bone is made possible by this fact of continuous modification, even in the fully developed tissue; this modification is carried out by alternate resorption and apposition from the Haversian canals. When there is a disturbance of the tissue equilibrium, and apposition does not follow resorption sufficiently, we get the wide marrow spaces associated with atrophy. This process of atrophy or osteoporosis, extending over long intervals, may be present in an advanced degree without the presence of many osteoclasts, and the type character of bone resorption and the limited bone apposition with concentric lamellae is entirely in accordance with the normal. In dystrophic processes in bone, on the other hand, there is not only a striking quantitative disparity between the alternate resorption and apposition, but, qualitatively, regulation has been to a great extent lost sight of and, instead of apposition, we get an alteration in the type of tissue, i.e. the cell proliferation functions in a wrong direction—a dystrophic process instead of an atrophic process.

Rickets.—The dystrophic process is here shown (1) in an exaggerated and irregular cartilage formation with deficient calcification; and (2) the mesenchyme cells, especially in the metaphysis, instead of differentiating into osteoblasts and osteoclasts, differentiate into fibroblasts and lay down fibrous tissue in which osteoid tissue (non-calcified) transformation takes place. There is, in addition (3) the gradual removal of
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this osteoid tissue and of the bone by a process (thrypsis) allied to halisteresis. If thrypsis prevails over apposition, a hypoplastic type of rickets results; if apposition prevails, a hyperplastic type is brought about. According to the degree and distribution of the change and the accidental mechanical factors brought into play, the types of rickets and the various postural deformities result.

Osteomalacia.—In contrast to rickets, this condition occurs in persons whose endochondral ossification is complete; the softening must be due, therefore, to the removal of lime salts, which seem at first as if they were simply dissolved out. Later, the decalcified tissue becomes resorbed and wide spaces are formed, in which the marrow changes are inconstant. The important distinction between rickets and osteomalacia is the existence of endochondral disturbance in rickets, its absence in osteomalacia; the essential distinction between osteomalacia and osteitis fibrosa is the slight reactive conditions in the Haversian spaces in the former with the absence therefore of a fibro-osteoid tissue substitution, and the absence to any great extent of osteoclast resorption—both changes being of a progressive character and very marked in osteitis fibrosa and in some forms of rickets. The distinction between simple atrophy (osteoporosis) and osteomalacia is that in the latter the lamellar bone shows a gradually increasing and irregular osteoid zone of decalcification by halisteresis—this bone removal is followed by bone apposition, which remains osteoid during the period of the disease.

Osteitis Deformans.—The histological picture in osteitis fibrosa closely resembles that described in osteitis deformans, with the exception of the giant cell areas and cysts. These must be looked upon as end-stages of, and not essential to, the changes in osteitis fibrosa, and the writers find it difficult not to regard the nature of the two diseases as identical—the variations depending upon such factors as proliferative activity. If the changes set in during a period of life when the response to stimuli is still active, the initial changes, degenerative or otherwise, would result in a reaction process that leads through stages of bone resorption and fibro-osteoid tissue formation with remissions and exacerbations, to the cell activity and vascularity that end in the formation of giant cell areas and cysts—a condition of osteitis fibrosa. If, on the other hand, the disease sets in later in adult life, the same initial change would result
in a lessened reaction process, which leads slowly to bone resorption and fibro-osteoid tissue substitution; and the cellular activity that leads to giant-celled areas and vascularity being absent, there results a gradually increasing bone apposition and calcification that leads to sclerosis. The resultant bone would rearrange itself architecturally in response to mechanical and other factors with irregular and narrow Haversian spaces. The softening permits of great deformity, but owing to the elasticity fractures are rare; in later stages, the bone apposition from within and from the periosteum results in a hyperplastic and sclerotic bone, which, when calcification sets in, retains its bent shape. Such a change, limited to the bones of the face, may result in leontiasis ossea.

The changes in osteomalacia, osteitis fibrosa and osteitis deformans, though so different, result in the same diminution of the stability of the bone and in the same deformities; the differential diagnosis during life, therefore, is often difficult. In the distinction between rickets, late rickets, and osteomalacia, there is traced a relative but not a specific distinction, and there are all gradations. In osteomalacia there would appear to be very little reactive process, so that the causal factor which damages the bone cell, acts only slightly as a proliferative stimulus to the other structural tissue elements; in osteitis fibrosa this reactive process is very marked and leads to a fibro-osteoid tissue substitution with the formation of giant cell areas and cysts; in osteitis deformans this reactive process is the outstanding feature and leads to repair, with a new architectural reconstruction of bone.

Localised Osteitis Fibrosa.—The histological appearances differ in no essential from those in the generalised type. The expansion of the bone outline, whether at the metaphysis or midshaft, is caused by the subperiosteal bone formation, while the whole of the cancellous tissue and bone marrow may be replaced by fibro-osteoid tissue in which giant cell areas and small cysts may form. The cell proliferation may be of such a progressive character that the whole portion of the shaft involved may be replaced by a cellular, vascular, giant-celled granulation-like tissue, enclosed in a subperiosteal membrane of new bone or a thin shell of old bone. This vascular tissue may penetrate the epiphysis and also extend along the shaft, but is usually fairly circumscribed; portions of this mass may
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remain fibro-osteoid, giving it a mottled appearance. Such a picture, macroscopically and microscopically, bears a striking resemblance to that which has been long designated “myeloma,” “myeloid sarcoma” or “giant cell sarcoma,” and von Recklinghausen extended his conception of metaplastic malacia to include these formations, which he considered metaplastic and not neoplastic.

Von Recklinghausen also related the solitary bone cyst to degenerative changes occurring in localised osteitis fibrosa. The tissue, badly nourished and oedematous, softened and gave rise to multiple cysts which became confluent, and in the wall or pseudo-membrane a giant-celled hæmorrhagic tissue arose. By a process of gradual disintegration and encroachment on the cortex a thin shell of bone would be left, with or without a thickened periosteum. Other solitary cysts might arise by hæmorrhage and softening in the vascular giant-celled tissue noted in the previous paragraph. The structure of such bone cysts again bears a striking resemblance to that found in cystic degeneration of a myeloid sarcoma, and again von Recklinghausen extended his conception to include such lesions as “cyst-forming metaplastic malacia.”

In spite of these morphological considerations which point to the identity of tumour-forming and cyst-forming metaplastic malacias, with the “myeloid sarcoma” and its cystic degeneration, and in spite of the presence of histological transitions between them, it has been concluded that there are lesions, solid and cystic, due to neoplastic processes distinct from lesions, solid and cystic, due to dystrophic processes.

(5) Nomenclature of the Bone Tumours referred to in the preceding pages.

Medullary tumours, which, macroscopically, are not markedly infiltrative, are very fragile and vascular, and resemble granulation tissue with mottled areas, and which, microscopically, show a polymorphous-celled structure with numerous giant cells and blood-vessels and a varying amount of fibrous tissue, have long been recognised under the terms “myeloma,” “myeloid sarcoma” or “giant cell sarcoma.” A tumour of similar structure, but as a rule more fibrous, is found subperiosteal, growing usually from the bones of the jaw. The giant cell in these tumours has a characteristic morphological structure, resembling the normal osteoclast. The belief that these giant cells, which dominate
the histological picture, were myeloplaxes (megakaryocytes), and therefore of myelogenous origin, accounted for the term “myeloma” or “myeloid,” and the very cellular character of the remaining tissue accounted for the name “sarcoma.”

It is suggested:—

(a) That, as the giant cells are not myeloplaxes, and therefore not of myelogenous origin, but are true osteopoietic cells of osteoclast type, the term “myeloma” is inapplicable and should be discarded. If the term “myeloma” be retained at all, it should be confined to the multiple myelomata of bone—tumours which arise from primitive cells of the haemopoietic series. The true myelomata are usually multiple in bone and their so-called metastases, in the internal organs, take the form of diffuse cell infiltrations occurring usually in, but not confined to, the organs related to a blood-forming function in early embryonic life. Microscopically such tumours have no point of contact with the “myeloid sarcoma”—so-called “myeloma.”

(b) That, as the tumours, even when infiltrative, remain comparatively benign, and have long a structural maturity of the cell elements approximating to a histioid tumour, the term “myeloid sarcoma” should also be discarded. The term “sarcoma” belies its relatively benign and slow growth, and the epithet “myeloid” leaves out of consideration the periosteal group (the epulis) which form the majority of so-called “myeloid sarcoma.”

(c) That the term “giant cell sarcoma” should also be discarded; the term “sarcoma” is again inapplicable and these tumours are not the only giant cell tumours of bone.

(d) That the term “benign giant cell tumour” of bone, advocated by Ewing, best characterises these growths, which have so characteristic a naked-eye appearance, whose cystic degenerations are well recognised, and which, microscopically, consist essentially of two varieties of cells; the one of cellular fibroblast type, the other of osteoclast giant cell type. It is further suggested that this group be subdivided into: (1) central or medullary, occurring usually, though not invariably, at the ends of the long bones; and (2) periosteal, of which the epulis is the chief member. It is to be remembered that these benign giant cell tumours, especially the central group, are, like other cellular fibromas, locally infiltrative, and recur locally if incompletely removed and, further, that in rare cases the stroma cell may take on a malignant proliferation with
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metastases. But we believe that there are no sufficiently authenticated cases of such metastases containing the osteoclast type of giant cell. In striking contrast to the rarity of this malignant change is the frequency of the occurrence of fibrosis in the benign giant-celled tumour. The fibrous transformation of parts of the periosteal type is a characteristic readily admitted, but it is a feature also of areas in the more haemorrhagic central variety. The fibrous tissue develops in part from the cell elements of the stroma and in part from the disintegration of the giant cells; both cell elements of this benign tumour, therefore, share in bringing about this fibrosis or repair. Subperiosteal new bone formation is frequently present, but new reticular bone is also formed in the fibrous tissue by metaplasia; this feature is not so constant as in the osteogenic sarcoma.

(e) That the malignant osteogenic sarcoma of the long bones, round- and spindle- and mixed-celled, may similarly be divided into central and periosteal. These tumours arise not from the connective tissue framework of the bone, but from its more differentiated cell—the endosteal and periosteal osteoblast, this circumstance giving the tumour its distinctive feature, the power of forming new bone, and its name—“osteogenic sarcoma.” This new formation of bone takes place first as an intercellular stroma in the form of delicate fibrils which become more and more dense and homogeneous until thick strands are developed; these, in their turn, undergo resorption, just as the old bone was resorbed. The (central and periosteal) osteogenic sarcoma is a sufficiently inclusive designation for such a tumour, but when rapidly growing, it develops mono- and multi-nucleated giant cells such as are found in proliferative sarcomata elsewhere. The presence of areas containing many such tumour giant cells amongst the rapidly multiplying uninucleated tumour cells justifies the term “malignant giant cell sarcoma”—central or periosteal. These tumours are frequently mistaken for the so-called “myeloid sarcoma” a term which we have just suggested should be replaced by “benign giant cell tumour” of bone, but the giant cells of the benign tumour are osteoclast in type and bear no morphological resemblance to the giant cells of the malignant tumour. There is no essential distinction between the endosteal (central) and periosteal growths; both ultimately destroy the cortex and the cancellous tissue, break through the periosteum and infiltrate the parosteal soft tissues,
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where an extensive reticular new bone is laid down in advance of the growing tumour cells.

The histological characteristics of the three types of giant cells: (1) the myeloplaxe (megakaryocyte) of the bone marrow; (2) the polykaryocyte or osteoclast giant cell of the "benign giant-cell tumour" (central or periosteal); and (3) the mono- and multi-nucleated true tumour giant cell of the "malignant giant cell sarcoma" (central and periosteal osteogenic sarcoma) have been illustrated in Plate IV., Fig. 2. The histological distinction between the benign and the malignant giant-cell tumours would seem from this figure to be sufficiently obvious, but there are many pitfalls. One of these may be mentioned: it has been stated in the preceding paragraph that an extensive reticular new bone formation may be found in the parosteal tissues in the malignant osteogenic sarcoma; in an earlier paragraph it was stated that a subperiosteal new bone formation, together with a metaplastic new bone—both reticular in type—may be present in the benign giant cell tumour; and in a still earlier section, it was stated that a subperiosteal reticular bone and a fibro-osteoid reticular bone may be substituted for the area of bone affected in localised osteitis fibrosa. If an exploratory incision be made, the small portion of tissue removed might contain only reticular new bone and lead to an error in diagnosis; for the time element which should prevent this error in the case of a malignant growth might be misleading.

It is the absence of a distinction being drawn between the two types of "giant cell sarcoma"—the one a benign giant cell tumour, the other a markedly malignant one—that is the cause of many errors in pathological diagnosis, and is one of the explanations of the marked discrepancy in the data dealing with the results of treatment and the prognosis of "sarcoma" of bone.

(6) Etiology.

Reasons have been adduced for the conclusion that the etiological factor acts primarily on the bone cell. It has been emphasised that the bone cell is a very specifically differentiated structure, that in its high degree of differentiation it has given up its vegetative powers, and carries out, by means of its processes in the bone canaliculi, its specific function of fixing the calcium and of controlling the metabolic activities of the
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area of bone as it were assigned to it. The premise has been accepted that there are sufficient grounds for believing that a hormone from the parathyroid glands enables the bone cell to carry out its specific function, and we have suggested that as long as the nutrition of the bone cell is sufficient, and the hormone secretion is undisturbed, bone metabolism will proceed normally. If, however, the bone cells are damaged by any injurious agents circulating in the blood, or if the regulating hormone is deficient or defective in any way, the control of the bone cells over adsorbed lime salts will be disturbed. This, we believe, is the essential and primary change in osteitis fibrosa—a perversion of the control which the bone cell exercises over the exchange of lime salts in its own area.

If, then, we postulate damage to the bone cell by an injurious agent circulating in the blood, the parathyroids may in some cases yield an increased supply of hormone products—the possibility of this automatic regulation has been noted—and the attempt to meet this need results in a hyperplasia, which in the present case has passed over into a true adenomatous formation. The presence of four normal or slightly enlarged parathyroids, and an adenomatous hyperplasia of an aberrant, probably undifferentiated remnant of parathyroid tissue has been taken as an indication of an attempt on the part of the glands concerned to meet the needs of the damaged bone cell by a hyperactivity, this hyperplasia being more readily responded to by aberrant undifferentiated than by the mature parathyroid elements.

The damage to the bone cell may be caused by any of the factors indicated which "exhaust metabolism," especially toxins resulting from faulty tissue metabolism, and those elaborated in the intestinal tract. The reasons have been given for assuming that this toxic factor in the present case did not act primarily on the parathyroids, giving a perverted hormone, as may be assumed in the case of the hormone of the disintegrated β-cells, of the islets of Langerhans, acting on the liver cells in diabetes.

Such an interpretation would relate the changes in our case to the action of an unknown causal factor primarily on the bone cell, with corresponding inability to respond to hormone stimulation and to regulate calcium exchange. The developmental factor, which has been accepted in the limited sense indicated in the text, may be the explanation of the widespread
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reversion of the cells of the Haversian system to an embryonic cellular tissue.

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Literature.

Adami, *The Principles of Pathology*, 1910, vol. i., p. 733.
Allison and Brooks, "Bone Atrophy," *Arch. Surg.*, 1922, vol. v., p. 499.
Axhausen, "Osteogenesis imperfecta," *Deuts. Zeitschr. f. Chir.*, 1908, Bd. xcii., S. 42.
Axhausen, "Arb. aus dem Gebiet der Knochenpathologie," *Arch. f. klin. Chir.*, 1911, Bd. xcvii., S. 241.
Bancroft, "The Use of Small Bone Transplants," *Ann. Surg.*, 1918, vol. lxvii., p. 457.
Barker, *Endocrinology and Metabolism*, vol. i., p. 696, London, 1922.
Barrie, "Cancellous Bone Lesions," *Ann. Surg.*, 1915, vol. lxii., p. 129.
Barrie, "The Significance of Giant Cells in Bone Lesions," *Ann. Surg.*, 1917, vol. lxv., p. 151.
Barrie, "Fibro-cystic and Cystic Lesions in Bone," *Ann. Surg.*, 1918, vol. lxvii., p. 354.
Barrie, "Multiple Hæmorrhagic Foci in Bone," *Ann. Surg.*, 1920, vol. lxxi., p. 580.
Generalised Osteitis Fibrosa

Barrie and Hillman, "Hæmorrhagic Osteomyelitis," *Surg. Gyn. and Obst.*, 1914, vol. xix., p. 42.

Barth, "Ueber histologische Befunde nach Knochenimplantationen," *Arch. f. klin. Chir.*, 1893, Bd. xlvii., S. 409.

Barth, "Histol. Untersuchungen über Knochenimplantationem," Ziegler's *Beitr. z. pathol. Anat.*, 1895, Bd. xvii., S. 65.

Bauer, "Ueber das Verhalten der Epithelkörperchen bei den Osteomalacie," *Frankf. Zeitschr. f. Pathol.*, 1911, Bd. vii., S. 231.

Beck, "Osseous Cysts of the Tibia," *Amer. Journ. Med. Sci.*, 1901, vol. cxxi., p. 666.

Benjamins, "Ueber die Glandulae parathyroideas," Ziegler's *Beitr. z. pathol. Anat.*, 1902, Bd. xxi., S. 143.

Berard et Alamartine, "Les dystrophies osseuses," *Rev. de Chir.*, 1914-15, vol. 1., p. 137.

Berg and Thalheimer, "Regeneration of Bone," *Ann. Surg.*, 1918, vol. lxvii., p. 331.

Berkeley and Beere, "The Physiology of the Parathyroid Gland," *Journ. Med. Res.*, 1909, vol. xx., p. 149.

Bloodgood, "Benign Bone Cysts, etc.," *Ann. Surg.*, 1910, vol. l., p. 145.

Bloodgood, "The Conservative Treatment of Giant Cell Sarcoma," *Ann. Surg.*, 1912, vol. lvi., p. 210.

Bloodgood, "Bone Tumours," *Ann. Surg.*, 1919, vol. lxix., p. 345.

Bloodgood, "Bone Tumours," *Ann. Surg.*, 1920, vol. lxxii., p. 712.

Bockenheimer, "Die Cysten der langen Röhrenknochen," *Arch. f. klin. Chir.*, 1906, Bd. lxxxi., S. 236.

Bockenheimer, "Virchow's Leontiasis ossea," *Arch. f. klin. Chir.*, 1908, Bd. lxxxv., S. 511.

Boit, "Ueber Leontiasis ossea and Ostitis fibrosa," *Arch. f. klin. Chir.*, 1912, Bd. xcvii., S. 515.

Braun, "Ueber Cysten in den langen Röhrenknochen," *Beitr. z. klin. Chir.*, 1907, Bd. lii., S. 476.

Bronson, "Fragilitas Ossium and its Association with Blue Sclerotics and Otosclerosis," *Edin. Med. Journ.*, 1917, vol. xviii., p. 240.

Brown, "A Case of Solitary Cyst in the Humerus," *Edin. Med. Journ.*, 1922, vol. xxix., p. 306.

v. Brunn, "Coxa vara im Gefolge von Ostitis fibrosa," *Beitr. z. klin. Chir.*, 1905, Bd. xlvi., S. 344.

v. Brunn, "Spontenfraktur als Frühsymptom der Ostitis fibrosa," *Beitr. z. klin. Chir.*, 1906, Bd. l., S. 70.

Coley, "Conservative Treatment of Sarcoma of the Long Bones," *Ann. Surg.*, 1919, vol. lxxx., p. 633.

Coirnil et Coudray, "Du Cal," *Journ. de l'Anat. et de la Physiologie*, 1904, vol. xl., p. 113.

Cramer, "Mode of Action of Vitamins," *Lancet*, 1923, vol. i., p. 1046.

Dalyell and Chick, "Hunger Osteomalacia in Vienna," *Lancet*, 1921, vol. ii., p. 842.

Davies-Colley, "Osteomalacia in a girl aged 13," *Trans. Path. Soc.*, 1884, vol. xxxv., p. 285.

Delafied and Prudden, *Textbook of Pathology*, 1920, p. 1042.

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James W. Dawson and John W. Struthers

Dobrowolskaja, "On the Regeneration of Bone," Brit. Journ. Surg., 1916, vol. iv., p. 382.

Eiken, "Ueber Osteogenesis imperfecta," Ziegler's Beitr. z. pathol. Anat., 1919, Bd. lxv., S. 285.

Elmslie, "Fibrous and Fibro-cystic Osteitis," Brit. Med. Journ., 1912, vol. ii., p. 1567.

Elmslie, "Fibro-cystic Disease of Bones," Brit. Journ. Surg., 1914, vol. ii., p. 17.

Erdheim, "Die Epithelkorperchen," Ziegler's Beitr. z. pathol. Anat., 1903, Bd. xxxiii., S. 158.

Erdheim, "Ueber den Kalkgehalt des wachsenden Knochens," Frankf. Zeitschr. f. Pathol., 1911, Bd. vii., S. 175.

Eve, "Central Fibro-sarcoma of Tibia," Trans. Path. Soc., 1888, vol. xxxix., p. 273.

Ewing, "Bone Sarcomas," Arch. Surg., 1922, vol. iv., p. 485.

Forbes, "The Origin and Development of Foreign Body Giant Cells," Journ. Med. Res., 1909, vol. xx., p. 45.

Fraser and Muir, "The Pathology of Otosclerosis," Journ. Laryngol., etc., 1916, vol. xxxi., No. 11.

Fromme, "Die Spätarthritis und die Kriegsosteomalacie," Ergeb. der Chirurg. und Orthopädie, 1922, Bd. xv., S. 1.

Fujii, "Ostitis Fibrosa," Deuts. Zeitschr. f. Chir., 1912, Bd. cxiv., S. 25.

Garrod, "Glimpses of the Higher Medicine," Lancet, 1923, vol. i., p. 1991.

Gaugele, "Zur Frage der Knochencysten," Arch. f. klin. Chir., 1907, Bd. lxxxiii., S. 953.

Gierke, "Störungen des Mineralstoffwechsels," Aschoff's Path. Anatomie, 1923, Bd. i., S. 445.

Gray, Otolosclerosis, vol. lxvi., Lewis, London, 1917.

Groves, "Operative Treatment of Fractures," Brit. Journ. Surg., 1913, vol. i., p. 438.

Groves, "Methods and Results of Transplantation of Bone," Brit. Journ. Surg., 1917-18, vol. v., p. 185.

Haberer, "Zur Casuistik der Knochencysten," Arch. f. klin. Chir., 1905, Bd. lxxvi., S. 559.

Harbitz, "On Tumours of the Parathyroid Glands," Journ. Med. Res., 1915, vol. xxxii., p. 361.

Hart, "Ein neuer Fall von Osteomalacie," Ziegler's Beitr. z. pathol. Anat., 1904, Bd. xxxvi., S. 353.

Hartmann, "Zur Kenntnis der Ostitis fibrosa (deformans)," Beitr. z. klin. Chir., 1911, Bd. lxxiii., S. 627.

Higbee and Ellis, "A Case of Osteitis Deformans," Journ. Med. Res., 1911, vol. xxiv., p. 43.

Hurwitz, "Osteitis Deformans," Johns Hopkins Hosp. Bull., 1913, vol. xxiv., p. 263.

Hutchison and Patel, "The Etiology of Osteomalacia in the City of Bombay," Glasg. Med. Journ., 1921, vol. xcv., p. 241.

Jefferson, "A Case of Paget's Disease," Brit. Journ. Surg., 1915-16, vol. iii., p. 219.

Jenkins, "Osteitis Deformans and Otosclerosis," Journ. Laryng. and Otol., 1923, vol. xxxviii., p. 344.
Generalised Osteitis Fibrosa

Jordan, “The Giant Cells of Haemopoietic and Osteolytic Foci,” Amer. Journ. Anat., 1918, vol. xxiv., p. 247.
Jores, “Experimentelle Untersuchungen,” Beitr. z. pathol. Anat., 1920, Bd. lxvi., S. 433.
Katase, “Experimentelle Verkalkung,” Ziegler’s Beitr. z. pathol. Anat., 1914, Bd. lvii., S. 516.
Klepperer, “Parathyroid Hyperplasia in Carcinomatosis,” Surg. Gyn. and Obst., 1923, vol. xxxvi., p. 11.
Knaggs, “Osteitis Fibrosa,” Brit. Journ. Surg., 1923, vol. x., p. 487.
Knaggs and Gruner, “Ossification in Sarcomata of Bone,” Brit. Journ. Surg., 1914, vol. ii., p. 366.
Korenchevsky, “The Influence of Parathyroidectomy,” Journ. Path. and Bad., vol. xxv., 1922, p. 366.
Landou, “Ostitis Fibrosa Cystica,” Ann. Surg., 1914, vol. lxix., p. 570.
Lane, “Cases of Mollities Ossium,” Trans. Path. Soc., 1884, vol. xxxv., p. 299.
Lexer, “Ueber die nicht parasitaren Cysten der langen Röhrenknochen,” Arch. f. klin. Chir., 1906, Bd. lxxxi., S. 368.
Lewis, “Fibrous Osteitis,” Internat. Clinics, series 28, vol. ii., p. 74.
Looser, “Über Spätfractitis und Osteomalacie,” Deuts. Zeitschr. f. Chir., 1920, Bd. cl., S. 210.
Lotsch, “Ueber generalisierte Ostitis Fibrosa,” Arch. f. klin. Chir., 1916, Bd. cvii., S. 1.
MacCallum, “Tumour of the Parathyroid Gland,” Johns Hopkins Hosp. Bull., 1905, vol. vii., p. 87.
MacCallum and Voegtlin, “Relation of Tetany to the Parathyroid Gland,” Journ. Exp. Med., 1909, vol. xi., p. 118.
MacCallum and Vogel, “Experimental Studies in Tetany,” Journ. Exp. Med., 1913, vol. xviii., p. 618.
Mailory, “Giant Cell Sarcoma,” Journ. Med. Res., 1911, vol. xxiv., p. 463.
Meyer, “Osteitis Fibrosa,” Frankf. Zeitschr. f. Pathol., 1917, Bd. xx., S. 113.
Milner, “Ueber Knochencysten,” Deuts. Zeitschr. f. Chir., 1908, Bd. xci., S. 328.
Molineus, “Ueber die multiple brannen Tumoren bei Osteomalacie,” Arch. f. klin. Chir., 1913, Bd. cl., S. 334.
Morel, “Les Parathyroides dans l’osteogenèse,” Comptes rendus de la Soc. Biol., 1909, vol. lxvii., p. 780.
Morpurgo, “Ueber eine infectiöse Form der Osteomalacie bei weissen Ratten,” Ziegler’s Beitr. z. pathol. Anat., 1900, Bd. xxviii., S. 620.
Morton, “The Generalised Type of Osteitis Fibrosa Cystica,” Arch. Surg., 1922, vol. iv., p. 504.
Naumann, “Ueber Osteomalacie und Ostitis fibrosa,” Deuts. Zeitschr. f. Chir., 1921, Bd. clxiv., S. 1.
Nicholson, “The Morbid Histology of Arthritis Deformans,” Bull. of the Comm. for the Study of Special Diseases, 1907, vol. i., p. 109.
Nicholson, “The Formation of Bone,” Journ. Path. and Bact., 1916-17, vol. xxi., p. 287.
Niklas, “Osteogenesis imperfecta,” Ziegler’s Beitr. z. pathol. Anat., 1916, Bd. lxi., S. 101.
James W. Dawson and John W. Struthers

Oehme, “Ueber die Beziehungen des Knochenmarkes,” Ziegler’s Beitr. z. pathol. Anat., 1908, Bd. xliv., S. 197.
Paget, “Osteitis Deformans,” Med. Chir. Trans., 1877, vol. lx., p. 37.
Paget, “Osteitis Deformans,” Med. Chir. Trans., 1882, vol. lxxv., p. 225.
Pappenheimer and Minor, “Parathyroids in Human Rickets,” Journ. Med. Res., 1920-21, vol. xlii., p. 392.
Parkard, Steele, and Kirkbride, “Osteitis Deformans,” Amer. Journ. Med. Sci., 1901, vol. cxxii., p. 552.
Paget, “Osteitis Deformans,” Med. Chir. Trans., 1877, vol. lx., p. 37.
Paget, “Osteitis Deformans,” Med. Chir. Trans., 1882, vol. lxv., p. 225.
Pappenheimer and Minor, “Parathyroids in Human Rickets,” Journ. Med. Res., 1920-21, vol. xlii., p. 392.
Parkard, Steele, and Kirkbride, “Osteitis Deformans,” Amer. Journ. Med. Sci., 1901, vol. cxxii., p. 552.
Paget, “Osteitis Deformans,” Med. Chir. Trans., 1877, vol. lx., p. 37.
Paget, “Osteitis Deformans,” Med. Chir. Trans., 1882, vol. lxv., p. 225.
Pappenheimer and Minor, “Parathyroids in Human Rickets,” Journ. Med. Res., 1920-21, vol. xlii., p. 392.
Parkard, Steele, and Kirkbride, “Osteitis Deformans,” Amer. Journ. Med. Sci., 1901, vol. cxxii., p. 552.
Generalised Osteitis Fibrosa

Stewart, J. C., “The Malignancy of Giant Cell Sarcoma,” Surg. Gyn. and Obst., 1913, vol. xvii., p. 30.

Stewart, M. J., “Observations on Myeloid Sarcoma,” Lancet, 1904, vol. ii., p. 1213.

Stewart, M. J., “Observations on Myeloid Tumour of Tendon Sheaths,” Brit. Journ. Surg., 1915, vol. iii., p. 90.

Stewart, M. J., “The Histogenesis of Myeloid Sarcoma,” Lancet, 1922, vol. ii., p. 1106.

Stewart, M. J., “Large Myeloid Sarcoma—White throughout,” Brit. Journ. Surg., 1923, vol. x., p. 322.

Stillinger, “Über Ostitis Deformans,” Virchow’s Arch. f. path. Anat., 1890, Bd. cxxv., S. 542.

Strangeways, “Cases of Rheumatoid Arthritis,” Bull. of the Comm. for the Study of Special Diseases, 1907, vol. i., p. 93.

Studeny, “Zur Casuistik der Knochencysten,” Arch. f. Klin. Chir., 1910, Bd. xxii., S. 1019.

Stumpf, “Über die cystische und cystische-fibrose Umwandlung einzelner Knochenabschnitte,” Deuts. Zeitschr. f. Chir., 1912, Bd. cxiv., S. 417.

Swale, Vincent, and Jolly, “The Functions of the Thyroid and Parathyroid Glands,” Journ. Phys., 1904-5, vol. xxxii., p. 65.

Symington and Alexis Thomson, “Defective Endochondral Ossification in a Human Foetus,” R.C.P. Ed. Lab. Reports, 1892, vol. iv., p. 238.

Symmers, “Multiple Myelomata,” Ann. Surg., 1918, vol. lxvii., p. 687.

Tanberg, “The Relation between the Thyroid and Parathyroid Glands,” Journ. Exp. Med., 1916, vol. xxiv., p. 547.

Thompson, “Tumour Metastases involving the Parathyroids,” Journ. Med. Res., 1911, vol. xxiv., p. 291.

Tietze, “Über Knochencysten,” Beitr. z. klin. Chir., 1907, Bd. lxxi., S. 495.

Todyo, “Die Epithelkörperchen bei Osteomalacie,” Frankf. Zeitschr. f. Path., 1912, Bd. x., S. 219.

Verebélly, “Beitr. z. Path. der bronchialen Epithelkörperchen,” Virchow’s Arch. f. path. Anat., Bd. clxxxvii., S. 100.

Verse, “Über Calcinosis Universalis,” Ziegler’s Beitr. z. pathol. Anat., 1912, Bd. liii., S. 212.

Wells, “Calcification and Ossification,” Arch. Int. Med., 1911, vol. vii., p. 721.

Welsh, “The Parathyroid Glands,” Journ. Anat. and Phys., 1898, vol. xxxii., p. 383.

Westmacott, “Chronic Hyperplasia of the Superior Maxilla,” Int. Med. Cong., 1913, section xv., p. 243.

Widdows, “Calcium Content of the Blood during Pregnancy,” Bio-Chem. Journ., 1923, vol. xvii., p. 34.

Young and Cooperman, “Osteitis Fibrosa,” Ann. Surg., 1922, vol. lxxv., p. 171.
DESCRIPTION OF PLATES.

The illustrations are grouped together, as far as is possible, to illustrate related aspects of the pathological changes. Plates II.-VIII. and Plate XXI. Fig. 1 are from drawings, Plates IX.-XXII. from photomicrographs.

Plate I. The X-ray changes.

Plate II. The naked eye appearances in skull, humerus, and femur.

Plates III., IV. Benign and malignant giant-celled tumour of bone.

Plate V. Bone resorption by lacunar erosion.

Plate VI. Bone resorption by halisteretic atrophy and new bone formation. (Schmorl's stain.)

Plate VII. Chiefly aspects of bone resorption.

Plate VIII. Stages of fibro-osteoid tissue transformation.

Plates IX.-XV. Large bone sections, showing early and late osteoporosis in the femur (IX.-X.); complete fibro-osteoid substitution in the humerus (XI.-XIV.); and transition stages in the vault of the skull and in the rib (XV.).

Plate XVI. Bone resorption in the femur (cf. Plate V.).

Plate XVII. Fibro-osteoid tissue substitution (cf. Plate VIII.).

Plate XVIII. Formation of giant cell areas and of cysts.

Plate XIX. Transition changes in rib (Figs. 1, 2) and in basi-sphenoid (Figs. 3, 4). Early reconstruction in the bone architecture (Figs. 5, 6).

Plate XX. Benign giant cell tumour of bone (Figs. 1, 2); malignant giant cell tumour of bone (Figs. 3, 4); osteoplastic carcinomatosis (Figs. 5, 6).

Plate XXI. Parathyroid tumour.

Plate XXII. Calcareous deposits in organs and tissues.

The following lettering is used in Plates IX.-XX. ß, bone fragments; ob, old bone; rb, new bone; rm, cellular bone marrow; fm, fatty marrow; c, cyst; ft, fibrillar tissue; gc, giant cell; ih, interstitial hemorrhage; obl, osteoblast; ocl, osteoclast; om, osseo-mucinic tissue; op, osteoporosis; oz, osteoid zone; Sm, Sharpey's fibres; sp, new Haversian space; tf, transitional fibres.

PLATE I.

Fig. 1.—Radiogram of left humerus when patient first came under observation in September 1920, showing general thickening, filling up of the medullary cavity, irregular calcification and recent fracture.

Fig. 2.—Radiogram of left humerus taken three and a half months later than that in Fig. 1, showing decalcification of the bone, especially below the fracture.

Fig. 3.—Radiogram of left humerus taken ten days later than that in Fig. 2, showing still greater decalcification.

Fig. 4.—Radiogram of left humerus taken three weeks after that in Fig. 3, showing redeposit of lime salts coincident with improvement in the patient's general health.

Fig. 5.—Radiogram of left humerus taken eleven weeks later than that in Fig. 4, showing the second fracture and a more regular distribution of lime salts, with a relatively dense cortical layer and a more rarefied central zone.

Fig. 6.—Radiogram of skull taken when decalcification of the humerus was most evident, showing conversion of the bones of the cranial vault into a thick layer of irregularly calcified bone, with complete loss of division into outer and inner tables.
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**Plate II.**

**Fig. 1.**—Frontal section of the left humerus, showing the conversion of the bone into an almost solid rod of fibro-calcaceous material which has entirely replaced the normal structure, except for an area in the head of the bone. (A. B. C. cf. Plates XII.-XIV.)

**Fig. 2.**—Horizontal section through the cranial vault, showing the conversion of the bones into an almost uniform layer of fibro-calcaceous material similar to that in the left humerus. A remnant of the left frontal sinus is seen. The dura mater shows patches of vascularisation, mottling due to calcareous deposits and thickening with striation along the mid-line.

**Fig. 3.**—Frontal section of the left femur, showing maroon coloured areas in the marrow, slight thickening of the cortex but no other definite changes to the naked eye.

**Plate III.**

**Fig. 1.**—Giant cell area in osteitis fibrosa. a, fibrillar tissue; b, polymorphous cells fusing to form multinucleated cells; c, capillary; d, osteoclast giant cell with vacuolation. *N.B.* This figure serves also for the similar picture seen in "benign giant cell tumour"—myeloid sarcoma (cf. Plate XVIII., Figs. 2, 3, and Plate XX., Fig. 1).

**Fig. 2.**—Fibrosing "epulis"—a, fibrous tissue stroma; b, breaking up giant cells; c, capillary; d, osteoclast type of giant cell. (Figs. 1, 2, van Gieson's stain x 1000.)

**Plate IV.**

**Fig. 1.**—Malignant giant cell tumour of femur. b, tumour cell in mitosis; b₂, mononucleated giant cell; b₃, multinucleated giant cell; c, capillary; d, osteoid tissue. (Van Gieson's stain x 1000.)

**Fig. 2.**—Types of giant cells. a₁, a₂, giant cells of benign giant cell area or tumour (cf. Plate III., Fig. 1); b₁, b₂, b₃, tumour cells of malignant giant-celled tumour (cf. Plate IV., Fig. 1); c, bone marrow giant cells—megakaryocyte. (Van Gieson's stain x 1000.)

**Plate V.**

**Fig. 1.**—Femur. Cortex undergoing lacunar erosion; the enlarged Haversian spaces showing capillary and cellular network. a, cells fusing to form giant cell; b, syncyial osteoclast giant cell with fibrillated border next bone; c, capillary.

**Fig. 2.**—Femur. Similar picture. Narrow bridge of old bone between two enlarged Haversian spaces. a, rows of proliferated osteoblasts—possibly osteolytic in function; b, row of syncyial osteoclast giant cells; c, fibrillar network—the earliest stage of the fibrous tissue substitution. (Figs. 1, 2, frozen sections; van Gieson's stain x 500.)

**Plate VI.**

**Figs. 1-3.**—Characteristics of old and new bone with Schmorl's stain.

**Fig. 1.**—Earliest stage of halaristeretic atrophy in Haversian space of cortex of femur. a, peripheral zone of decalcification; b, bone corpuscle, showing canalicular processes. (x 1000.)

**Fig. 2.**—Slightly later stage. a, irregular decalcification of peripheral zone; b, pericellular zone of decalcification with loss of canalicular processes. (x 1000.)

**Fig. 3.**—New bone in humerus. a, irregular grouping of bone cells and radiating arrangement of canalicular processes; b, newest zone of osteoid tissue deposited by osteoblasts. (x 1000.)

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Plate VII.

Figs. 1-3.—Various aspects of bone resorption in the basi-sphenoid and the continuity of the fibres of the connective tissue with the fibres in the bone (Sharpey’s fibres). 

- **a**, fibrillar tissue; 
- **b**, old bone; 
- **c**, bone cell; 
- **d**, Sharpey’s fibres; 
- **e**, proliferated osteoblasts; 
- **f**, osteoclast giant cells. (Van Gieson’s stain × 500.)

Fig. 4.—Subperiosteal new bone formation in early stage of osteitis fibrosa. 

- **a**, old bone; 
- **b**, network of new bone forming from deep layer of periosteum; 
- **c**, periosteum. (Van Gieson’s stain × 400.)

Fig. 5.—Formation of giant cell area in fibrous tissue of humerus. 

- **a**, fibrous tissue; 
- **b**, cells fusing to form giant cells; 
- **c**, capillary with endothelial cells in mitosis; 
- **e’**, cells proliferating off from capillary; 
- **d**, osteoclast giant cell. (Van Gieson’s stain × 500.)

Fig. 6.—Osteoclast giant cell in lacunar erosion. 

- **a**, old bone; 
- **b**, osteoclast cell; 
- **b’**, its fibrillar border; 
- **c**, embryonic uninucleated cells. (Van Gieson’s stain × 500.)

Plate VIII.

Figs. 1-3.—Showing stages in the transformation of the fibrillar tissue into a fibro-osseoid tissue. 

- **a**, fibrillar tissue; 
- **b**, the osteoid transformation—osseo-mucin instead of fibrogen; 
- **c**, capillary. (Van Gieson’s stain × 500.)

Figs. 4-5.—The osseo-mucinic tissue becoming arranged into trabecular strands, in which the original connective tissue cells become enclosed as bone cells. 

- **a**, fibrillar tissue; 
- **b**, osteoid tissue; 
- **c**, bone corpuscle; 
- **d**, Sharpey’s fibres—continuous with fibres of fibrous tissue; 
- **e**, osteoblasts aligning themselves on the borders of the trabeculae to lay down lamellar bone. (Van Gieson’s stain × 500.)

Fig. 6.—Tip of a trabecular strand cut transversely. (Van Gieson’s stain × 500.)

Plate IX.

Longitudinal section of shaft of the femur showing osteoporosis. (Van Gieson’s stain × 3.)

Plate X.

Transverse section of shaft of the femur. 

- **x** = Plate XVI., Fig. 1; 
- **y** = Plate XVI., Fig. 2. (Van Gieson’s stain × 8.)

Plate XI.

Transverse section of the shaft of the humerus, showing complete fibro-osseoid tissue substitution. 

- **x** = Plate VIII., Figs. 1-6; 
- **y** = Plate XVIII., Figs. 2, 3. (Hæmatoxylin and eosin × 6.)

Plates XII.-XIV.

Head, shaft, and lower end of humerus, showing complete fibro-osseoid tissue substitution. Plate XIII. includes the portion of the shaft with the sites of both fractures; these are almost impossible to recognise in the reconstruction of new bone. (Hæmatoxylin and eosin × 2½. Cf. Plate II. Fig. 1, A. B. C.)

Plate XV.

Fig. 1.—Vault of the skull, showing complete fibro-osseoid tissue substitution and numerous giant cell areas. 

- **a’,** calcareous deposit in the dura mater. (Hæmatoxylin and eosin × 6.)

Fig. 2.—Cross-section of rib, showing disappearance of central trabeculae and osteoporosis of cortex. 

- **x** = Plate XIX., Fig. 1. (Hæmatoxylin and eosin × 6.)

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PLATE XVI.

Various stages and aspects of bone resorption in the femur. Frozen sections. Figs. 1-5; van Gieson's stain. a, osteoclast resorption; b, cellular content of Haversian space; f, commencing fibrous tissue formation.

Fig. 1.—Plate X. x. Early stage in bone removal. x = Plate VI., Fig. 1. (x 30.)

Fig. 2.—Plate X. y. Late stage in bone removal. x = Fig. 3; y = Fig. 4; z = Plate V., Fig. 2; p, periosteum. (x 30.)

Figs. 3, 4.—Lacunar erosion and commencing fibrous tissue substitution; correspond to Fig. 2, x and y. z = Plate V., Fig. 2. (x 400.)

Fig. 5.—Similar changes—showing osteoblast proliferation—possibly osteolytic in function (l) and osteoclast resorption (a) and bone cell with pericellular halisteresis (c). (x 400.)

Fig. 6.—Schmorl's stain to bring out canalicular processes of bone cells (bc.) (x 500.)

PLATE XVII.

Showing various stages of fibro-osseous tissue substitution—all the figures (except No. 3) taken from Plate XI. x, Figs. 1-5. (Van Gieson's stain.)

Fig. 1.—Fibrillar tissue in its transition to strands of osseo-mucin. (x 60.)

Figs. 2, 3, 4.—Similar pictures, showing continuity between fibres of the connective tissue and the fibres forming the reticular groundwork of the osseo-mucinous strands (Figs. 2-4 x 100).

Fig. 5.—New bone trabeculae arranged in a network. By deposition of new bone by the layers of osteoblasts (obl) lamellar bone is laid down by apposition and this, together with lacunar erosion by osteoclasts (ocl) leads to the reconstruction of bone architecture. (x 70.)

Fig. 6.—Strands of new bone in a fibrillar tissue, showing the osteoid zone on the older axial portion. (Schmorl's stain x 100.)

PLATE XVIII.

Figs. 1-3.—Stages in the formation of giant cell areas; Figs. 4-6 types of early cyst formation.

Fig. 1.—Fragments of bone surrounded by osteoclasts; other giant cells, scattered in the fibro-cellular tissue, left after the complete resorption of other bone fragments. (Van Gieson's stain x 70.)

Figs. 2 and 3.—Low and high power view of a giant cell area (Plate III., Fig. 1, and Plate XI. y). Hematoxylin and eosin (Fig. 2, x 70; Fig. 3, x 500).

Fig. 4.—Pre-cystic stages from edema. (Van Gieson's stain x 70.)

Fig. 5.—Pre-cystic stages from hemorrhages round giant cells. (Hematoxylin and eosin x 70.)

Fig. 6.—Small cysts from retraction of fibrous and osseo-mucinous tissue. (Van Gieson's stain x 60.)

PLATE XIX.

Fig. 1.—Rib (Plate XV., Fig. 2a) showing (1) resorption of old bone without the aid of osteoclasts—probably by the osteolytic activity of proliferated osteoblasts (obl); (2) fibrosis of the bone marrow commencing as a connective zone tissue at the periphery of the cancellous spaces (fd). (Hematoxylin and eosin x 40.)

Fig. 2.—Rib. Similar resorption of old bone by osteoblast activity (obl) and fibrous tissue substitution of cellular bone marrow (fd). (Van Gieson's stain x 40.)

Fig. 3.—Basi-sphenoid. Cancellous bone undergoing resorption by osteoclasts (ocl) and fibrous tissue substitution (fd). p. b. v., a perforating blood-vessel. (Frozen section. Van Gieson's stain x 30.)
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Fig. 4.—Basi-sphenoid. Bone resorption and complete fibrous tissue substitution of the cellular bone marrow. (Frozen section. Van Gieson's stain × 30.)

Figs. 5, 6.—Early stages of reconstruction of bone architecture. The reticular bone showing lamellar apposition and osteoclast resorption. (Van Gieson's stain, Fig. 5, × 50; Fig. 6, × 50.)

**Plate XX.**

Fig. 1.—Benign giant-celled tumour of bone epulis (cf. Plate III., Fig. 1, and Plate XVIII., Figs. 2, 3). (Hæmat. and eosin. × 50.)

Fig. 2.—Epulis becoming fibrous and showing new bone formation in the fibrous tissue. (Frozen section. Van Gieson's stain × 50.)

Fig. 3.—Malignant giant-celled tumour of femur—osteogenic sarcoma with finer and coarser strands of new bone and numerous tumour giant cells. ogc, osteogenic tumour cells (cf. Pl. IV., Figs. 1, 2.) (Van Gieson's stain × 70.)

Fig. 4.—Strands of reticular new bone (parosteal) in the malignant giant-celled tumour of Fig. 3. Such a portion of tissue might be removed for diagnosis. (Hæmat. and eosin. × 70.)

Figs. 5, 6.—Osteoplastic carcinomatosis of rib in case of scirrhus of breast, showing destruction of old bone by osteolytic action of tumour cells (kc) and intense new formation of osteoid reticular bone in the fibrous tissue (Fig. 5, van Gieson's stain, × 50; Fig. 6, van Gieson's stain, × 150).

**Plate XXI.**

Fig. 1.—Natural size drawing of parathyroid tumour P.T. in its relation to the thyroid gland—viewed from posterior aspect. R.T. and L.T., right and left thyroid lobes; N.P., Normal parathyroid gland; E., oesophagus; E-G, epiglottis.

Fig. 2.—Structure of parathyroid tumour. a, fine papillary strands; b, connective tissue septum dividing tumour into lobules. (Hæmat. and eosin. × 80.)

Fig. 3.—Structure of normal parathyroid gland. a, “chief” cells; b, oxyphile cells; c, lining of small cyst. (Hæmat. and eosin. × 300.)

**Plate XXII.**

Figs. 1-3.—Calcareous deposits in the various organs. (Hæmat. and eosin.)

Fig. 1.—Blood-vessels in the outer coat of the stomach wall. ( × 50.)

Fig. 2.—Stomach wall—mucosa and muscularis mucosae; replacement of the interglandular tissue by a network of calcareous fibrils and granules; muscularis mucosae intact. (Fig. 2 × 50.)

Fig. 3.—Liver; change in the portal tracts and sinusoids. ( × 40.)
