BONE FORMATION IN SCLEROTIC ARTERIES.*

By LEO BUERGER and ADÈLE OPPENHEIMER.

(*From the Pathological Laboratory, Mt. Sinai Hospital, New York.*)

PLATES XXIV AND XXV.

In recent years a number of papers have appeared tending to show that the formation of bone in arteries is not as rare as has been generally supposed. In the large vessels in six cases of arteriosclerosis, Mönckeberg was able to find sixteen osseous foci. The older literature seems to indicate that the aorta and heart valves are the favorite sites for ossifying processes in the cardio-vascular system. Mönckeberg's contribution, however, has clearly demonstrated that not only the aorta, but also vessels of the extremities, such as the femoral, the anterior and posterior tibial arteries may not infrequently be involved.

While engaged in a study of the pathology of vessels in gangrene of the lower extremities, we encountered rather extensive areas of ossification in the arteries of two limbs, both obtained from patients afflicted with advanced arteriosclerosis. We wish to record the histological features presented by one of the cases, to point out how these differ from what has been observed by other authors and to discuss in brief the theories that have been advanced in explanation of heteroplastic bone formation.

Our case was particularly interesting because of the large number of bony plaques and because so many of the larger arteries of the extremity were affected. Either true bone or osteoid tissue was found distributed throughout their length in the following arteries: the anterior and posterior tibial, the peroneal, and the plantar; in short, in all of the five vessels examined except the dorsalis pedis.[1] A perusal of the literature failed to reveal any record of bone for-

* Received for publication February 18, 1908.

[1] We are unable to state the extent of the areas of ossification because we made no serial sections; but in one instance, as was seen in longitudinal section, the osteoid patch extended the entire length of the piece, namely, 3 mm.

mation in either the plantar or peroneal vessels and our case seems therefore to be unique in the distribution of the lesions.

The arteries removed for examination were dissected out in continuity from the limb. The macroscopic lesions of interest may be embodied in a brief description of the extremity, as follows: The left leg has been amputated 15 cm. above the knee joint. The second toe is greenish black, dry and mummified. On the inner side of the big toe is a large bulla filled with serum and blood. The anterior tibial artery shows typical changes of arteriosclerosis in various stages; numerous patches of atheroma, white areas of thickened intima and calcification. In places there is a large accumulation of atheromatous tissue which presents itself on section as a crescentic obturating mass and leaves but a small portion of the lumen of the vessels patent. The dorsalis pedis artery is similarly affected. The posterior tibial and peroneal arteries are also sclerotic; in some parts they are patent, in others filled by recent thrombi. The plantar arteries are of the pipe-stem variety. The lesions, in short, are those of advanced arteriosclerosis with calcification.

A number of pieces were removed for histological study from each of the following arteries: anterior and posterior tibial, dorsalis pedis, peroneal and plantar. The tissues were decalcified with 5 per cent. nitric acid in the usual way, imbedded in celloidin and stained with hematoxylin, with hematoxylin and eosin, by Van Giesen's method, with Unna's polychrome methylene blue, with orcein, and with Weigert's elastic tissue stain. Special methods were employed in the search for hemosiderin and amyloid changes.[2]

Before describing the histologic picture we may call particular attention not only to the identity of location of the ossifying process in the various arteries, but also to the uniformity in the structure in different situations. Osseous and osteoid tissue were only discovered in the middle coat; and the process of bone formation showed but slight variations from a fixed type. We will therefore discuss in detail the most common appearances, namely those exemplified in many of the sections of the posterior tibial artery, and

[2] The test for amyloid proved negative; so that the presence of amyloid, which has been pointed out by Poscharissky as important, does not seem in our case to be essential to ossification.

only mention in brief any deviations or peculiarities encountered elsewhere.

Histology.—The most striking pathological changes may be classified under the following groups: (1) the lesions of arteriosclerosis; (2) the lesions dependent upon thrombosis; (3) the lesions belonging to the ossifying process.

1. *The Lesions of Arteriosclerosis.*—The arteriosclerotic changes involve both the intima and media. In the intima we find the usual proliferative process, varying considerably in degree in the same and in different vessels. Wherever the lesions are advanced, degeneration and atheroma are also to be seen. The media of almost all the vessels is the site of calcific deposits, either in the shape of lime plates which occupy a large part of the circumference of the artery, in the form of irregular nodular plaques representing calcified atheromatous areas, or as a diffuse infiltration of the media with lime salts (see Fig. 1).

2. *Thrombosis.*—Thrombosis with vascularization and connective tissue proliferation in the clot is seen in the posterior tibial (see Fig. 1). The various stages of organization are well represented in different situations along the course of the artery; in some places there is very recent thrombosis, in others the lumen of the vessel is obliterated by well-organized, canalized tissue.

3. *The Ossifying Process.*—This occurs only in the media, and for the most part in the presence of lime (see Fig. 1). Calcific deposits and young connective tissue appear to be the *sine qua non* for the genesis of bony proliferation; we see the lime and connective tissue intimately associated with the process of bone formation in all the specimens studied (see Fig. 2).

Occupying a large portion of the media, in the form of an arc-like band, varying considerably in thickness and extent, we find a zone of young connective tissue. This is composed of numerous capillaries, spindle-shaped cells, lymphoid cells and a small amount of fibrillar substance. It apparently invades, destroys and replaces the muscle fibers. Evidence of the disintegration and substitution of the musculature is furnished by degenerate muscle cells without nuclei, by nuclei which fail to stain, and by reactive changes on the part of the muscle. These last are multiplication of the nuclei, the formation of muscle giant cells and the conversion of many muscular elements into strands of connective tissue.

The young vascular fibrous tissue communicates at frequent intervals with the adventitia by means of well developed smaller or larger capillaries. These penetrate the media obliquely in cross-sections of the arteries and are often seen surrounded by a few round and spindle-shaped cells. As regards the constitution of the young connective tissue certain variations may be observed; the differences are mainly in the vascularity, density or fibrous nature, and in the presence of lymphoid or round cells. Wherever the process is an old one we are apt to encounter tissue rich in fibrous elements, and this sometimes in the vicinity of well developed and maturing bony tissue; on the other hand, there are many areas made up of round cells infiltrating the media in streaks, or larger, broader conglomerations which probably represent very early stages in the origin of the connective tissue above described.

The Osseous and Osteoid Tissue.—Where the young connective tissue comes into contact with a lime plaque a conversion of a portion of the latter into osteoid tissue sometimes occurs. Thus we find large portions of some of the lime plaques altered into a homogeneous substance which stains well with eosin and in which a few or a moderate number of nucleated elements are included. It is most frequently seen along the outer margins and at extremities of the calcareous plaques as a narrow strip bordering a plate of lime or as a peninsular projection capping a calcareous plate (see Fig. 3). Close scrutiny makes it evident that this new tissue always substitutes an area previously occupied by lime, in other words, represents a transformation of part of a lime plaque into a peculiar new substance—the ground substance of bone. A very sharp, notched line with the concavities toward the ground substance of the bone separates this from the lime. On the other side there is connective tissue varying somewhat in its architecture. It is in such places, then, that a deposition of osteoid tissue occurs *pari passu* with an absorption or erosion of the calcified media.

All the stages from the youngest variety of osteoid tissue up to true bone can be traced in the sections. Where the process is recent, the number of included cells is small; the nuclei of the cells are large, and signs of compression, shrinkage and alteration in cellular outline are not manifest. In the older types we see a gradual change into true bone corpuscles. Between the young and the old variety an interesting series of cytomorphic changes may be seen. The ground substance, too, although for the most part of the "osteoid" type, shows varying degrees of calcification, and is in places practically indistinguishable from true bone matrix.

That side of the osteoid or osseous patch which is opposed to the lime plate is applied directly to the osteogenetic connective tissue. Nowhere, however, are typical osteoblasts to be found; in place of these there are flattened endothelial cells, or larger elements of the fibroblast type. Such cells are actively engaged in a double process, one, bone resorption, another, the deposition of either bone matrix or osteoid substance.

The Process of Resorption of Calcific Material.—Resorption of calcific material is evidently an essential stage in the production of bony tissue and is effected in main by the action of giant cells and by the young connective tissue cells themselves (see Figs. 4 and 5). That still another modus can play a rôle in this process is seen in a number of places where capillaries appear to empty their contents along one margin of a lime plate. In such places, a notched border bears testimony to the fact that resorption is taking place. Sometimes large blood sinuses adjoin the lime plates, particularly where marrow spaces are being formed (see Figs. 2 and 4).

This resorptive metamorphosis is usually accompanied by a deposition of osteoid tissue, corresponding in extent and conformation to the areas previously occupied by lime (see Fig. 3). Here and there, however, large bays have been produced in the ends of lime plates by the invasion of young connective tissue without any vestige of osteoid or osseous tissue (see Fig. 5), and the old site of the lime plates may be occupied by the persisting young connective tissue or by the marrow cavities which are being formed.

The most advanced resorptive changes—and with these the most marked osteoplasia—occur at the extremities of the lime plates. Here the connective tissue cells lying in concavities or notches of the lime patches seem to invade and cause the disappearance of the calcific material. When a band of osteoid tissue intervenes between osteogenetic connective tissue and the lime plate, the same resorption takes place except that it goes hand in hand with a deposition of osteoid substance. It is in such areas that the wide sphere of influence exerted by the osteogenetic tissue becomes notable. Separated from the lime by newly deposited ground substance, the cellular elements still manifest their power of inducing active resorption.

The Formation of Marrow Spaces.—Where the transformation of the lime plates into osteoid or osseous tissue has evidently been of long duration, and where the trabeculæ of bone matrix include larger or smaller areas of young connective tissue, there we may speak of the production of marrow spaces. In such places the connective tissue usually shows large dilated capillaries and blood sinuses. The former are filled with blood, but show no bone-marrow cells. The latter adjoin eroded lime plates or lie between such plates and bands of osteoid tissue. They contain red and white blood cells and a few giant cells resembling osteoclasts. The picture presented gives the impression of an unfinished stage in production of bone marrow. However the elements of true bone marrow are absent; and we have here rather the result of the inclusion of osteogenetic connective tissue between bony trabeculæ than the primary production of true marrow.

Giant Cells.—Giant cells of various types are found scattered throughout the media where the latter shows invasion by young connective tissue. Usually they lie in concavities of the lime plaques which they are apparently engaged in resorbing. Others are seen where there is no lime and still others where there is a very faint pulverous infiltration with calcium salts. As a rule they have rather large irregularly shaped bodies which stain well with eosin, and show small ovoid nuclei situated either centrally or scattered without definite arrangement throughout the cell body. Here and there a giant cell of bizarre form appears to be almost a continuation of a lime spicule; for the line of demarcation between calcium and body of the cell is incomplete (see Fig. 5). Such cells remind one of osteoid tissue. Some of the giant cells have very long bodies that seem to be adapted to the concavities of the lime plates in which they lie.

Variations in Histological Picture.—A very few sections showed the following deviations from the usual type above described: the construction of Haversian canals, the formation of osteoid tissue by a modification of the collagenous fibrils, and finally small areas resembling embryonic cartilage.

Fig. 6 shows a longitudinal section of the posterior tibial artery with one complete Haversian canal, another in the making. Here, too, there are indications of concentric disposition of the bone cells, and the apposition of new bone in the normal fashion.

A number of specimens exemplified a more unusual type of osteogenesis by transformation of connective or possible degenerate muscle fibers adjoining a lime plaque into strands of bone matrix. This may be seen in Fig. 7, where a tongue-like process of osteoid tissue has its origin in fibrous tissue quite independent of the neighboring calcific patch. Here, too, the young ossifying connective tissue plays a rôle, for it can be traced directly into the newly formed matrix, in whose production it is evidently engaged.

Finally, interesting foci of cartilage similar to the embryonal type were found in the plantar arteries. Such areas replace calcified atheromatous nodules and are made up of large polygonal or spheroidal cells, at times grouped in twos or fours, at times in the shape of larger conglomerations of cells with varying amount of intercellular substances. Cells not unlike these were seen in calcified atheromatous patches and at the extremities of calcified plaques in other arteries. Such cells are usually surrounded by a well-defined, somewhat refractile layer; and now and again appear to take part in laying down a homogeneous substance similar to the usual osteoid matrix.

Summarizing our anatomical findings we may say that we are dealing with an exquisite example of extensive bone formation in practically all of the larger arteries of the lower extremity; that the process is evoked in the media by the activity of a young connective tissue, the original elements of which apparently have migrated from the adventitia in the shape of vascular sprouts; and that where the proliferating connective tissue comes into contact with calcium salts, either true osteoid tissue or true bone is elaborated. The osteoid tissue arises in a manner analogous to the origin of true bone; sometimes strands of the ground substance of bone appear in the connective tissue and merge into the collagenous fibrils as if they were a modification of these; and more frequently osteoid material is formed in lime plaques. The process is therefore for the most part not unlike that of endochondral bone formation. The lime plates of the media may be said to correspond to the calcified cartilaginous matrix of the long bone; the penetration of a blood vessel or bud from the periosteum into the calcified cartilage finds its parallel in the invasion of the media by the young vascular tissue; the disintegration of the calcified cartilaginous substance, the lodging of an osteogenetic layer of so-called osteoblasts, the appearance of osteoclasts are simulated. The progressive differentiation of the connective tissue cell into a true bone cell with canaliculi is also imitated. It is only in the absence of true primary marrow spaces which develop in the embryonal bone that we find a marked deviation from the normal process.

The occurrence of newly formed bone outside of the cardiovascular system is not at all infrequent. The following sites have been recorded in the literature: pia and choroid (Virchow), adductor muscles (Ponfick), bladder mucosa (Morpurgo), laparotomy scar (Askanazy), lung (Pollack, Poscharissky), pleura (Laboulin, Hurtado and Pollack), dura (Cruveillhier), eye (Pagenstecher, Klebs, Knapp), stomach (Minkiewicz), liver (Cornil, Ranvier), and lymph nodes (Pollack and Poscharissky). In an examination of the lungs from one hundred autopsies, Pollack was able to demonstrate the presence of osseous nodules in sixteen cases; and Poscharissky, limiting his search to calcareous foci, succeeded in demonstrating bone in fully 60.7 per cent. of the foci examined.

When we compare the frequency of these findings with the relatively small number of reported instances of bone production in arteries, we can not but believe, with Mönckeberg and Bunting, that a more thorough investigation of sclerotic arteries of the lower extremity would substantiate the view that the process is not at all uncommon. Whereas, before the year 1901, we had only the few isolated examples recorded by Howse, Marchand, Paul, Cohn, Kryloff, v. Schrötter and Röhmer, since then the publication of Mönckeberg's paper, confirmed by our own observations, has enlarged the number of cases and has changed our notion as to their rarity.

If we now direct our attention to the histological features of the process, we find that, although certain essentials in the production of osseous tissue are regularly seen in all the cases, quite a variety of deviations from normal physiological osteoplastic changes have been described by different authors. Most observers are agreed in the opinion that lime and a vascular young connective tissue are most frequently engaged in, and apparently directly responsible for, the changes leading to heteroplastic bone formation. Bone without marrow and bone with true fatty, or even with red, cellular marrow, have been encountered. Sometimes the so-called osteoid tissue preponderates, at other times progressive metamorphosis into mature bone is evident. Thus Bunting found bone enclosing spaces in which a delicate reticulum, fat cells and cells of bone-marrow type gave the picture of true red marrow. In fact practically all the elements of red marrow were represented. In his case the site of the process was a sclerotic aorta; the intima was penetrated by vessels surrounded by young connective tissue and showed production of cancellous bone at points where the connective tissue found its way into lime plates.

The minute and carefully detailed description given by Mönckeberg in h paper is particularly illuminating and interesting from our standpoint because our findings so nearly correspond with his. In his arteries, too, there was an invasion of the media with vessels which gave rise to the appearance of young connective tissue, due, in his opinion, not only to a proliferation of the newly immigrated elements, but also to a hyperplasia of the preëxisting connective tissue cells of the media.[3] He considers the presence of lime and of young connective tissue and the process of resorption, the essential factors underlying the genesis of the bone. His view of the sequence of changes that occur may be thus summarized *seriatim:* (1) The immigration of vessels into the diseased vessel wall. (2) The production of a loose tissue, rich in cells, around the vessels and in the vicinity of lime plates. (3) Lacunar resorption of lime

[3] Pollack, too, believes that the old scar tissue rather than new granulation tissue forms osteoid tissue and bone by metaplasia.

and hyaline tissue by virtue of the activity of the newly formed tissue especially of certain pigment cells. (4) Lodging of connective tissue cells along the borders of lime areas with deposition of bone ground substance, inclusion of the cells and their transformation into true bone corpuscles. (5) Conversion of the osteogenetic tissue secondarily into marrow. Inasmuch as the initial stages of the process show no primary marrow formation, Mönckeberg holds that we are not justified in speaking of the presence of true osteoblasts; indeed we should regard the ossific changes as being produced by a metaplasia of connective tissue.

Quite a different view has been propounded by Röhmer who declares that the formation of primary marrow spaces marks the inception of the ossification. There is first a lymphoid tissue, then the building up of fatty marrow, the peripheral cells of which become osteoblasts and form bone out of lime. Cohn, from a study of calcareous plates in the aorta and in the heart valves, concurs in this conception.

In a scholarly paper on bone formation Bunting has recently discussed at length the various theories that have been advanced in explanation of the very interesting phenomena of heteroplastic bone formation in arteries. He showed that Cohnheim's theory of embryonal displacement was not applicable, and suggests two views, either of which may obtain: first, that there is a direct metaplasia of connective tissue into bone after the manner of callus formation, and second, that the calcific material is eroded with the formation of vascularized spaces containing young connective tissue cells, some of which take on the function of osteoblasts and lay down bone, some of the osteoblasts becoming included and forming the bone corpuscles.

Whereas the advocates of the "metaplasia theory" argue that a change of connective tissue into osseous tissue may occur, their opponents wish to show that bone can only be formed in connection with cartilaginous or osteogenetic layers, or from some displaced embryonal bone or cartilage matrix. Von Hansemann and Ribbert are of the opinion that metaplasia rarely comes into play. Whereas Lubarsch and Pollack, finding bone in almost every calcareous nodule of the lung examined by them, think that it arises by metaplasia from connective tissue, von Hansemann believes that it has its origin in islands of perichondrium or cartilage. Whatever the conditions may be in other organs, the bone formation in arteries must certainly be explained on the basis of a theory of metaplasia. It would be a work of supererogation to dilate at length upon this phase of the subject; and we will therefore confine ourselves to the conclusions which we have been able to draw from a study of our own cases and from the consideration of the findings of other authors.

It is generally conceded that the presence of lime and young connective tissue is essential to heteroplastic bone formation.[4] The young mesoblastic elements evidently are engaged in the deposition of osteoid substance. The following questions then arise: What influences are exerted by the lime? What causes the appearance of the connective tissue? The intimate association of the lime with the osteogenetic tissue makes it more than likely that the calcium exerts some stimulus upon the young connective tissue which is possibly effective in producing a transformation from the undifferentiated mesoblastic cell into an element comparable in its function to the so-called osteoblast. Although Mönckeberg refuses to call the cells osteoblasts, because they are not developed in primary marrow, we cannot but attribute to them the same rôle that belongs to normal bone-producing elements. Perhaps the lime has not such an important rôle, but the metaplasia into osteogenetic tissue has already occurred before the young connective tissue comes into contact with it. At all events the presence of the lime is essential inasmuch as its erosion or resorption furnishes the proper condition for the elaboration by the connective tissue cells of a homogeneous ground substance, the matrix of bone.

As regards the invasion of the media by vascular connective tissue, this phenomenon may probably be evoked by a variety of causes. Bunting suggests with Paul, that the fracture of lime plates calls forth this immigration of vessels and proliferation of tissue. In our specimens, however, this was not the case; for although old fractures of lime plates undergoing consolidation could

[4] The fact that most of the osteoid tissue lies along the outer margins of the calcified plaques, namely, where the incoming vascular young connective tissue must first meet the lime, is significant.

be observed, such places were neither the seat of young connective tissue infiltrations nor could any bone formation be discovered in their vicinity. In our studies on diseased vessels we have encountered vascular and connective tissue proliferation in the media in the following conditions: as a reparative process, as a compensatory process and as a manifestation of inflammatory change. Thus we frequently find invasion of the media in attempts at organization of thrombi, in the production of collateral circulation by canalization and vascularization of obliterating intima and in disease of the middle coat itself. The most extensive proliferative changes and the most marked instances of ossification seem in our cases to occur in the vessels which are the site of either organizing thrombi or vascularized obliterating thickenings of the intima. These circumstances would seem to point to the view that perhaps the primary entrance of vessels in the media is incited by the changes incident to thrombosis and vascularization of the intima. And further that when the new tissue comes into contact with the lime, certain new influences come into play which cause a renewed activity, a transformation into osteogenetic tissue with the consequent production of true bone. Be this as it may, we cannot ignore the presence of the lime plates themselves as factors in the connective tissue invasion as such, all the more so as now and then connective tissue may be present without vascularized obliterating intima or without canalized thrombi. Doubtless all of the causative factors mentioned may exert their part in the process.

It is of interest in this connection to call attention to the recent work of Harvey who was able to induce bone production in the aorta of rabbits by the application of irritants to the vessel wall. After painting the outer surface of the aorta in some cases with a three per cent. solution of silver nitrate and in others with a two per cent. solution of cupric sulphate, bone with Haversian canals, with bone marrow or bone alone, or osteoid tissue developed, in areas of calcareous degeneration, in a number of rabbits after about two to six months had elapsed. Harvey accepts the hypothesis that there is a metaplasia of connective tissue, that is, a direct conversion of young fibrotic tissue into bone with possibly an intermediate step of cartilage-like tissue formation.

In our own cases we meet with two types of metaplasia: one is evidenced in the young tissue which lays down the ground substance of bone in eroded or absorbed lime areas; the other is shown in those elements that cause the deposition of ground substance in preëxisting connective tissue. In a very few places there are suggestions of cartilage production; but this cartilage is never transformed into bone.

Summing up our own view of the process we may say that by virtue of some stimulus, be it an organizing thrombus, an attempt at vascularization of obliterating pathological intima, or possibly the presence in the diseased mesial coat of lime alone, a penetration of the media with vessels takes place. This is followed by the proliferation of young connective tissue in the media which comes into contact with the lime; at such points of meeting, the young connective tissue cells manifest a new function by producing the ground substance of true bone.

We wish to express our indebtedness to Dr. F. S. Mandlebaum, director of the laboratory of Mt. Sinai Hospital, for the preparation of the photo-micrographs.

Explanation of Plates XXIV and XXV.

Fig. 1. Transverse section of posterior tibial artery. Lower left hand quadrant shows a lime plaque with bone formation in its right extremity. On the right the media shows a calcified atheromatous nodule. In the upper half there is considerable infiltration of the media with vascular young connective tissue. The lumen of the vessel is obliterated by an organizing thrombus.

Fig. 2. Bone and marrow formation in a lime plaque.

Fig. 3. A portion of the wall of the peroneal artery. The extremities of the dark calcified plaques on the right and left are tipped by osteoid tissue, which takes the place of areas previously occupied by lime.

Fig. 4. Posterior tibial artery (high power). The upper left hand quadrant shows pale osteoid and darker osseous tissue. The greater portion of the photograph is occupied by young vascular connective tissue. Below and to the right there is erosion of a lime plaque by blood and by an osteoclast in a free space.

Fig. 5. A portion of the media of the posterior tibial artery (high power). On the right is the eroded extremity of a lime plaque penetrated by young connective tissue and bordered by osteoclasts.

Fig. 6. Longitudinal section of posterior tibial artery. The dark area on the right is lime. In the concavity of the lime plaque is an annular area of osteoid tissue containing an Haversian canal.

Fig. 7. Media of posterior tibial artery. The dark area on the extreme

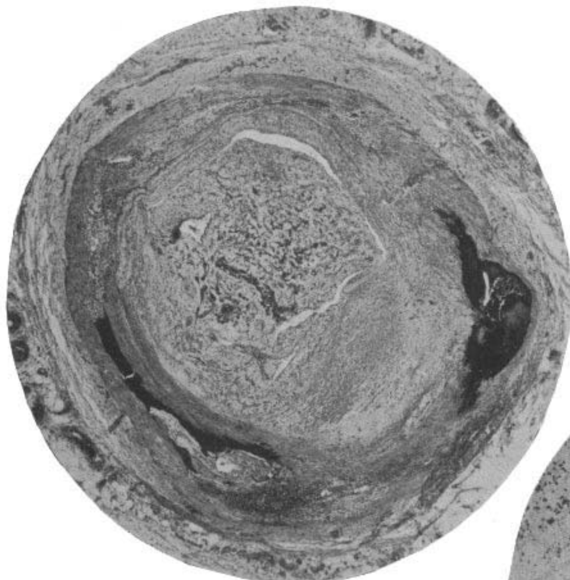

FIG. 1.

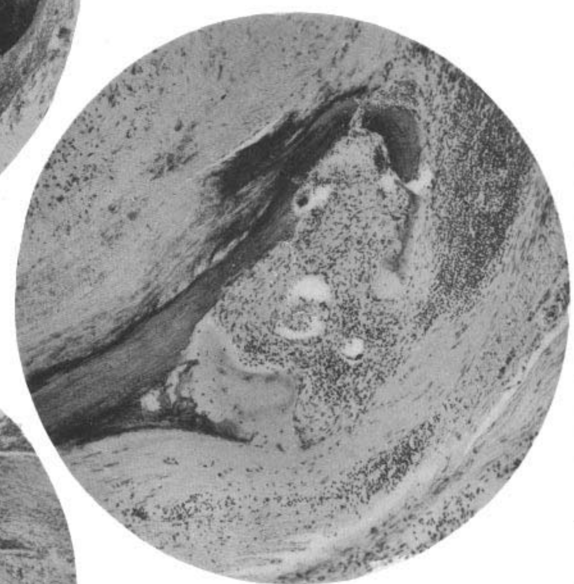

FIG. 2

FIG. 3.

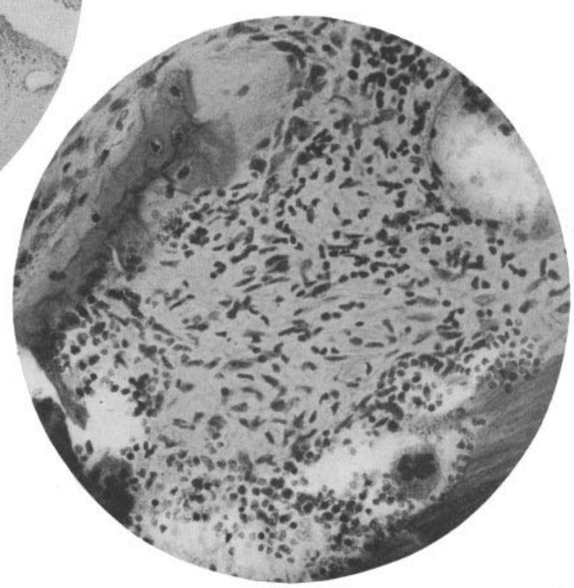

FIG. 4.

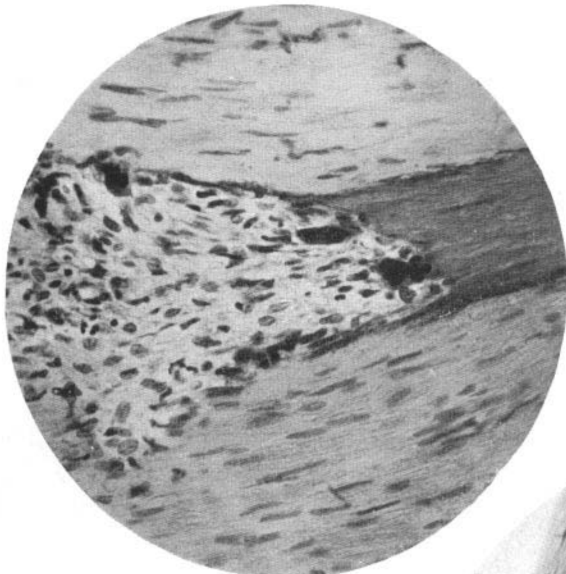

FIG. 5.

FIG. 6.

FIG. 7.

right is osteoid tissue which is drawn out into a tongue-like process. This represents connective tissue which has been directly changed into osteoid tissue by metaplasia.

BIBLIOGRAPHY.

Barth, *Ziegler's Beiträge,* 1895, xvii, 65.

Bensen, Beiträge z. Kenntniss von der heteroplastischen Knochenbildung, Göttingen, 1898, Inaug. Dissert. Cited by Pollack.

Bunting, *Jour. of Exper. Med.,* 1906, viii, 365.

Bunting, *Folia Hæmatol.,* 1906, iii, 245.

Cohn, *Virchow's Archiv,* 1886, cvi, 378.

Harvey, *Jour. of Med. Research,* 1907, xvii, 25.

Howse, *Trans. of Path. Soc.,* London, 1877, xxviii, 90.

Klebs, Path. Anat., i, p. 408. Cited by Poscharissky.

Marchand, Eulenberg's Real-Encyclopädie, 2d Edition, 1885, i, 693.

Mönckeberg, *Virchow's Archiv,* clxvii, 1902, 191.

Paul, *Brit. Med. Jour.,* 1886, i, 546.

Pollack, *Virchow's Archiv,* 1901, clxv, 129.

Poscharissky, *Ziegler's Beiträge,* 1905, xxxviii, 135.

Röhmer, *Virchow's Archiv,* 1901, clxvi, 13.

Rosenstein, *Virchow's Archiv,* 1900, clxii, 100.

Sacerdotti and Frattin, *Virchow's Archiv,* 1902, clxviii, 431.

Satterlee, *Proc. New York Path. Soc.,* 1906, vi, 124.

Thoma, General Pathology (Bruce), 1896, i, 499.

Thorel, *Ergebnisse d. allg. Path. und path. Anat.,* 1904, ix, 936.

v. Schrötter, Nothnagels Handbuch, 1901, xv, Part 2.