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Journal of Anatomy and Physiology.

OBSERVATIONS ON THE HISTOLOGY OF FRACTURE REPAIR IN MAN.

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In 1853 Sir James Paget wrote[1]—"I cannot tell the conditions which will determine in each case the route of development towards bone that the reparative material (in fractures) will take, nor in what measure the differences that may be observed are to be ascribed to the seat or nature of the injury, or to the conditions of the patient. All these things have yet to be determined; and I believe that years of patient and well-directed investigation will be requisite for them."

The state of our knowledge on this subject is to-day but little advanced from what it was thirty years ago. Opportunities of studying the repair of fractures in man are so rare, and the modes of preparing the tissues for histological examination are so tedious and troublesome, that it is not surprising that few have directed close or prolonged attention to the subject. Such investigations as have been recorded refer almost entirely to fractures in the lower animals, which, as Sir James Paget has pointed out, but others seem to have forgotten, are to be taken only in a limited sense as illustrative of the process of fracture repair in man.

Proposing to myself the line of inquiry suggested in the above quotation, I have, during the past three years, made careful studies of all the cases of uniting fracture which have come into the dead-house of the Bristol Infirmary. Those cases of fracture, numerous in every large accident hospital, which are caused by severe crushes or falls, and in which death takes place

[1] *Lectures on Surgical Pathology*, vol. i. p. 244.

in a few days from shock or other complications, are excluded from the list. Such cases, though they have their value as illustrating the very first changes common to all fractures, are of little use towards the study of special features of bone repair. A few specimens of fracture of from three to five days' standing (three of ribs, one of humerus, one of thigh, two of radius, and one of spine) were examined, with special reference to the amount and condition of the effused blood. These presented no peculiar features, and need not be more particularly referred to. The cases which were fully studied, and from which the material for the following paper was chiefly drawn, must be separately described. They were—

1. A museum preparation, injected, of a simple fracture of the femur of a child a year old. This preparation had been mounted for some years in spirit, with simply the soft tissues removed. When bisected longitudinally it proved to be a beautiful specimen, showing ensheathing and intermediate callus in the most perfect manner. There was scarcely any displacement, and the ensheathing callus, of spongy porous bone with its trabeculæ arranged perpendicularly to the surface of the shaft, was of a regular ovoid shape. The intermediate callus was only partially infiltrated with bone salts. The specimen is a typical one of the normal mode of repair as seen in fractures in the lower animals, and fully bears out Sir J. Paget's supposition that in fractures of long bones in young children the process of repair is "very like that described from the experiments on animals." Half the section was used up for microscopic study, but the soft tissues, from prolonged soaking in spirit, were not in good preservation.

2. An oblique fracture of the tibia, extending into the ankle joint, in a man aged thirty-six, who died on the ninth day of delirium tremens. There was double comminution of the fragments, and the periosteum was completely torn through, except over a portion of the smallest fragment. The fissures were filled with blood-clot in various stages of transformation. The specimen was valuable also as showing an early stage of periosteal inflammation, and the first beginnings of calcification in the powerful ligament which unites the lower extremities of the tibia and fibula. For this specimen I am indebted to the courtesy of Mr Pickering, house surgeon to the Bristol General Hospital.

3. A case of simple fracture of the femur in a man aged sixty-one, who died of an acute attack of erysipelas twenty-one days after receipt of the injury. The fracture was moderately oblique, and there was overlapping to the extent of about an inch, as well as some rotatory displacement of the fragments. The exposed medullary canal was, in each fragment, plugged with partially decolorised blood-clot, and a mass of brownish red clot lay at a little distance from the line of fracture in the sodden and condensed muscular tissue. Blood extravasations in various stages of decolorisation extended for several inches above and below the line of fracture into the various muscular septa. The periosteum was everywhere completely torn through except where it covered the linea aspera; and here it remained intact, stretched between the displaced fragments, enormously thickened, and traversed by several spicules of calcified material. Tracts of cartilaginous-looking substance ran in various directions through the condensed tissues surrounding the fracture; at many points these tracts were impregnated with calcareous salts.

4. A case of fracture of the body of a lower dorsal vertebra in a man aged thirty, who died, a month after the accident, from injury to the spinal cord. A wedge-shaped portion of the body had been pushed backwards, leaving a gap between the upper and the lower fragments of the vertebra, which was filled with organised blood-clot. New bone, developed chiefly in the ligamentous tissues overlying the vertebræ, had almost completely filled up the irregularities produced by the displacement of the comminuted fragment. Very little change, beyond a slight condensation, had taken place in the cancellated bone through which the fissures extended.

5. A compound fracture of the tibia and fibula in a man aged thirty-five. The limb was amputated on the twenty-second day, on account of extensive sloughing of the soft parts on the front of the leg. The case was treated antiseptically, the temperature being normal, and the slough being absolutely free from odour throughout. The front of the tibia was denuded for 3 inches above and 2 inches below the line of fracture; and here there was no sign of callus material. There was a considerable development of reparative material between the two bones, and a small amount of the same behind the tibia. The material

surrounding the fibula afforded many admirable specimens of the process of repair. This preparation had a practical as well as a pathological interest, proving that under antiseptics at least we may get a compound fracture repaired in the same way as a simple fracture, and not necessarily, as Dupuytren and others supposed, through the medium of granulation tissue only. But such a proof is, in these days, almost superfluous.

6. A simple fracture of the tibia and fibula in a woman aged forty, who died of an attack of acute bronchitis twenty-five days after the accident. This was a typical case of repair, there being no comminution and little displacement. Except in the exposed medullary canals, where there were some remains of partially decolorised clot, all appearances of blood-extravasation had disappeared. The reparative material, fibrous, cartilaginous, and in parts bony, surrounded and glued together the severed extremities.

7. An intra-capsular fracture of the neck of the femur in a woman aged sixty-one, who died of bronchitis four weeks after the accident. The fracture was close to the head of the femur, and traversed the neck in a plane at right angles to its axis. The crevices in the spongy bone were filled with partially organised blood-clot. On the upper aspect a bridge of fibro-cartilage united the fragments, in the substance of which, but not continuous with the old bone, was a nodule of calcified tissue about the size of a pea.

9. A case of fracture of an upper dorsal vertebra in a man aged twenty-five, who died of disease of the cord eleven months after the injury. A fracture very similar to that in case 4 was found perfectly united by the development of osseous material in the overlying ligamentous tissues. There was thickening of the bony trabeculæ along the lines of fracture, and partial calcification of the adjacent intervertebral fibro-cartilages.

10. A wet preparation in the Infirmary museum of a fractured femur in the adult afforded some good specimens of callus calcification, but was not fully examined.

Each of these specimens was prepared in various ways. Portions of the surrounding soft tissues, in which it was important to preserve the first appearances of calcification, were cut off and hardened in Müller's fluid, or in spirit. For decalcifica-

tion, chromic acid and various mixtures with nitric, hydrochloric, and picric acids, were used, parts of each being prepared in several ways for comparison. On the whole, the specimens prepared in a mixture of chromic and nitric acids were the best. Blood-clot hardens admirably in a two per cent. solution of chromic acid.

These specimens, though small in number, may be taken as fairly illustrative of the mode of fracture repair in man as it occurs under the direction of the surgeon. And this, I take it, is what medical men, practically concerned in the treatment of injuries, chiefly desire. In its legitimate position as a branch of comparative histology, the study of fracture repair in rabbits, dogs, cats, frogs, &c. has been of extreme value to the surgeon. But these studies in comparative histology have not retained their true position. In most works the repair of fractures in man is described as a heterogeneous generalisation of the varieties observed by various experimenters on different animals; and, with the material at hand, perhaps this was the best that could be done. The following paper is offered as a contribution towards the placing of our knowledge of the repair of fractures in man on an independent footing. Many links in the chain of events are unavoidably missing; it is only in an imperfect way that the appearances in one case complete the history of the changes in another. Particularly have I to regret this in the case of blood-clot, which in these times has come to possess a high interest in surgical pathology.

The development of the uniting medium in broken bones in man takes place in parts which are usually kept at perfect rest. We use every means to minimise the inflammatory process; but, under varying circumstances of injury at the time of, or unrest after the accident, we may get every grade of inflammation up to strangulation and sloughing. In children a moderate amount of movement, coupled with mechanical elasticity and active nutritive changes, may give us a mode of repair simulating that in the lower animals. Another variety may be seen in a fractured rib, where the periosteum is lacerated on one side and entire on the other, and where, also, there is always a certain amount of limited but continuous movement. The most common form of fracture is seen in the long bones of an adult, kept

at more or less perfect rest, and, so far at least as surgical pathology is concerned, we must look upon these as our most important fields for study. In most of these the periosteum is completely torn through, and the harassed question of subperiosteal callus is at once rendered subordinate. The displacement in man is measured by the inch, where in the lower animals usually experimented upon, it would be reckoned perhaps by the line. The elements of repair in ultimate size and strength are identical; and the problem has to be solved, as an engineering one would be where a different strength on a different scale of magnitude has to be secured with a similar material. All these conditions involve an endless variety in fracture repair. Ultimately, however, the whole study resolves itself into the capabilities of the various tissues surrounding a fracture, to develope new bone. In each individualised tissue there is a certain course of events which, within certain definable limits, will be constant. In the pulpy coherent mass which surrounds the fractured ends we can recognise the fibres of periosteum, muscle, and areolar tissue, traversed perhaps by tendons and vessels and nerves, and bound closely together by coagulated blood and inflammatory exudation. Roughly speaking, this is the matrix in which the bony reparative material is to be developed. New embryonic tissue is introduced; old tissues are inflamed, and revert in varying degrees to their embryonic types of structure; and, generally, where any special function is resident in a tissue, we shall have exaggerated display of that function. The question is thus a double one—the degree of conversion to embryonic form which a tissue will undergo; and the amount of ossification or calcification which it will tolerate. In each fracture these degrees or amounts will vary, the changes in one stopping short of what they will reach in another. The descriptions will be given as if the process were completed in every instance for each tissue.

Blood-Clot.—The first question relates to the disposal of the blood which, in varying amount, is poured out into the bruised and lacerated tissues. Hunter thought that all callus material was derived from blood-clot. Amesbury and Dupuytren described it as becoming firm, coherent, and ultimately organised in the exposed medullary canals and between the separated

fragments. Paget says that blood-clot may organise in fractures, but that, as a rule, it completely disappears, to be replaced by the material fibrous, fibro-cartilaginous, and cellular, in which the new bone is to be developed. Billroth leaves it an open question whether it is entirely re-absorbed or becomes partly organised.

Undoubtedly, especially where the extravasation is abundant, a great portion of the blood is absorbed, and in no way helps repair; but it is equally true that, in certain positions and under certain conditions, not only does blood-clot become fully organised, but it may serve as a nidus or parent tissue in which the new bone is developed. Under certain circumstances, as we shall see, it may be the most important means of repair in the fracture.

Objection has been taken to the term "clot organisation." Of course blood-clot does not exist in the organism as a permanent tissue, and in this strict sense the term is a misnomer. But it is certainly true that clot may exist in the body over a period of time and under conditions of vitality which justify its elevation for the time to the dignity of an independent tissue. In this sense the term "organisation," in default of a better, may be admissible. A further justification of the use of the term will be given in the sequel, when its peculiarities as a specialised tissue will be described.

Blood-clot is an unstable structure, very prone to become disorganised or absorbed. What conditions determine the permanency of clot in fractures? It would appear that perfect rest at least is necessary to clot organisation. It is found most constantly in protected positions—filling up the jagged hollows in the fractured bones, plugging the medullary openings, and occupying the spaces between comminuted fragments. In these positions it is more or less perfectly protected from muscular and other movements. In fissured and impacted fractures I have always found it present. It is a matter of practical experience in antiseptic surgery that rest is necessary to clot organisation. Rough handling, or a momentary separation of the clot from the outlying tissues, is enough to cause subsequent disintegration. It is always easier to get a clot to organise inside a bony cavity than in soft tissues. Once the clot sub-

stance is disturbed it is very unlikely to recover itself. One reason why fractures of the neck of the femur so seldom unite, I believe to be that the clot between the fragments, which is the only medium available for union, cannot be kept at rest, but is rubbed off and broken down. In a fractured vertebra or skull bone there is little movement, and union will in time take place.

It would seem also that a moderate and not excessive degree of vascularity in the surrounding tissues is necessary for clot survival. In fractures, one reason why we find clot organising by preference over the bones and not in the soft tissues may be that the bone is not so vascular. The process of revascularisation is necessarily much more tedious in bone than in the soft tissues; the areas available are smaller, and the formation of new vascular channels slower. So we find it in practical surgery. In a bad case of excision of the elbow under my care, I tried to fill a large abscess cavity over the joint with blood-clot, so that a greater amount of new tissue less likely to form contractile cicatrix might be left to cover the new joint. The clot organised and bled on scratching on the fourth day; but, as inflammation came on in the surrounding abscess wall, the periphery of the clot broke down while the central mass lived and became decolorised. It was only after the clot became fully vascularised that it united with the surrounding tissues, and this it did by granulation. It is also a matter of experience that we are not likely to get clot organisation inside a cavity that has been scraped or washed out with a powerful chemical fluid—that is where the resulting inflammation is intense. Generally speaking, in simple aseptic wounds which heal without irritation, there can be no doubt that the uniting medium is blood-clot rather than "coagulable lymph."

We may therefore say, with some degree of confidence, that where blood-clot is most perfectly protected from mechanical disturbance, and where it is least liable to be invaded by excessive vascularisation from the surrounding tissues, there it is most likely to survive and become organised. It need scarcely be added that deficiency of vascular supply is likely to be as fatal to its survival as excess thereof.

We take up the organisation of clot at the point where ordi-

nary coagulation of blood outside the body ceases. The fibrin has formed a regular and delicate honey-combed network around each cell; this network towards the upper surface of the clot becomes coarser in texture, and is gathered into broader strands with fewer embedded cells, till, when the surface is reached, the fibrin, with more than its due proportion of leucocytes, is the chief constituent of the clot mass. Here there is no evidence of cellular activity. If there is any cellular change at all it is in the direction of decay, not of vitality.

In clot that is to survive, the first change to be noted relates to the disposition of the fibrin. The regular arrangement around individual blood-cells still remaining, but in attenuated form, there is observed at points in the clot substance a tendency to the formation of leading strands, which may become many times thicker than the original fibrils (Pl. VI. fig. 9, *c,c*). In the immediate neighbourhood of these strands appear rounded cavities, each containing a deeply stained rounded cell with granular contents and a prominent nucleus (*a,a*). These are white blood-cells. They are here among the fibrin presiding over their special areas of nutrition, and directing the first steps of the tissue in which they lie towards vital organisation.

These leading strands, as well as the delicate network which they traverse, always stain readily. But the embedded blood-cells retain their yellow colour for a longer period, and, unless soaked for a considerable time, refuse to absorb the staining material. After a time, on the appearance of certain large granular yellow cells to be presently described, the blood discs are decolorised, and at the same time appear to lose their distinctive shape, becoming more or less spherical. In the end it would be impossible to say that the clear highly refracting substance traversed by delicate honey-combed fibrils had originally been red blood-cells. In the meantime the collection of the fibrin into leading strands has gone on, the large ones becoming larger, and new ones appearing. By contrast, as well as in reality, the original honeycomb network now appears to be of extreme tenuity (Pl. VI. fig. 3). The leucocytes undergo little change in their cavities. Here and there evidences of fission can be detected, but these are less frequent than might have been expected. They are always surrounded by a clear space,

appearing to fill only a part of the cavity provided for them. This may be an effect of the mode of preparation.

At this point the clot consists of fibrinous trabeculæ which give off smaller and smaller branches, enclosing areas of the original but much attenuated network, and having scattered throughout, but chiefly near the trabeculæ, numbers of the above mentioned rounded cells. Up to this point it may be said that the progress of organisation is uniform. But hereafter divergences take place which demand separate consideration. At every step we are reminded of the many-sided nature of clot tissue, ready, according to the situation in which it is placed—we may say according to the manner in which it is infected—to mimic almost any form of connective tissue.

The first change falling to be described relates to the appearance of round spaces, each surrounded with a row of large epithelioid cells, and containing a clear gelatinous substance which usually falls out on making the section (Pl. VI. figs. 2, 4, 5). These spaces usually occur in clusters, several large ones, with a good many small ones, being grouped together. In every direction of cutting they come out circular, therefore they must be hollow spheres. The largest ones, always few in number in a given section, can be seen with the naked eye, but by far the greater number are microscopic. They are most abundant in the central portions of clot, but they are by no means confined to these parts.

This process of alveolation—for such it practically is—is peculiarly interesting and beautiful. In all the specimens which I have studied, the steps of formation were strikingly similar.

The first evidence of alveolation is a grouping together of three or four epithelial-looking cells, with granular contents and a well-defined nucleus (Pl. VI. fig. 1). These cells are at first rounded in contour, but present flattened faces towards each other. They multiply excentrically, encroaching on the clot-tissue outside, and leaving a cavity inside. In size they vary greatly, but are always large; while a few in the largest cavities attain to enormous dimensions (Pl. VI. fig. 5). They are more or less flattened, adhering by their broadest surface to the wall of the cavity. Each cell contains a round nucleus

of very constant size—about that of a blood-disc. Some cells are vacuolated, and many contain drops of fat. They lie with great regularity, and usually in a single row on the wall of the cavity. In all stages of growth they are yellow in colour. They take on staining, not very readily however, with log-wood, aniline blue, or carmine.

As alveolation advances the network forming the cavity wall becomes more dense and closely set (Pl. VI. fig. 5). When alveolation has gone to its full extent, the clot-tissue consists simply of the close-meshed network of thick fibres which forms the walls of the cavities with its embedded leucocytes and the enclosed granular cells and gelatinous material. One of my specimens actually shows complete calcification of these fibrinous festoons. Rarely, however, do the changes go so far as this.

To help our understanding of this process some analogous appearances may be described. Where blood-clot overlies yellow marrow we frequently find rounded masses of pure fat, usually much larger than ordinary fat-cells, which appear in their aggregation to have displaced the clot-tissue proper. Fig. 16 is a drawing of such a condition, in which the fatty aggregations are small and the clot-tissue has become calcified. Similar masses of fat may nearly always be found in clots formed outside the body, and especially in clots that are swollen from having been hardened in too weak solutions of chromic acid. There is no appearance of cells around such cavities; the process probably depends on the general tendency of fatty molecules to gather themselves into larger and larger masses.

But, although the processes are, thus far, dissimilar, they may be to some extent related. The crude aggregation of fatty molecules outside, or, where there is excess of fat, inside the body, may, under ordinary circumstances, in the living clot, be represented by a more elaborate segregation and collection. I cannot be certain that the contents of these cavities are pure fat, but I believe they are fatty in nature. They are probably to be looked upon as an early effort of the clot-tissue to differentiate its component elements. Their never getting beyond the condition of hollow spheres, and the

nature of their contents, forbid any supposition that they may be vascular in nature. They are probably rather destructive than formative in their tendency. Their usual position, in the part of the clot furthest removed from blood-supply, and their universal tendency, if not arrested, to eat up the clot-tissue proper, point to such an interpretation. They exist by reason of the peculiar instability of clot-tissue, ready to be preyed upon by any special activity which may lay hold of it.

But this process of alveolation rarely invades more than one-eighth or one-tenth part of the organising clot; and even when it has advanced to its farthest extent, it may leave behind it a tissue which, as we shall see, takes its share in the repair of the fracture.

Another element in the tissue fabric is a large yellow granular cell (Pl. VI. fig. 6). Free of any connection with the tissue structure, and standing out of yellow colour in the midst of the blue or violet field, it is a striking object in most preparations. It is about twice or thrice as large as a leucocyte, is devoid of a nucleus, and is contained within a well-defined cell-wall. It usually appears about the third or fourth day, and disappears again about the eighth or tenth.

I think there can be no doubt that this cell is concerned in the collection of the colouring matter of the blood from the extravasated blood-discs, and perhaps even in the disintegration of the discs themselves. There need be no question as to their yellow granular contents being the same as that of the blood-discs; and the appearances often seen inside the cells lend a high probability to the view that they also lay hold of many of the discs bodily, and break them up in their interior. In this sense they are, in the fullest meaning of the word, hæmatoclasts, analogous to the large granular yellow cells of the spleen and other blood-granular bodies. We can guess that they are leucocytes to which this new function has been relegated; what ultimately becomes of them I cannot say. It is not unlikely that they, like their splenic congeners, are fated to help in the manufacture of new blood-discs, this function being long in abeyance owing to the tardy process of vascularisation in clot. They are certainly found in greatest abundance around areas of special activity which are to be the seats of vascular for-

mation; but I cannot say that I have found direct proof of their hæmatoblastic function in the way of fission or budding. Such a function is highly probable, but cannot be described as certain.

At this stage we may take up the vascularisation of clot. And here I may at once say that I believe there occurs in clot organisation an independent and original formation of blood-vessels, similar to what occurs in some other embryonic tissues, such as inflammatory exudations, sarcomata, placental tissues, &c. *A priori* we might have suspected this. This special vaso-formative function being found in rapidly growing tissues of simple type, apparently as a condition of their existence and growth, we might have reasonably enough concluded that a blood extravasation—the most rapidly produced of all tissues, and apparently the least stable—would be endowed with similar aid to survival. The preformation of blood-channels in the clot-substance, ready to be joined on to the general circulation, must very materially contribute to the rapidity of its organisation, and thereby to the probability of its survival.

The vaso-formative process is seen at its simplest in clot which is at a distance from any heterogeneous tissue such as bone,ligament, or muscle. Here it is seen to consist essentially in the collection into a tubular form of the protoplasmic or fibrinous strands which traverse the tissue in every direction. A chance parallel arrangement of a couple of thick trabeculæ must not be mistaken for the formation of a vessel. In such a case the original network remains between the thick trabeculæ, and there is no true tubular formation. When a vessel is to be formed the matrix gathers itself round a central axis to form a tube (fig. 9, *b*), and the fine cellular network is pushed aside. In this condition the young vessels bear a striking resemblance to the venous radicles of the spleen (figs 10 and 11). A vascular territory is one of special activity, and is a marked object in the field from its deeply stained appearance and its abundance of cells. The suggestive meaning of the crowding of large granular yellow cells in these areas has already been alluded to.

But the most active element in these vascular areas are those round deeply-stained cells already described as each lying in a fibrinous nest. An evident purpose in their multi-

plication and arrangement can now be made out (Pl. VI. figs. 10 and 11). They lie at commanding points among the chief strands, foreshadowing in their own arrangement and in that of their subsidiary trabeculæ the formation of the young vascular tubes. They are always round or oval, are usually very deeply stained, and not infrequently exhibit a small dark excentric nucleus. These are the true angioblasts in clot-tissue.

Other forms of vascular development which are met with are probably predetermined, either by the tissue into which the blood has infiltrated or to the inflammatory exudation with which part of the clot may be commingled. Fibres of periosteum or ordinary areolar tissue are sometimes found traversing a clot in all directions, importing new elements and new influences. Therefore, though here also the vaso-formative process may be independent of the general vascular system, it would be wrong to describe it as purely inherent in clot. A common form of vessel growth is drawn in fig. 12, from the margin of a clot. Figs. 13 and 14 are small portions of a similar tissue in other sections in which the vaso-formative action was resident. Here there is nothing peculiar to be noted; and the drawings sufficiently explain themselves.

The young clot tissue thus endowed with potentialities of independent existence, assumes many peculiarities of form. Some of these changes, appearing, as they do, to bear important relations to the process of fracture repair, require special notice.

One of the most important of these changes, pregnant with a far-reaching suggestiveness as to the capabilities of blood-clot in fracture repair, is a transformation into a tissue which exactly resembles pure cartilage. Fig. 7 is a drawing of such a condition. There is no possibility of mistaking the appearances. There is a distinct gradation, more marked in the actual specimen than in the drawing, between the familiar young clot-tissue, with its vaguely striated trabeculæ and round cells, to the glassy matrix and encapsuled cell groups of the cartilage. The clot fibres, becoming more and more swollen, are ultimately transformed into a continuous matrix, while the encapsuled cells multiply in broods round a mother cell and become surrounded singly or

in groups with new matrix. The resemblance to cartilage here, at the apex of the transformed tissue, is complete enough, but lower down it was even more perfect, and underwent an infiltration with calcareous salts in a manner no way different from what is seen in ordinary calcification of cartilage.

This was a change striking enough to deserve most careful investigation, and the appearances were closely observed in every specimen. One point to be decided was, What determined the transformation? for it was scarcely conceivable that blood-clot *sua sponte* should thus specially prepare itself for becoming calcified. It was noted that such cartilaginous areas ran into the clot substance on the side next the bone, and that they could often be traced down to a bed of fibro-cartilage representing a muscular insertion. It seemed, in fact, as if the inflamed cartilage had first infected the inflammatory neoplasm in its neighbourhood with its histological peculiarities, and that this infection, carried out into the young clot, had been immediately taken up by that versatile tissue. In nearly every case of fracture such cartilaginous tracts can be followed through the sodden tissues, and some of them can, with care, be traced to an area of coagulated blood. The infection is handed on from one tissue to another, and the transformation only ceases with the exhaustion of the stimulus, or the obstruction of a heterologous tissue such as muscle. That this tissue is pure cartilage I very much doubt; that it is a parent tissue specially adapted for the development of bone is perfectly clear. It is, furthermore the undoubted representative of that ill-understood tissue which is so abundant in fractures of the lower animals, and which has given us the name "callus cartilage." More will have to be said on this subject presently.

The most varied changes in clot are found in the sites most favourable to its existence, namely, plugging the marrow cavity and filling up the jagged hollows in the fractured ends.

Running into clot in these situations we always find numerous bony spicules or trabeculæ. The immediate neighbourhood of such spicules is always the seat of some special change in the clot-tissue. Fig. 15 is a drawing of one of the most common appearances. Trabeculæ are gathered together from outlying portions, meeting at the tip and lying alongside of the spicule.

Abutting on the bone the clot trabeculæ are so closely arranged as to be almost continuous, and the imprisoned cells assume a rough similarity to the neighbouring bone corpuscles. The structure of true bone is, in fact, very closely mimicked. The assimilation is further carried out when this transformed clot-matrix becomes, as it frequently does, impregnated with calcareous material.

Some of the most striking preparations which I possess are derived from specimens in which ossification had invaded the alveolated tissue described above. Beyond the broad fact that calcification had invaded the clot trabeculæ left surrounding the nests, and that the imprisoned cells closely resembled true bone cells, there was nothing very special to be noted histologically in these preparations. In these regions, the ossific stimulus being very near and powerful, every available matrix was laid hold of and calcified. Fig. 16 is a drawing showing calcification in the matrix around fatty aggregations, which are so frequently found where clot overlies yellow marrow.

It would seem that, given the adaptable leucocyte and the equally plastic clot-fibrin, there is scarcely a limit to the permutations and combinations that may arise therefrom. Even the sluggish articular cartilage is not without its influence on this versatile tissue. In case 2, which was only eight days old, the foreshadowing of a cartilaginous structure was observable in the clot all along the line of rupture of the articular cartilage. Fig. 8 is a drawing of such a condition, not very striking in itself, but eminently suggestive as to the ultimate capabilities of the young tissue.

It is scarcely possible to exhaust the multiple aspects of organised blood-clot in the midst of heterogeneous and inflamed tissues. The above description will perhaps suffice to show the nature and value of the young tissue in fracture repair. Wherever it lies it goes some distance towards assimilating itself to the tissues which surround or traverse it. If the ossific stimulus reaches it, it undergoes changes similar to those which would be undergone by the tissue it mimics. Even after making allowance for the unstable nature of clot-tissue, and for the manifold influences which militate against its survival, we cannot fail to perceive its importance in the healing process of fractures.

When no other tissue competent to develop bone is at hand, it steps in and fulfils this function; or when only heterogeneous tissues are present it meets them half way, and, bridging over the difficulty, carries the ossific stimulus on to another tissue which is competent to serve as a bony matrix.

But we must not exaggerate the value of clot in fractures. Clot is the least valuable of all repairing mediums. Its sluggish nature, hovering for days between life and death, and prone to destruction on the slightest disturbance; and the crude simplicity of its elements, far removed from that form of structure which is most suitable to development of bone, place it behind all the other tissues which surround a fracture as a medium of union. But there it is, for better or for worse, and we must accept it.

It is the last of all tissues to become ossified. Nearly all observers agree in describing the medullary plug as the last to develop bone. Through all its changes of decolorisation and subsequent vascularisation it has been described with a wonderful amount of uniformity by numerous observers; it had even been raised, under the name of "substantia intermedia" (Breschet), to something of the dignity of an independent existence. Evidences of its delay in ossification are seen in macerated specimens of imperfectly united fractures in most museums, where its previous existence is represented either by a complete gap or by very imperfect ossification. A practical proof of its drawbacks as an uniting medium is seen in fractures of the neck of the femur, where its friability and sluggishness render union almost impossible. Its existence anywhere in excess cannot be otherwise than deleterious.

Nothing need be said of the cessation of clot transformation at the stage of fibrous tissue. It is impossible to say whence the fibrous material so frequently found sealing up the displaced ends of a fractured bone derived its origin. It is just as likely to have sprung from clot as from anything else.

Here, then, we leave the process of clot organisation in fracture repair. Assimilated to surrounding structures either by calcification or fibrillation, it ceases to exist as an independent tissue, and its history is hereafter incorporated with that of its neighbours.

Periosteum.—As a rule, in fractures in man, the periosteum is

completely torn through. But the exceptions to this rule are somewhat numerous. In fractures of the ribs, for instance, the laceration is on one side only; on the other side, outer or inner, according to the mode of fracture, though partially detached, it usually remains entire. The same is true of fractures of the clavicle, and, with some limitations, of the fibula and radius. In fractures of the flat bones there may be no tearing of the periosteum, and only slight detachment thereof. And in many fractures of the long bones a few shreds of periosteum are frequently left stretching between the fragments.

When the periosteum has not been stripped from the bone at the time of the accident, it continues adherent during the progress of repair, and no amount of inflammation that is not suppurative will separate it. When it has been peeled off, as nearly always happens for some distance above the fracture, a sero-sanguinolent effusion, which has been described by most observers, lies between the periosteum and the bone. In considering the peculiar functions of periosteum in fracture repair, all these conditions must be remembered.

At the outset it is necessary to give a definition of terms. According to general usage, the term ossification may mean anything from the crude infiltration of a vitreous humour or of a pleuritic effusion with calcareous material up to the fully elaborated process as seen in the extremity of a fœtal long bone; and calcification may mean almost the same thing. With such laxity of meaning it is impossible to make our terms understood. I shall therefore make use of the terms calcification and ossification in the following senses:—Calcification is taken to represent a simple deposit or infiltration of amorphous or nodular salts in a pre-existing matrix; the cells are the proper ones of the tissue, simply imprisoned and not specially developed. Ossification is the formation of a specialised tissue by specialised cells ("osteoblasts"), the protoplasmic being formed *pari passu* with the calcareous material; and true ossification is, in the first place, a sequel to the destruction of a previously calcified tissue. A tissue of calcification may never become ossified, continuing permanent or being completely absorbed. But an ossified tissue in its first development always succeeds a calcified precursor.

I am aware that the highest possible authorities might be cited in opposition to the above definitions. It is in sheer despair of making myself understood, unless some such rigid line be drawn between the two processes, that I so restrict the meaning of the terms. A correct appreciation of the differences between the two processes lies at the root of our understanding of the process of bony repair.

Thus defined, we see very little of true ossification in the early stages of callus development. It is nearly all simple calcification. The furious advent of the inflammatory process provides an abundance of succulent matrix and blood supply. In the presence of the ossific stimulus there is a hurried preparation for true ossification, consisting of an irregular but not altogether indiscriminate deposit of calcareous material in the inflammatory blastema. To some extent the matrix is an infiltrated product of inflammation, but the greater portion of it is derived from the swollen and otherwise transformed tissues around the fracture. One of the most important of these parent tissues is the periosteum.

Here it is expedient to interpolate a reminder on the periosteal function of bone production. The normal process of bony growth under periosteum is not, rigidly speaking, periosteal at all, but medullary. The periosteal osteoblasts are medullary in structure as well as in function. A slight periostitis, such as may be found under an ulcer of the skin, gives an increased development of bone, which is of the ordinary lamellar type, arranged regularly in Haversian systems. A greater amount of inflammation induces a new departure in osteogenesis. In this latter case the new growth is through calcification as a first step. The ready-made swollen periosteal fibres are made use of just as any other suitable matrix would be, and without any regard to its supposed function of osteogenesis, for the deposition of calcareous salts. The first is true permanent ossification; the second is only calcification of a fortuitously provided matrix, and is merely temporary. The one is analogous to the calcification of cartilage, which in the fœtus precedes true bony growth; the other corresponds to the development of lamellar bone by medullary osteoblasts.

Looked at in this view, the whole question of the periosteal

origin of callus is much simplified. The function of the development of true bone being dependent on the sub-periosteal osteoblasts, and being medullary in nature, a normal ossifying periostitis is possible only when the periosteum is undetached and the osteoblasts undisturbed. But, as a matter of fact, we know that a detached or even transplanted periosteum carries with it a power not only of calcification but of ossification. All that we need in this case postulate is that some of the osteoblasts shall have been borne away with it. It is, however, a deeper question than the mere presence of osteoblasts; it is a question of degree of inflammation, anything between plastic growth and suppurative destruction. We find that the mean between these extremes is the hurried and histologically incomplete process of calcification. And experience shows that in fractures the degree of inflammation is in most instances enough for calcification of periosteal fibre, but too much for the direct formation of medullary bone.

The development of callus in periosteum presents a considerable variety of histological appearances. We find one prevailing type of growth in the more outlying portions of fibre, where it is less dense and more abundantly infiltrated with inflammatory material. Where it is in close contact with, and firmly adherent to the bone, another type of calcification is met with. Those instances in which the periosteum has been peeled off the bone and gelatinous material separates the two will be best included under this head. And, lastly, that more complete but less important development of bone, which is one effect of a low form of periosteal inflammation, and is produced by the periosteal osteoblasts, may be here considered.

Rindfleisch, while speaking of this subject, expresses his surprise that, according to Virchow's careful investigations, in ossifying periostitis bone may be developed outside the periosteum ("parostosis"); for periosteum ordinarily produces bone on its inner aspect.[1] In such cases I believe we ought to consider it only in a very limited sense as an "ossifying periostitis;" in a broader and more legitimate sense it is simply an "ossifying cellulitis," or, still more correctly, a "calcifying cellulitis." Where the cambium layer under the periosteum

[1] Rindfleisch's "Path. Hist." *New Syd. Soc. Trans.* 1873, vol. i. p. 244.

is destroyed, its specialised function follows suit; and any new function which the periosteum takes up must be in virtue simply of its capabilities as an inflamed fibrous tissue. As such, it may be infected with tendencies to calcification, but it is of itself incapable of developing true bone.

Of course it is not denied that a true ossifying periostitis might occur in fractures. The periosteum may be only slightly injured, and the resulting inflammation may be of a mild nature, and thus we might get an example of genuine periostitic bony growth. As a matter of fact, such examples are, in man at least, very rare. The limited capabilities of the cambium layer of osteoblasts are far from being equal to the rapid and excessive callus growth seen after fractures. Starting at innumerable points throughout the prepared matrix, and traversing many courses through the fibrous bundles, the calcifying process proceeds with a rapidity many times greater than could be brought about by a true ossifying periostitis.

Many experiments have been made on the lower animals with a view to teaching us the natural history of ossifying periostitis. Conspicuous among these are those by Busch, of Berlin, of inserting laminaria tents into the medullary cavities of bones. In these the periosteum was for the most part intact; and if we might deduce from an undisturbed condition of tissue a retention of functions, we should find it in such experiments. That is to say, we should have expected the new bone to be of medullary rather than of fibrous origin. The oncome of inflammation was slower than it would have been in fracture; and the inflammatory stimulus was handed on from the compact bone to the periosteum. Starting with an inflammatory hyperplasia of the medullary bone-producing elements, the new growth is laid down on the compact bone and grows outwards. Some slides in my possession, and for which I am indebted to the courtesy of Professor Busch, seem to show all this. Now, we know that in fractures a development of bone—or at least an infiltration with calcareous salts—often takes place at a distance from the old bone. In these specimens there is a striking similarity in general arrangement of trabeculæ to what existed in the callus developed in Case 1; but it was easy to make out fundamental differences in the processes of growth. The one was in all its chief features

a growth in membrane, the other a development by true osteoblasts. In that fracture also there had been but little or no laceration of the periosteum, and only slight displacement of the fragments. In fact, the periosteum had been left in a position histologically not unlike that in Professor Busch's experiments on artificial necrosis. We may contrast such a condition with the appearances depicted in fig. 1, Pl. VII., where true ossification and periosteal calcification are going on side by side, but not in unison. To appreciate the distinctions fully, decalcification by acids must have been very sparingly adopted; and the sections must not have been soaked in oil of cloves, nor mounted in balsam.

On the whole, therefore, I should characterise periosteal callus rather as a calcifying cellulitis than as an ossifying periostitis. We are to look for its true homologue in the membranous development of bone. The osteogenetic material which is always found at the tip of a calcifying spicule in ordinary intramembranous ossification is here represented by modified periosteal fibre (Pl. VII., figs. 2 and 3). Fig. 2 is a drawing of a section made transversely through the tip of a spicule. A zone of deeply stained protoplasmic material, which, before decalcification, had probably been infiltrated with nodules of calcareous salts, surrounds the substance proper of the spicule. This last appears as a granular matrix containing three branching and anastomosing corpuscles. At several points in the protoplasmic zone the amalgamation of round granular cells with the osteogenetic material is seen. Fig. 3 represents the tip of such a spicule undecalcified, and completes and explains the appearances drawn in fig. 2.

After this manner the first development of periosteal callus takes place. From many centres lines of calcification run along the bundles of periosteal fibre, leaving an areolar arrangement, whose leading trabeculæ follow the course of the periosteal fibres—that is to say, parallel to the shaft of the bone. Between these calcified trabeculæ there lies a succulent young tissue, with numerous large, rounded or tailed nucleated cells and a few fibres. Numerous blood-vessels of simple structure (fig. 4, Pl. VII.) traverse the young tissue in every direction. Occasionally some attempts at the lamellar development of bone by true osteoblasts

are seen; but this is not common. The trabeculæ of periosteal callus show in their rough or granular structure the indiscriminate arrangement of their embedded cells, and the complete absence of anything like lamellation—wide differences from ordinary cancellous bone.

On peeling off the superficial, perhaps calcified, periosteal callus, we frequently find closely adherent to the underlying bone long ridges of hard glistening material traversing the strands of fibrous tissue. Sections in longitudinal direction can readily be made, though the tissues have not been decalcified. This dense calcified tissue is simply periosteum, the bundles of which have not been separated by injury or inflammatory exudation, and which have been thoroughly impregnated *en masse* with fine calcareous material. The changes in the histological elements are so inconsiderable that the process might be likened rather to an impregnation with some hardening material, such as Canada balsam, than to an organic or physiological proceeding. The wavy bundles of connective tissue can be readily detected in the hardened substance, and here and there the connective tissue cells stand out with abnormal prominence in the field. On the surface of such ridges and at transitional points elsewhere, a more marked change in the fibre cells, similar in nature to a more complete transformation, to be described under another head, can often be detected. Curiously enough, I found that this calcareous infiltration occasionally followed bundles of perivascular periosteum for some little way into the pores in the compact bone.

Why this hurried and imperfect form of calcification should be found next the bone, where we might expect it to be most complete, is difficult of explanation. It may depend on lowered vitality of the periosteum itself. The layers next the bone may have suffered most (as is conceivable if the injury were direct), or the vessels running between periosteum and bone may have been blocked. It is scarcely conceivable that it may have been caused by a simple superabundance of calcareous material in the neighbourhood which is poured into the fibrous matrix before it has undergone those elemental changes which indicate the oncome of inflammation.

Where the periosteum is peeled off the bone we find intervening a pinkish gelatinous material which is, histologically, composed of the elements of inflammation mixed with blood corpuscles, and traversed by shreds of periosteum. In its ulterior changes this material may assume an appearance similar to some forms of callus cartilage. Rokitansky describes this gelatinous material as of constant occurrence in the lower animals. I regret that I have had only slight opportunities of studying it. Either by absorption or by ossific invasion it is soon lost sight of, leaving behind it a trabecular calcified growth which is very similar to that found in periosteum generally.

On careful examination of the new material under a stripped periosteal membrane, groups of nodular osteophytes may be found here and there closely adherent to the underlying bone. These sedentary osteophytes I believe to have a similar origin to the spicular or lamellar osteophytes found in the substance of subperiosteal sarcomata.[1] That is to say, I believe them to be partly periosteal, partly medullary in origin. The periosteal tissue is usually the adventitia of a vessel which has escaped laceration; the medullary tissue is derived from a vascular opening in the compact bone. The apex of the nodule or spicule is developed in the periosteal fibre, and is solid or areolar. The base is developed from medulla in the ordinary way, by alveolation and redeposition, and is hollow, and arranged in concentric lamellæ. The periosteal fibre leads the way, and develops the solid apex; the medullary tissue follows it up, alveolating and redepositing. These nodules, then, are little hollow cones attached by their bases to the periphery of a vascular aperture in the compact bone. Though they lie in the gelatinous subperiosteal layer, they are not, properly speaking, a development therefrom.

This pink gelatinous material is described as playing an important part in the repair of fractures in the lower animals. It has been spoken of as a special secretion for a special purpose. If we are to regard it as a secretion, it must be only in a limited sense, and with that antiquated meaning which regards even bone itself as a secretion. It is simply an inflammatory

[1] "The Mode of Growth of Spicular Osteophytes," *Bristol Infirmary Reports*, 1878-79.

exudation poured into an artificially formed space, and behaves in the manner that such a neoplasm lying between such tissues would be expected to behave. So far as I have seen, it plays an unimportant part in human fractures.

True periosteal bony growth is of little importance in fracture repair, and does not require special consideration. At some distance above the line of fracture we do usually find that a thin shell of new compact bone has been, or is being, laid down around the bony shaft. The long centripetal course of the leading vascular channels is usually a striking feature in such specimens. It is as if the bony new growth were forced outwards against the periosteal membrane, stretching its vessels as it advances. And if we are to speak of such bone as medullary in origin, such language would be more than figuratively correct.

Tendon and Ligament.—In most fractures some tendinous or ligamentous tissue is implicated, and is frequently concerned in the process of repair. The tendons proper require less consideration than the muscular insertions. Ligamentous tissues everywhere, interosseous, capsular, &c., when involved in a fracture, respond readily to the ossific stimulus.

It might almost be said that tendons or ligaments are endowed with an excessive or morbid tendency to become ossified. Even where there may have been no fracture of bone, only rupture of tendon, instances of development of new bone in the lacerated tissue are by no means rare. The best known examples of this occur after rupture of the tendon of the adductor longus muscle of the thigh in horse exercise. In the interosseous ligaments of the arm and the leg, an excessive development of bone is liable to take place after fracture or other injury or inflammatory disease. Bony ridges or spicules are sometimes found springing from the bone, and replacing intermuscular septa, and probably owned similar causes. And cases have been recorded in which, without any external traumatic cause, there seems to be a general tendency to the growth of bone in the ligamentous tissues throughout the body.[1] It is evident, therefore, that fibrous tissue is a medium favourable for the development of new

[1] *Cf.* Hancock, *Lancet*, 1866, vols. i. ii.; Bennet, *Dub. Journ. Med. Sc.* 1872, vol. i.–iv. p. 510; Hamilton, *loc. cit.* p. 508; Henry, *Phil. Trans. Lond.* 1759, vol. li. p. 89.

bone; and in a less direct, but more important manner, it may be the means of carrying the ossific stimulus outwards into other tissues which might otherwise remain passive in fracture repair.

In the embryo the junction of tendon with bone is effected by means of a tissue which resembles true cartilage, and which has been spoken of as tendon cartilage. The insertion of the tendo Achillis of the frog will give good examples of this tissue.[1] In the human adult the plump round cells of the tendon cartilage are replaced by the flattened obscure cells of true tendon, and there is nothing left to indicate that the tendinous insertion had differed in any way from the rest of the tendon. But the advent of the inflammatory stimulus at once resuscitates the embryonic memory, and demonstrates the true nature of the tissue. There is not only a reversion to the embryonic cartilaginous structure, but there is superadded to this an influence which the cartilage never succumbed to before—that of calcification and ossification. And not only does the immediate insertion become calcified like ordinary cartilage, but the tendon proper at some distance from the bone may be similarly infected and transformed.

Having taken for granted the ordinary descriptions of ossification of tendons in birds,[2] I was not prepared for the thoroughness of the process in fractures in man. Suspecting that the process of so-called tendinous ossification had not been pursued to its finality, I secured some tendons of old turkeys and examined them carefully. This investigation proved to me that the ordinary descriptions of tendon ossification in birds were not complete; that this so-called ossification is only the preparatory stage of calcification; and that, in old birds and in special positions, we may find a true ossification following up and replacing the calcifying process (fig. 5, Pl. VII.). It happens that calcareous infiltration in birds' tendons begins early and lasts long; and its successor, true ossification, comes on late, after the period that birds most convenient for study are usually killed. So the process may have been overlooked.

It will be convenient shortly to describe the process of ossification of tendons in birds. In a longitudinal section of one of the long tendons the proximity of the calcifying process

[1] Stricker's "Histology," *New Syd. Soc. Trans.* vol. i. p. 107.

[2] Ranvier, *Traité Technique d'Histologie*, p. 455 *et seq.*

is indicated by the swollen and prominent aspect of the small, flat, almost invisible tendon cells that lie in rows between the bundles of fibre. They lie in straight parallel rows and gradually increase in breadth, but are always longer than broad. Calcareous salts are thrown down in the fibrinous matrix between these cell rows, and ultimately between the individual cells. The calcareous material is very faintly granular, and is in a state of very fine subdivision. The tendon now loses its glassy striated appearance, and ceases to polarise light. The cells, still continuing in rows, increase slightly in size, and send minute processes into the calcified tendon matrix. This is still pure calcification, only it is far more permanent than the like process anywhere else. The great length (comparatively speaking) of the tendons, their compact sparsely vascularised structure, and the absence of overlying muscle on the tarso-metatarsal bones of birds, may help to account for this.

For a considerable distance down the tendon no new appearances may be visible; but in old birds in the middle of the tendon examples of true ossification replacing the calcified tissue may be met with. Fig. 5 is a drawing of such a condition. The tendon has been cut transversely. At the periphery the fibrous sheath is seen surrounding the calcified bundles and sending septa down between them. The tendinous bundles of bony density are seen in transverse section imperfectly isolated by deeply stained cells, which in this aspect appear tailed and branched. These have been called bone corpuscles; and if the tendon in this condition is called bone, we need not object to the term. Lower down we meet with a dark zone of rough granular material which is the calcified tendon tissue disfracted and broken up preparatory to being transformed by osteoblasts into true bone. Below this we meet with the typical lamellar bone with its lacunæ, canaliculi, and Haversian channels all complete.

Longitudinal sections show the same process going on, and in addition gives us good views of the part which vessels play in the process. The vessels of ordinary calcified tendon observe, in the main, a longitudinal course; but channels of considerable size run inwards from the periphery. A deeply stained band of true bone, less granular and opaque than the calcified tendon

tissue, can often be seen surrounding such a vascular channel, in specimens where ossification properly so-called has not appeared. But true ossification is simply an extension of this perivascular growth; more thorough in its preparatory tissue disintegration; more extended in its area; and accompanied with, we might say caused by, a great increase in the number of vessels. True osteoblasts may be seen; and though anything like a specialised marrow cavity is never present, yet spaces of considerable magnitude, containing true myeloid tissue, are frequently met with. But the bone is always very compact. Altogether, with the exception that we have no primary medullary spaces, and that the process of destruction of the calcified matrix is altogether less complete and elaborate, we have here a close resemblance in all essential points to the ordinary forms of ossification in cartilage. The prime distinction, however, relates to the duration of the two tissues. If we regard the life of the bird, calcification is the normal and permanent process; ossification comes in towards the end of the life it is permitted to lead, and may be regarded as unimportant, almost fortuitous. But still it comes in to remind us once more of the completeness and harmony of allied processes throughout the animal kingdom.

This normal ossification of tendons in birds is imitated with considerable exactitude in the inflammatory osteogenesis which lays hold of tendons and ligaments implicated in fractures in man. The similarity to intracartilaginous ossification is more close in the latter even than in the former case. The steps of the process may be followed in figs. 6, 5, and 10. The flattened cells, which in their normal state can scarcely be detected as they lie between the tendinous bundles, start forth from their concealment and appear in closely-set regular rows. They go on increasing in size, becoming oval or even round, and ultimately appearing surrounded by a distinct cell wall and a varying amount of clear pellucid cell contents. The intervening fibrous bundles swell, and become more wavy in texture and more vague in outline (fig. 5). At this stage the structure is very similar to normal temporary cartilage, except that the cells are always in rows, and that the matrix is obscurely striated in lines parallel with these rows. The tissue is now ready for

calcification. As in ordinary calcification, the nodular salts are laid down primarily in the areas of matrix most distant from the cells, and gradually encroaches on the cell capsule. But the calcareous infiltration need not take place in a direction identical with the cell rows. The "piling" of cells in rows is here determined by their normal arrangement between the bundles, and not by any developmental preparation for calcification as in health (fig. 10). Frequently, as we should have expected, the invasion with calcareous material takes place from the side of the bundles, and not along their course.

After a longer or shorter area of calcification, we meet with attempts at vacuolation which correspond to the primary medullary spaces in the normal process. Thereafter may be found examples of the development of true bone by osteoblasts in orthodox manner, and the history of the process is then completed.

But, as a matter of fact, it is not always that the process reaches the stage of true ossification. The advent of the young medullary tissue may cause complete absorption without the formation of any true bone. And it must not be supposed that the changes can be seen taking place evenly or on one level; irregular spicules run in varying directions and at different rates through the parent tissue, and it is only by comparing numerous sections at various levels that the course of events can be followed.

No more beautiful example could be cited of the closeness with which, under novel conditions, a tissue remains true to traditions of its descent than the behaviour of tendinous structures in the neighbourhood of fractures. Dr. Creighton has shown (in a previous number of this *Journal*) how tendon cells exposed to the influence of granulation tissue may become assimilated thereto both in shape and in function. Here we have a change more far-reaching in variety and extent; though perhaps less so in real nature. In fractures the reversion to embryonic form ceases at the stage of fibro-cartilage; having got so far, the ossific stimulus lays hold of it and transforms it in its own direction for its own purposes.

In illustration of this process of tendon ossification, I cannot refrain from alluding to a closely allied one which I found going on in the periosteum overlying two specimens of carious bone. On the anterior aspect of the great trochanter of a femur excised

for hip-joint disease there existed a few hard nodules, the largest about the size and shape of a split pea, rising abruptly from the surrounding bone, and covered with what appeared to be periosteum. On making sections of these I found that they consisted of an outer shell, which was simply a zone of calcifying cartilage, and contents composed of areolar bone and inflamed medullary tissue. Very similar appearances were subsequently found on the under surface of a carious os calcis. The inflamed medullary tissue had burst the compact shell, elevating a blister of periosteum; a protective periostitis was set up, followed by attempts at calcification. The interest was in the fact that the development of new bone was not such as we find subsequently to periosteal inflammation (and such as existed in other parts of these bones), but apparently through the medium of temporary cartilage. The bone had chanced to give way under a ligamentous insertion, the tendon became embryonic and cartilaginous, and behaved under the ossific stimulus as cartilage usually does. No pure periosteal tissue, except, perhaps, under the influence of a very near and very powerful infection, could exhibit such changes.

Such is the nature of the typical transformations of ligamentous tissues concerned in fracture repair. But the other fibrous or cellular tissues abounding in the neighbourhood exhibit similar or allied changes. Sometimes, as in fig. 7, we see a decided change to the cartilaginous form. Fig. 9 shows a mixture of the fibrous and cartilaginous forms, only the cartilaginous tissue is breaking up before it has been calcified. In fig. 13, again, we have a good specimen of calcifying cellulitis abutting on an area of cartilaginous structure. It is curious that in both these specimens the cellular tissue should have become impregnated with calcareous material before the cartilaginous; and this is no uncommon occurrence. Transitional appearances in great variety, many of them of great beauty and interest, but too numerous to be particularly specified, are met with in every specimen of fracture repair.

I believe that the ligamentous tissues and their congeners are of prime importance in fracture repair. They stand pre-eminent in their capacity for becoming ossified. Their wide distribution enables them to carry the ossific infection far out

into the surrounding transformed and neoplastic tissues. If we include ordinary cellular or areolar tissues—which we may with justice do—and remember how readily its meshes become charged with the products of inflammation, we cannot fail to put a high value on this variety of tissue as an element in callus growth.

Fibro-cartilage.—Under ordinary circumstances this tissue does not play an important part in the repair of fractures. I have had opportunities of studying its behaviour only in three of these cases, viz., 4, 7, and 9—one of the neck of the femur and two of the vertebræ.

In the femoral fracture a bridge of white fibro-cartilage united the margin of the articular cartilage above with the perichondrium of the neck, and this was infiltrated with bone salts, except where it was in immediate contact with the bone, that is, where movement was most felt. The tissue itself had undergone little change. Irresponsive to the inflammatory stimulus, and being a ready-made matrix for calcareous invasion, this was just as we might have expected.

Very slight changes were found in the intervertebral cartilages. Here the calcareous material was very dense, and the tissue was very hard, clear, and glistening. As a result probably of the fine subdivision of the salts, this form of calcification would seem to be very permanent, for it existed in the case of eleven months standing (fig. 12). In both the cases of fractured vertebra the calcified fibro-cartilage took an important share in consolidating the union. At parts where the overlying ligaments came in contact with the intervertebral fibro-cartilage, the different behaviour of the two tissues under the ossific infection stood out in striking contrast. In the intervertebral disks, the calcifying process showed a distinct preference for the more purely fibrous portions of the tissue; the central portions were calcified only slightly at their attachment to the bone.

Indications of similar changes were visible in the fibro-cartilage forming the grooves for the tendons of the peronei on a fractured fibula. Slight participation in the inflammatory change, and a passive infiltration with bone salts, seems to be the ordinary behaviour of fibro-cartilage involved in fracture. This is in accord with what we should expect from the normal histology of the tissue.

Medulla.—The behaviour of medulla where it makes an exit through vascular foramina and commingles with the exudative material thrown out under a stripped periosteum has already been considered. Yellow marrow can have an influence on fracture repair only by virtue of its sparse connective tissue and small round cells; and this influence, from the very nature of the tissue, must be small. But more is to be expected from the highly organised and sensitive pink marrow which fills up the spaces in cancellous bone.

The existence of living bone may be described as a sort of equipoise between the cotemporaneous processes of absorption and deposition. An increment of nutrition begotten of inflammation may, according to its amount, result in a simple addition of new bony tissue or in an absorption of old. Most frequently it starts with excess of absorption, and goes on to increased deposition. In the end the proper balance is recovered by a absorption of the neoplastic bony growth.

In every case the amount of primary rarefaction will vary with the degree of inflammation and the reactive power of the tissues; and the oncome of sclerosis will depend on the rapidity with which the inflammatory excess of nutrition fades away. Though, at the time of examination of any given instance, the naked eye might find very little evidence of sclerosis or rarefaction; yet the microscope seldom fails to reveal evidences of previous bony new growth and absorption. This may be concluded when we find numerous deeply, stained laminæ overlying the old bony trabeculæ, and filling up jagged hollows caused by the primary absorption; and when also we find that these new laminæ themselves are undergoing absorption with more rapidity than is observed in the normal process during health.

Here we are brought face to face with the harassed question as to the part which the bone corpuscles play in the disintegration of bone. The more I see of the process of absorption of bone, the more I am convinced of the comparatively insignificant part which the bone corpuscles play therein. In the most varied forms of bony absorption I have never met with convincing proof that the bone cells take any active or initiatory function. Conclusions drawn from the appearance of lacunar hollows representing the disintegration of corpuscular areas of

nutrition are not wholly to be trusted. These hollows are just as likely to have been formed by a passive disintegration along the primary lines of construction as by an active absorption by a bone cell extending as far as its limits of vital activity can go. The best specimens of lacunæ which I have seen were derived from the stump of a femur which protruded after amputation, and which was undergoing absorption by healthy granulations. On comparing the leading positions and shapes of these hollows, it appeared that they exhibited a decided preference for certain positions among the Haversian systems, and in these selected spots observed a peculiarity of shape which suggested a different mode of origin. Such positions were where three or more ossicles meet, that is, where the outer lamellæ of several Haversian systems abut on each other. At such points there is a packing of bone which differs in several respects from true lamellar bone. It is always irregular, is not disposed in lamellæ, and, in bones not too old, frequently retains a remnant of the originally calcified framework of the primary medullary spaces. The first deposit of bone is in globes filling up those festooned hollows in the calcified framework, and a considerable amount of it is left behind among the ossicles far removed from vascular influence and subject to little change. The process of pulling down proceeds on the lines of the building up. These calcified globes being removed, rounded hollows are left; the cell support being broken down, the cell is set free. Over and over again the same appearances repeated themselves, viz., the three or four sides of a large absorption cavity composed of lamellæ becoming disfracted in layers; and the angles, which represented also the points where several ossicles joined dug out into several lacunæ filled with granular detritus and active marrow cells. Regarding such instances as crucial, and extending our generalisation from these to less striking examples, we are driven to the conclusion that the bone corpuscles take little share in the process of bony disintegration.

The function of giant cells in absorption is still a matter of some obscurity. I have elsewhere expressed an opinion that their function and purpose have been exaggerated in one form of bony absorption—the carious; and further experience confirms me in the belief that they have generally been made too much

of. There is no doubt that they are found in greatest abundance where bony absorption is going on actively, and in positions which strongly suggest that they take an active part therein. But constant concomitance need not imply a relation of cause and effect. *A priori* it would seem surprising that a large unwieldy mass of granular protoplasm with a few imprisoned nuclei should be chosen for the delicate and difficult process of bony absorption. And, in the face of the fact that by far the greatest amount of bony disintegration takes place in the presence of small round succulent cells with abundant vascular supply, we must admit that giant cells are at least unnecessary to absorption. Everywhere else in the economy special nutritive activity is attended with increase in the number and diminution in the size of the engaged cells. Why should bone be the only exception? I would, therefore, conclude that the giant cells in bony absorption are effects rather than causes;—masses of granular protoplasm which have remained coherent, partly because they happen to have the protection of a bony hollow, partly because they have not been brought under the disintegrating influence of abundant vascular supply.

Whatever may be the part played by the individual tissue elements, there need be no dispute as to the aggregate result. When the pink marrow has responded to the inflammatory stimulus, and become fully vascularised, it causes bony rarefaction to begin with. But alongside of this a development of new bone by the marrow tissue proper is begun on the surface of the old bone, and this new growth is carried out for varying distances, to meet the periosteal callus material. This increment of new bone is usually confined at first to the periphery of the compact bone; over the fractured ends new bone does not appear till a period considerably later. The delay in the latter case is caused, as has been already indicated, by the presence of a greater or less amount of the sluggish clot tissue entangled in the jagged fragments.

So far as I have seen, medullary tissue contributes to fracture repair only by the direct development of true bone. As a connective tissue we might have expected that it would sometimes undergo changes similar to its congeners and become calcified; but I have never found evidence that it does so. This may be

explained by the fact that an inflammation in marrow runs rather to cellular hyperplasia than to serous exudation, and an important desideratum in a tissue of calcification is that it shall be provided with an abundance of extra-cellular matrix.

By causing rarefaction of the surface of compact bone in the neighbourhood of a fracture, and by sending out new bony material into the overlying callus tissue, the marrow may be said to take the chief share in welding together the parts which are to form the permanent bond of union.

The ordinary calcified callus material, by its very nature unstable, is soon completely removed, perhaps never to be replaced by true bone, but the bone that is produced by marrow is perfect from the beginning, and need never be absorbed. The slow restitution of the balance between bony growth and repair, and the general resumption of their proper functions by the injured marrow and periosteum, bring about a removal of surplus bone wherever it may be, and a deposit of new bone wherever it may be required. The rounding off of protruding points, and the restitution of the medullary cavity, processes which may take years to complete, now conclude the cycle of fracture repair.

Callus Cartilage.—Billroth,[1] speaking of the appearances met with in a fracture in the rabbit of ten to twelve days' standing, thus refers to callus cartilage:—"The spindle-shaped swelling of the soft parts has, for the most part, the appearance and consistence of cartilage, and agrees therewith microscopically; in the medullary canal also we find fresh formation of cartilage in the vicinity of the fracture. The broken bone lies in this cartilage, just as if the two fragments had been dipped into sealing-wax and stuck together." If it were necessary specially to emphasise the fact that the repair of fractures in man is widely different from the same process among the lower animals, such a description as the above might be appealed to. Except perhaps in young children, we see nothing approaching to this abundant formation of the so-called callus cartilage in man.

In the specimens which I have examined the part played by callus cartilage in repair was almost ridiculously small. In fact, judging from the above, I should scarcely have postulated the existence of such a tissue as callus cartilage at all. I know of no

[1] "Surgical Pathology," *New Syd. Soc. Trans.* vol. i. p. 247.

new tissue resembling cartilage that cannot be referred to a metamorphosis of old tissue. The most perfect mimicry of cartilaginous tissue is provided by transformed fibrous and ligamentous structures. Coming after this, the œdematous outlying areolar tissues with sparse fibres and large round cells lying in a glassy homogeneous matrix, often have a close resemblance to true hyaline cartilage. Even clot tissue may, as we have seen, be transformed by a process of infection carried bodily through it into something very like cartilage; and other tissues in various degrees carry out the resemblance.

But none of these are true cartilage. They are old tissues transformed into a condition which we know to be histologically suitable for infiltration with calcareous salts, and nothing more. Where these old tissues do not readily undergo inflammatory changes in this direction, the calcifying influence still does its best, and lays hold of them also. This influence does not overlook those sluggish tissues and have recourse only to the specially prepared callus cartilage. Doubtless if the nidus for bony new growth in man were callus cartilage alone, the repair of fractures would be a more rapid and perfect proceeding altogether. But tissues thirty or forty years old in the human adult are not so plastic as in one of the lower animals, which will probably have reached only its fourth or fifth year. An ideally perfect nidus for bony development in human fractures not being forthcoming, the best is made of an imperfect transformation of the old.

I do not argue that this callus cartilage in the lower animals is not a new growth specially provided for the purposes of fracture repair. All I would maintain is that I have seen nothing to show that it is such in man. In fact, had our investigations been confined to human fractures, I doubt if we should ever have heard the term "callus cartilage" at all. At all events we should never have credited the small tracts and areas of cartilaginous-looking tissue which run ahead of a line of calcification or traverse the mass of inflammatory embryonic tissue with being the only, or even the chief medium in which the uniting bone is to be developed.

For the whole process of fracture repair we might give a generalised summary as follows:—

A plastic parent tissue is provided partly by the swollen and inflamed pre-existing tissues, partly by organised inflammatory neoplasm. The ossific stimulus lays hold of this parent tissue and infects it with the first change towards ossification, viz., calcification. The calcifying process proceeds along numerous irregularly disposed lines through the parent tissue modifying it finally before it completely invades it. This modification of matrix ahead of the line of calcification consists chiefly of a swelling of the intercellular substance bringing about an occasional resemblance to ordinary hyaline cartilage. When the process is completed by the formation of an areolar calcified tissue containing variously modified embryonic substance in its meshes, we have the great mass of so-called bony callus. This callus material soon begins to undergo the further changes towards true ossification; namely, absorption of the calcified substance and development on these calcified lines of true lamellar bone by osteoblasts derived from outgrowing marrow or cambium layer of periosteum.

But, as a matter of fact, except in special positions, the completion of the ossific process is rarely reached. The physiological completion in the development of true lamellar bone is seen in the permanent uniting medium between the fractured ends.

A summarised statement of the parts played by the individual tissues concerned may be given as follows:—

Blood Clot.—The greater part of the effused blood is absorbed and disappears. Some amount of blood clot usually remains in certain positions to become organized. After organisation, more or less perfect, it may either directly become a parent tissue for bony growth, or undergo further transformation towards this end. Blood clot organises by preference in the exposed medullary canals and over the jagged ends of the broken bones. Where it forms the chief nidus for ossification, bony union is longest delayed.

Periosteum.—Periosteum contributes to fracture repair rather by virtue of its position as a fibrous tissue than through its ordinary function as a bone producer. Periosteal callus is rather a calcifying cellulitis than an ossifying periostitis. Periosteum does not undergo very much change preparatory to calcification. The calcified periosteal trabeculæ are the least

perfectly developed and the most unstable of all the areolar bony callus material. Shreds of periosteal fibre traversing embryonic inflammatory tissue contribute materially to the rapidity with which calcification is carried out.

Tendon and Ligament.—Where present these tissues play an important part in the ossifying process. Sometimes undergoing calcification without exhibiting material change of structure, they frequently, however, are subjected to preparatory modifications which assimilate them in appearance to true cartilage, and thereafter behave in ossification as ordinary cartilage does. The presence of an abundance of ligamentous tissue should warn us of a possible overgrowth of uniting bone.

Fibro-cartilage.—White fibro-cartilage may become calcified without undergoing preliminary structural changes. The calcareous deposit is finely divided and dense; and the advent of the absorptive process is long delayed. As a temporary bond of union it is, when once formed, the strongest of all.

New inflammatory tissue contributes to bony growth after it has been in varying degrees assimilated to the formed tissues in its neighbourhood. Occasionally it assumes a resemblance in structure to hyaline cartilage.

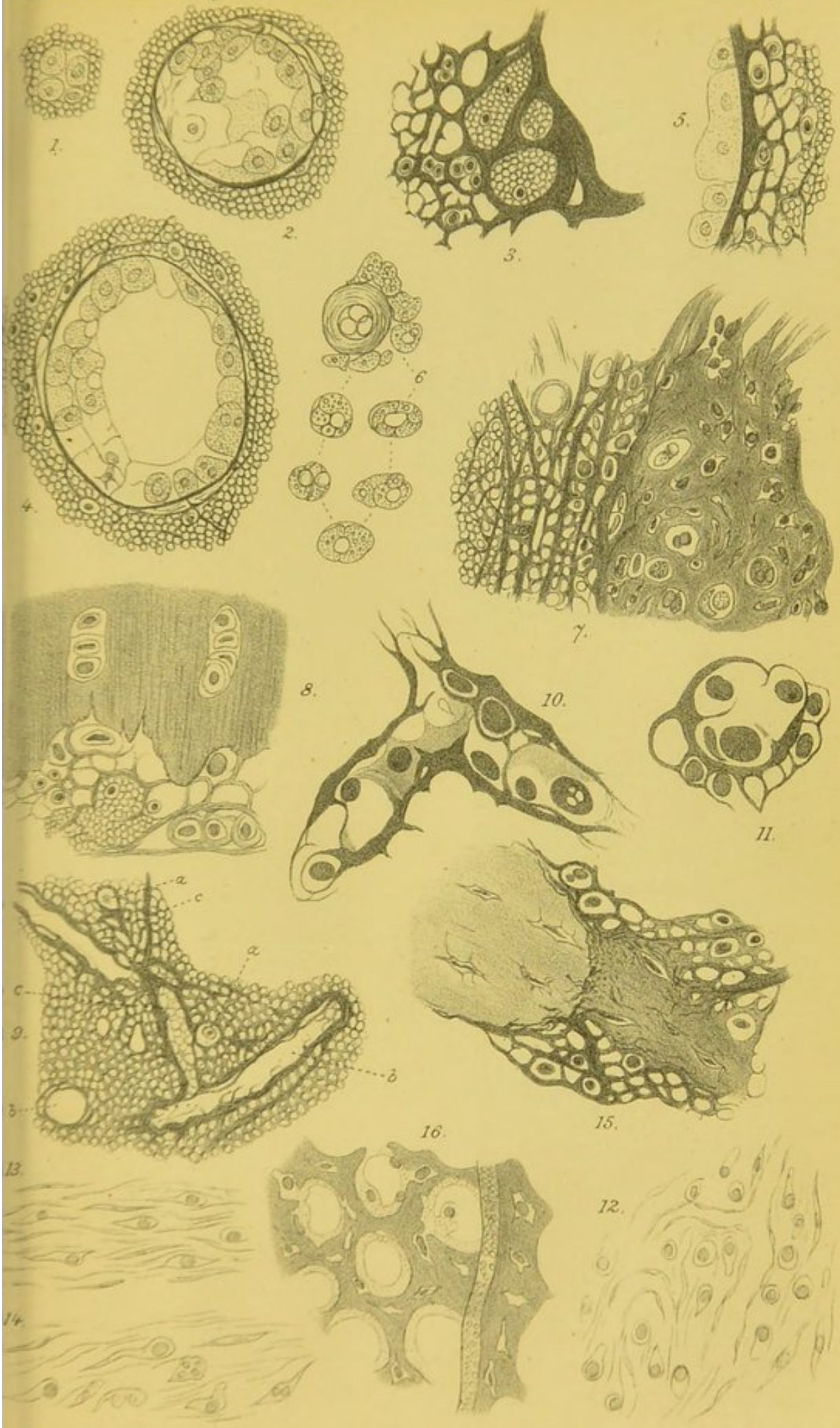
This must conclude for the present our study of fracture repair. In a future paper I hope to extend these observations by clinical applications. If for any given case of fracture, by forming an estimate of the amount of injury present, and by bearing in mind the nature of the tissues involved and the potentiality of these to serve as bases for bony growth, we should be able to observe special precautions towards the promotion of union, or to give a more certain prognosis as to the period when union will be complete, we should have made a step forward in our treatment of this large class of surgical injuries. In most cases I believe this can be done. Some fractures I believe to be systematically overtreated; others are not kept for a sufficient time at rest. Occasionally, where there is a superabundance of callus matrix, our determination to secure perfect union runs to the extreme of bony overgrowth and perhaps anchylosis. And, on the other hand, are we not too prone to act upon the experience that certain fractures rarely

unite by treating them as if union never were possible? To the solution of these and such problems our study of the process of fracture repair ought to be directed.

EXPLANATION OF PLATES VI. AND VII.

PLATE VI.—Figs. 1, 2, 4, and 5. Representing the process of alveolation of blood-clot. Fig. 1 (× 300) shows four epithelial cells embedded among the blood cells. Fig. 2 (× 300) represents the formation of a hollow apparently by means of those large cells. Fig. 3. The commonest forms of trabeculæ in clot, the largest and smallest being here in contact. Fig. 4 (× 300). A more advanced stage of the same. Fig. 5 (× 300). A portion of the wall of a large cavity which was surrounded by thick trabeculæ, and lined with large flattened cells. Fig. 6 (× 500). Specimens of large yellow granular cells (? hæmatoclasts) distributed through the clot tissue. In some of them are red blood discs. Fig. 7 (× 300). Represents a transformation of blood clot into a structure resembling hyaline cartilage. The gradations are drawn only at one side. Fig. 8 (× 300). Section through fractured articular cartilage with adherent blood clot. Fig. 9 (× 300). A young vascular area in clot tissue. Two tubes are seen in longitudinal, one in transverse section. Figs. 10 and 11 (× 800). Longitudinal and transverse views of the earliest stages of vascular growth. Fig. 12 (× 300). Young vessels in inflammatory callus matrix. Figs. 13 and 14 (× 300). Familiar forms of embryonic tissue, in which the chief amount of bony callus is developed. Fig. 15 (× 300). Changes in clot adherent to a spicule of bone. Fig. 16 (× 300). Calcification of matrix around fat cells.

PLATE VII.—Fig. 1 (× 100). Areolar calcification of periosteal fibre and growth of true bone by periosteal osteoblasts going on side by side. Fig. 2 (× 350). Transverse section through the tip of a calcifying spicule developing in periosteal fibre. Dense calcified area containing three lacunæ is surrounded by a deeply-stained zone of osteogenetic substance. Fig. 3 (× 150). A longitudinal section of a similar spicule. Fig. 4 (× 300). Absorption of areolar calcified callus. (The shading is done too smoothly and regularly.) Fig. 5 (× 100). Transverse section of portion of a turkey's tendon, showing calcification at the periphery (top of drawing), and true ossification in the centre (bottom). Figs. 6, 8, and 10 (× 200). Illustrating the steps in calcification and ossification of tendinous structures in fracture. Fig. 7 (× 300). Transformation of ligamentous tissue into one resembling cartilage, with incipient calcification at bottom. Figs. 9 and 13 (× 300). Transverse and longitudinal sections of calcified fibrous tissue, each with portions of a substance resembling cartilage. Fig. 11 (× 300). Calcified "callus cartilage" on the top of a spicule of bone. Fig. 12 (× 150). Calcified fibro-cartilage of great density, showing little structural change, and becoming absorbed on one side.



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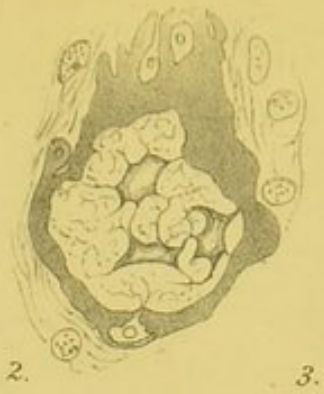

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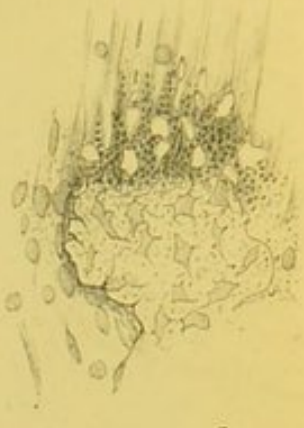

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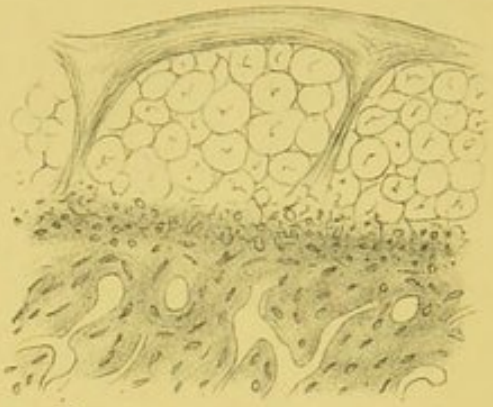

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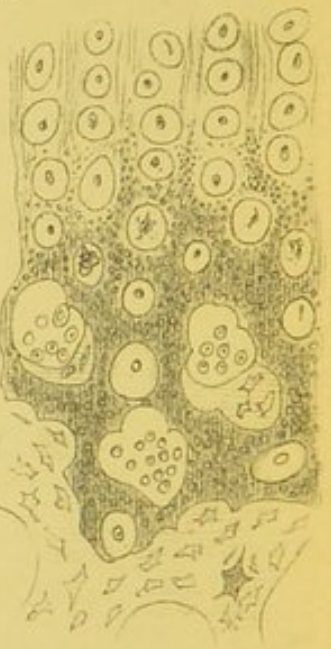

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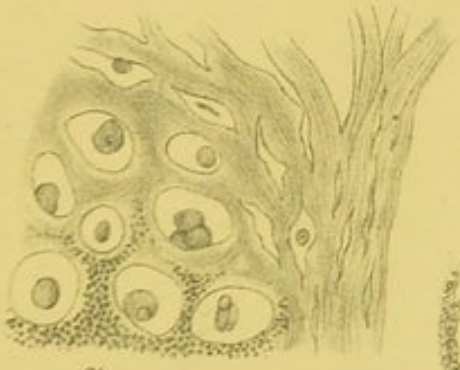

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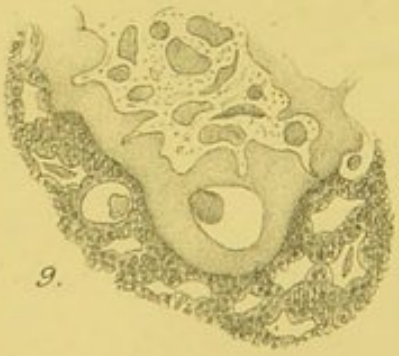

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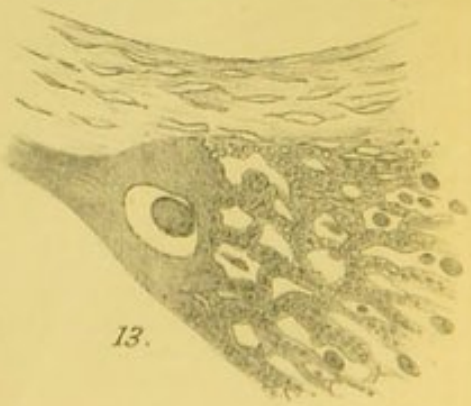

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