THE AMERICAN JOURNAL OF PATHOLOGY

VOLUME II NOVEMBER, 1926 NUMBER 6

A STUDY OF HYPERPLASIA OF THE BONE MARROW IN MAN*

FRANCIS W. PEABODY, M.D.

(From the Thorndike Memorial Laboratory, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass.)

Clinical observations and studies of the peripheral blood have made important contributions to the differentiation and classification of the various types of anemia, but a cloud of mystery still obscures many of the fundamental processes which underlie the diseases of the blood-forming organs. Even when the ultimate cause of an anemia is recognized, the way in which it is produced often remains entirely unknown. The problem of the pathology of the diseases of the blood appears at first sight to be wholly one of physiology, but the trend of recent investigation indicates that in no other field are structure and function more closely interrelated, and it soon becomes apparent that the study of the normal and pathologic physiology of the blood cannot be approached without a simultaneous study of the morphology of the bone marrow. Unfortunately the structure of active human bone marrow, even under normal circumstances, is extremely complex, and in many pathologic conditions the histology is so confused as to defy direct analysis. If, therefore, the diseases of the hematopoietic system are to be satisfactorily interpreted in terms of bone marrow function it would seem worth while to pay attention to the simplest pathologic changes, and the observations to be reported in this paper are the result of a study of the early stages of hyperplasia developing in the atrophic femoral bone marrow in man.

* Received for publication July 15, 1926.

The fact that comparatively little is known at present about the pathology of the diseases of the blood is largely due to the imperfect and inaccurate information available as to the processes of normal blood formation and destruction, and the many opinions and hypotheses which have been hitherto put forward in this field have contributed little of significance when applied to clinical conditions. Much new light has been thrown on the subject, however, by the recent work of Sabin, Doan and Cunningham[1,2,3,4] and their observations (based on animal experiments, with occasional references to man) appear to be a starting point from which the pathology of the clinical anemias may be gradually built up. Doan recognized that it is almost impossible to determine the structure of a tissue which is as complex as normal animal bone marrow, and in order to simplify the conditions he produced an experimental hypoplasia and then studied the successive stages of the hyperplasia which developed as the marrow returned to normal. In man, however, the conditions are in some ways more favorable to the investigator than they are in the lower animals, for while the active marrow of the vertebrae and flat bones is extremely complex, the marrow of the long bones is normally, at least in greater part, fatty and hypoplastic. Man, therefore, normally provides the necessary hypoplastic and relatively simple bone marrow, and in pathologic conditions one can find the different stages of hyperplasia which correspond to those produced in animal experiments.

Hyperplasia of the bone marrow, in the sense of an increase of cellularity, is a very common type of reaction in human disease and while the more extreme forms, with complete replacement of fat by marrow cells, are usually associated with diseases primarily affecting blood formation, less extensive degrees of hyperplasia are met with in a great variety of conditions, including many acute infections. It would be unwarranted to suggest that the changes which take place in the bone marrow in different acute infections are always similar in character or that any of them necessarily represent early stages of what is found in any particular form of severe anemia, for there is plenty of evidence to indicate that there are many types of bone marrow hyperplasia. It is reasonable, however, to suppose that a study of the simpler hyperplasias of acute infections and the steps in their development from normal hypoplastic marrow may assist the subsequent analysis of more complex pathologic pictures.

The present paper deals directly with the bone marrow of a single case of typhus fever, but the main observations have been confirmed in other cases of the same disease and in other pathologic conditions. This case was selected because of the excellent state of preservation of the tissue and because it shows so many of the stages in the transition from a completely fatty bone marrow to one with a cellularity approaching that of normal human vertebral marrow in the area of a single section. Fig. 1 illustrates, with low magnification, the general character of the material. In passing from the normal to the cellular part of the section it is comparatively easy to trace the successive steps in the development of the hyperplasia. The tissue is an example of relatively pure erythropoiesis and it is fortunately in a state of vascular engorgement in which many of the blood vessels are defined by blood cells almost as clearly as they would be by an artificial injection mass.

The necropsy was performed by Dr. S. B. Wolbach in Poland in 1920, and I am indebted to him for permission to use the material from the case.

The tissue, which was from the femur, was cut in serial sections 6 microns thick, and emphasis must be laid on the fact that many of the observations recorded can only be made by a study of serial sections. In describing the tissue an attempt will be made to consider the various steps in the progressive development of the hyperplasia as nearly as possible in the sequence in which they probably occur. The anatomic nomenclature of Sabin and her collaborators will be followed.

Before proceeding to a description of the pathologic material, brief mention may be made of some of the characteristics of normal human bone marrow from the shaft of the femur. In contrast to the marrow from the epiphyses, which may be moderately cellular and active in a functional sense, the marrow of the shaft of the femur is essentially hypoplastic, inactive and almost without true marrow cells. It consists of large fat cells closely packed together, with occasional elongated, darkly staining nuclei compressed between the fat globules (Fig. 3). As shown much more clearly in the early stages of hyperplasia, these are the nuclei of endothelial cells. The nuclei of the fat cells are not at all prominent and the reticular cells described by Sabin are rare and difficult to distinguish. Another striking feature is the limited degree of vascularity. Small arteries and veins are

present, but the venous sinusoids which are so evident in normal vertebral and in many hyperplastic marrows are narrow and relatively few in number.

It is difficult to determine from the histologic evidence presented by the pathologic tissue under consideration as to what is actually the initial step in the development of hyperplasia in a fatty bone marrow, for two changes are found in areas that are otherwise entirely normal and they apparently take place almost synchronously. One of these is a proliferation of the endothelial cells situated between the fat cells. Instead of the few scattered nuclei which are found in aplastic fatty marrow (Fig. 3), there are large numbers of endothelial nuclei (Fig. 2), and instead of elongated, darkly staining nuclei with little visible protoplasm, there are large, oval, vesicular nuclei with prominent cell bodies lying closely adjacent to the fat globules (Figs. 4 and 5). Doan, Cunningham and Sabin [4] also describe this hyperplasia and hypertrophy of the endothelium.

The second early change is an increase of blood supply, as shown by the appearance of new, wide venous sinusoids, and more particularly by the opening up of collapsed vessels lying between the fat cells. By means of injections with India ink, Doan [3] was able to demonstrate that the narrow, elongated endothelial nuclei lying between the fat cells in atrophic marrow are in fact the nuclei of the endothelial walls of capillaries which are not open to the circulation and which are collapsed by the pressure of the tightly packed fat cells. Drinker [6] also found evidence suggesting the presence of the same vessels. The existence of these "intersinusoidal capillaries" was indicated by the entrance into them of particles of the injection mass, but it is still more clearly shown in the stage of vascular engorgement which is part of the earliest phase of the hyperplasia in the human tissue now under consideration. At this stage, coincident with the appearance of many venous sinusoids, the intersinusoidal capillaries become injected with blood and a vast system of blood vessels, lying between the individual fat cells, is revealed. Fig. 6 illustrates, with low magnification, this early stage in the development of hyperplasia — the large venous sinusoids and the network of intersinusoidal capillaries outlining the fat cells. Some of the fat cells are sectioned at such a level that they are almost completely surrounded by patent capillaries (Fig. 8), and others have an open capillary containing blood cells on one side, and collapsed capillaries

which may be indicated by the long, narrow nuclei of endothelial cells, on the other sides. When blood enters an intersinusoidal capillary and the lumen becomes patent, the walls of the capillary are seen to be attached to the fat cells between which they have been compressed, and as the capillary lumen becomes wider the walls of the capillary remain in contact with the fat cells while the latter become in turn compressed. The structure of the wall of the intersinusoidal capillaries is similar to that of the venous sinusoids, consisting only of a single layer of endothelium, and the fact that, with the development of hyperplasia, venous sinusoids appear where one would only expect to find collapsed capillaries in the atrophic marrow, is evidence that the venous sinusoids are merely capillaries which have become widely open to the blood stream. As Doan, Cunningham and Sabin [4] have stated: "A sinus is a patent intersinusoidal capillary and an intersinusoidal capillary is a collapsed sinus, the state of dilatation or collapse normally depending upon, or at least accompanying, the specific functional capacity shown by the endothelial cells at the moment." The system of intersinusoidal capillaries may be almost completely collapsed in fatty marrow such as that of the normal human femur, and it probably takes little part in the actual nutrition of tissue. This function is carried on by a rather limited number of "transition capillaries" (Doan) which act as intermediary communications between arterioles and venous sinusoids. Fig. 9 shows one of these vessels with a small side branch, lying between fat cells and traversing a widely dilated intersinusoidal capillary.

While the extensive network of intersinusoidal capillaries seems to play no significant part in the nutrition of the bone marrow, Sabin and her associates have shown that it has a most important function in relation to the formation of red blood corpuscles, for the primitive precursors of the erythrocytes apparently arise from the endothelium which forms its walls. This phase of the problem of hyperplasia will be taken up, however, only after the question of the anatomic relationship of the intersinusoidal capillaries to the venous sinusoids has been considered, — a relationship which bears directly on the problem of the delivery of young erythrocytes into the blood stream, and one which can be studied best in the first stage of marrow hyperplasia. The failure of early investigators to recognize this system of intersinusoidal capillaries is probably explained by the

fact that they have usually concerned themselves with the study of animal marrows and the advanced pathologic changes in man, and in such tissues the intersinusoidal capillaries become masked by the enormous numbers of true marrow cells. It is only in the first stage of hyperplasia, when the marrow consists essentially of fat cells and of an open vascular bed, that one can see the relations of the intersinusoidal capillary field to the general circulation.

Doan [3] not only discovered the intersinusoidal capillary bed but he also described the manner in which the capillaries open into the venous sinusoids by means of conical openings in the walls of the sinusoids. These openings are very easily made out in the present case, for many of the capillaries are wide open and filled with red blood cells so that their ramifications can be easily followed. The large venous sinusoids are surrounded by spherical fat cells and between two fat cells one may find a capillary, which has opened up and contains blood, leading toward a venous sinusoid into which it opens by a conical aperture. The sides of the opening are formed by the endothelium of the sinusoid being carried over the convex surfaces of the fat cells so that it becomes continuous with the endothelium of the capillary. The "mouth" of the capillary, where the vessel widens out to enter the sinusoid, frequently contains a number of red blood corpuscles which appear to be about to enter the sinusoid. The upper and lower borders of the conical openings are often defined by the nucleus of an endothelial cell which lies in the horizontal plane, and in favorable places one can make out, by focusing, that the endothelium of the sinusoid bends outward in the direction of the capillary. These openings are illustrated in Figs. 7 and 10. Fig. 11 is a drawing of two openings from intersinusoidal capillaries, one on either side of a fat cell, into a venous sinusoid, and Figs. 12 and 13 are photographs, with high magnification, of each of the openings. These illustrations indicate the character of the openings with unusual clearness, especially when it is considered that they show only a single plane. Convincing evidence, as far as this can be derived from the histology, of the fact that the intersinusoidal capillaries connect with the venous sinusoids by means of conical openings in the walls of the sinusoids, is only to be obtained by focusing and by the examination of serial sections. The study of serial sections also shows that there are innumerable anastomoses between the intersinusoidal capillaries and that the openings into the venous sinusoids

are extremely numerous. In many places the openings appear to come between each pair of fat cells. The mesh of the capillary network is so complex that it unquestionably results in the formation of anastomoses between the venous sinusoids, but whether this intersinusoidal capillary bed is also directly connected with the arterioles is somewhat more uncertain. Large open capillary spaces are often found in close association with arterioles but no openings between the two have been definitely demonstrated. Histologic evidence on this point might well be unobtainable, while the finding by Doan of India ink particles, injected into the arterial circulation, in the collapsed intersinusoidal capillaries suggests they may have reached the capillaries from arterioles, although it is perhaps more probable that the granules entered the capillaries from the venous sinusoids. In the animals injected by Doan, however, the intersinusoidal capillaries were closed and the pressure in the venous sinusoids must have been low. The study of tissue, like that of the present case, in which there are areas with open capillaries and areas with closed capillaries suggests some control over the capillary bed such as is known to exist in other organs. This control over the opening and closing of the capillaries is considered by many to be regulated by the tone of the precapillary arterioles. The venous sinusoids of the bone marrow are formed by a single layer of endothelium and they are without muscular or elastic tissue. It is difficult to see, therefore, how they could regulate a flow of blood out into the capillary bed. Possibly some specific stimulus, acting directly on the cells of the intersinusoidal capillaries or on the arterioles determines their opening as well as their functional state.

Thus far only the earliest phases in the development of hyperplasia of the bone marrow have been described, and it has been shown that in the part of the tissue in which there is least deviation from the normal, the changes consist of an increased vascularization which results largely from the opening of the vast network of intersinusoidal capillaries, and the hypertrophy and hyperplasia of the endothelium of these capillaries.

The second stage in the development of bone marrow hyperplasia is characterized by the appearance of the true marrow cells from which the mature blood cells are derived. As has already been stated, the tissue under consideration shows an unusually pure erythropoiesis and no attention will be paid to the question of leucocyte formation.

The smallest cell groups in which there are only a few very primitive cells may be taken as representing the earliest step toward blood formation. In this tissue there are many areas consisting of endothelial cells and one or more definite megaloblasts, and the striking feature of these cell groups is that the megaloblasts are either attached to the endothelium which forms the intersinusoidal capillaries or they are free, within the intersinusoidal capillaries. Sabin [1] observed the formation of megaloblasts from the capillary endothelium of the living chick blastoderm and watched the megaloblasts drop off the endothelium into the lumen of the capillary. Subsequently she and her associates [4] showed that red cell formation takes place in a similar manner in adult birds and mammals. The histologic evidence derived from the study of early bone marrow hyperplasia in adult man, as illustrated by the present case, is entirely in harmony with the conception that the primitive cells of the erythrocyte series are derived from the endothelium forming the intersinusoidal capillaries, that they separate off into the lumina of these capillaries and develop to maturity within these endothelial-lined spaces. According to this view of erythropoiesis the red blood cells are formed within endothelial-lined spaces which are directly connected with the venous sinusoids and thus within the vascular system. Fig. 14 illustrates the hypertrophy of the endothelium of an intersinusoidal capillary, such as has already been seen in Figs. 4 and 5, and in addition it shows three very early cells of the erythrocyte series, probably megaloblasts, in close association with the endothelium. Fig. 15 is a photograph of a space between four fat cells, such as has been found in the stage of vascularization to be lined by the endothelium of intersinusoidal capillaries, filled by five cells of which three are probably to be classed as endothelial cells and two as megaloblasts, one of the latter being in mitosis. In Fig. 16 there is an endothelial cell, out of focus, lying adjacent to the lower fat cell, and there are two definite megaloblasts in a similar relation to the upper fat cell on the left. At this earliest stage of cellular proliferation, areas may be found in which the fat cells are entirely separated by cords of large cuboidal cells which resemble megaloblasts more than endothelial cells, but some of which are probably erythroblasts. Sabin believes that the megaloblastic stage is usually of short duration and that these cells quickly divide and become what she terms erythroblasts. Fig. 17 is a drawing to illustrate such

an area. Below is an endothelial cell filling the space between two fat cells, and the other spaces which represent intersinusoidal capillaries are largely filled by rows of megaloblasts, erythroblasts and a few more mature cells of the erythrocyte series. Fig. 20 is a photograph of the same area under higher magnification. The spaces between the fat cells, which during the stage of vascular engorgement were seen to consist of capillaries lined with flat endothelium, are in this later stage filled with columns and clumps of cells which are frequently in a state of active proliferation, as shown by the number of mitoses. Double columns of cells may also appear, indicating that the formation of megaloblasts is taking place from the endothelium on both sides of the capillary, and the capillary lumen is usually completely occluded by the cell growth. Where the section cuts the plane between the lower aspect of one fat globule and the upper aspect of the globule below it, one gets, not a column of cells, but a more or less extensive island of primitive cells of the erythrocyte series. At this stage, when active proliferation is in progress, the flat endothelium with its long narrow nuclei is much less apparent than under normal conditions and it seems to be largely replaced by the bigger cuboidal cells which line the capillary spaces. In the areas of early cellular hyperplasia the venous sinusoids are numerous, large and prominent, and the most striking areas of cellular proliferation are usually found in close relation to a venous sinusoid. This is not in harmony with the observation of Doan [4] who found in experimental animals that erythropoiesis was most marked in places in which the circulation was relatively inactive. Not infrequently a row or group of megaloblasts is situated along the outside of a venous sinusoid, between the sinus and an adjacent fat cell; the endothelium of the sinusoid, however, retains its usual flat character with long thin nuclei. It is most probable that the megaloblasts arise from endothelium covering the fat cell rather than from the endothelium of the venous sinusoid which in the case under consideration shows no evidence of taking on any erythropoietic function.

The next stage in the development of the hyperplasia of the marrow is that in which cells of more mature type than the megaloblast and erythroblast make their appearance. Again the process can be best analyzed in the smaller cell groups. After the megaloblasts have become detached from the endothelium of the intersinusoidal

capillaries, they may divide, as shown by mitotic figures, and go through the process of maturation, so that erythroblasts, normoblasts and extruded normoblastic nuclei may be found free in the capillary spaces. Mature erythrocytes may also be present, but it is, of course, impossible to determine whether these cells have developed in the intersinusoidal capillaries or whether they have been brought in from the general circulation. The fact that in the earliest stages of megaloblastic hyperplasia the intersinusoidal capillaries may be occluded by endothelial cells and megaloblasts, and contain very few erythrocytes, suggests that the erythrocytes which reappear in the capillaries with the normoblasts have actually been formed locally. The degree of maturity of the cells varies from field to field and normoblasts are often found grouped together in considerable numbers. These clumps of normoblasts may be found in the center of the capillary space, surrounded by more primitive cells, and they are also likely to lie in close relation to a venous sinusoid. Fig. 18 illustrates this phase of the process. It shows a somewhat larger space between fat cells, filled with a clump of cells containing several erythroblasts, many normoblasts with typical pyknotic nuclei and a few erythrocytes. Reasoning by analogy it may be assumed that this space is a dilated intersinusoidal capillary and the conception is borne out by the presence of the endothelial cell, with elongated nucleus, which lies closely adherent to the upper fat cell.

Up to this point the process of hyperplasia, with the development of cells of the erythrocyte series from the endothelium of the intersinusoidal capillaries and within these capillary spaces, has been comparatively easy to trace, but from now on it becomes more confusing. The cellular areas grow larger and they appear as complex masses of cells without definite structure. All the cell types thus far observed are present and new ones enter into the picture. Endothelial cells, still a part of the capillary wall, may become phagocytes of red blood cells; clasmatocytes with ingested normoblasts or erythrocytes are free in the cell mass; leucocytes of various types have made their appearance; and megalokaryocytes may also be found. Although these larger areas of hyperplasia are without doubt the seat of active erythropoiesis, they may contain comparatively few mature red cells, and these are often grouped near the venous sinusoids, as if they were ready to slip into the circulation. Fig. 19 illustrates a cellular area situated near a large venous sinusoid (on right). The

elongated nucleus of the flat endothelium of the sinusoid may be compared with vesicular nuclei of the hypertrophied endothelial cells in the angle between the two fat cells above and on the left. The latter, in close relation to the fat cell, undoubtedly belong to the endothelium lining the now greatly distended intersinusoidal capillary, and they represent the type of active endothelium from which megaloblasts originate. Free in the cell group are megaloblasts (several near the sinusoid in the upper right corner), erythroblasts, normoblasts, erythrocytes, clasmatocytes which have ingested red blood cells, and a few myelocytes and leucocytes. Fig. 22 is a drawing of a similar group of cells also near two venous sinusoids (upper right and lower left). It is impossible to illustrate these areas satisfactorily with photographs as many of the cells are indistinct at any one level of focusing. The endothelial border of this space is indicated by the flat endothelium along the upper middle fat cell and the hypertrophied endothelial cell lying next to the upper left fat cell. In the center, just below the large sinusoid, is a group of large early cells of the erythrocyte series — megaloblasts and erythroblasts. The shapes of these cells suggest that they were closely adherent to one another and that they have shrunk apart in the process of fixation. The same relationship is seen in the four megaloblasts which lie along the right middle fat cell. This tendency for early megaloblasts to remain closely attached to one another, like the component cells of a tissue, is extremely common and they are often found in rows or double columns. As they develop they seem to lose this adhesiveness and become separate, independent cells, the process being analogous to what Key [5] has described as taking place in the maturation of erythrocytes. Just below the center of the field in Fig. 22 is a megaloblast in mitosis. Fig. 23 is a drawing of a larger cellular area and one which is approximately the size of the cell areas in normal vertebral marrow. Evidences of the endothelium bordering the cell group may be found along the fat cells and the general cytology is similar to that in the smaller cellular areas but it has become complicated through the entrance of more cells of the leucocyte series. It remains, however, much less confused than the picture of normal active marrow as the number of leucocytes is relatively small, the process continuing to be, even in these most hyperplastic areas, one of comparatively pure erythropoiesis.

The bone marrow is enclosed in a rigid container, and cellular

hyperplasia with its associated vascular engorgement can only take place at the expense of something which filled the marrow cavity during the state of aplasia. Fat tissue is peculiarly adapted to being the complementary substance, for fat cells can give up their charge of fat rapidly and can become infinitely smaller without loss of function. Compression, at least within wide limits, does not injure them, for they retain their ability to take up fat again and thus fill any space that results from subsequent retrogression of the hyperplasia. Between marrow cells and fat cells there exists a remarkable reciprocal relationship, in which the former appear to dominate while the latter serve the subsidiary function of filling in any space not occupied by active myeloid tissue. Evidence of this relationship is seen in many experimental conditions in which marrow hyperplasia or aplasia, accompanied by a decrease or increase of fat, arise with extraordinary rapidity. When the cellular areas increase in size there is a simultaneous diminution in the amount of fat. Gradual compression of the fat cells produces a decrease in their size before they disappear completely, and in a very hyperplastic marrow the few remaining fat cells are usually much smaller than the fat cells in an aplastic marrow. In the tissue now under consideration the most highly cellular parts contain about twenty fat cells per high dry field as against approximately thirty per field in the aplastic areas and the individual fat cells are definitely smaller. In a highly cellular marrow, such as the typical marrow of pernicious anemia, the fat often seems to have been completely displaced, but it is certain that the fat cells continue to ırvive, for as soon as a remission of the disease sets in the hyperplasia of the marrow cells retrogresses and fat is again deposited in the fat cells. The manner in which the bone marrow can alternately take up and give up fat indicates that the fat cells are as constant a part of its structure as the blood vessels and the supporting framework of reticulum. When marrow hyperplasia recedes and the myeloid cells disappear there is not only a new deposition of fat in the fat cells but there is a complete, and often an extraordinarily rapid return to the structure of typical aplastic marrow.

In the highly cellular areas of the marrow, illustrated by Figs. 19, 22 and 23, the venous sinusoids are large, numerous and engorged with blood. They appear to be surrounded by an intact wall of endothelium and there is little to suggest the openings of the inter-

sinusoidal capillaries that are so clearly made out in the areas which show the very earliest stage of hyperplasia. The only possible indication of these openings, indeed, is to be found in the occasional small clumps of mature erythrocytes situated just at the edge of the sinusoid and which may mark points of entrance into the vessel. It is, however, not remarkable that the openings into the venous sinusoids are thus obscured, for the whole structure of the tissue has been completely altered. In the first stage of hyperplasia these openings connected the venous sinusoids with delicate intersinusoidal capillaries, some of which were collapsed and others, more easily distinguished, were filled with mature red blood corpuscles. This was followed by the development of cells of the erythrocyte series within the capillaries, the compression of fat cells and the formation of large cell masses within the intersinusoidal capillaries. In this late stage of hyperplasia the intersinusoidal capillaries have become wide cell beds and their individual limits have become indistinguishable just as a series of brooks which flow through a field lose their identity when the spring floods cause them to swell until they merge and convert the field into a great lake.

In spite of the fact that in a highly cellular marrow it is impossible to observe definite openings between the intracapillary cell areas which form so much of the tissue and the venous sinusoids, the study of the development of hyperplasia certainly indicates that such openings exist and that through them the mature erythrocytes enter the circulation. The process by which the cells pass from their position in the intersinusoidal capillaries into the venous sinusoids is not, however, clear. Histologic evidence shows that the more immature cells are often at the periphery of the capillary and either adherent to the endothelium or adherent to one another so as to form groups or columns, while the more mature cells occupy a central position in the cell mass. It is possible that the latter cells, which have lost their adhesive qualities, are gradually forced towards the venous sinusoid by the pressure of cell growth in the sense of Drinker,[6] and it is also possible that a true circulation through the venous sinusoids, such as appears to be present in the earliest stage of hyperplasia, persists and washes out the mature cells into the veins.

While the tissue which has been described is an example of relatively pure erythropoietic hyperplasia, it also shows a considerable

development of megalokaryocytes. Little is known about the origin of these cells but the fact that in the early phases of hyperplasia they are often found closely adherent to fat cells, in the position occupied by the endothelium of the intersinusoid capillaries, suggests that they, as well as megaloblasts, may arise from endothelium. Fig. 21 is a photograph of a megalokaryocyte in such a position.

Summary and Conclusions

In an attempt to throw light on the pathology of the bone marrow and thus on the fundamental factors which underlie the diseases of the hematopoietic system, the histology of the femoral marrow from a case of typhus fever has been described. This tissue was selected because it is an example of almost pure erythropoiesis and because it shows the various steps in the development from an atrophic to a relatively hyperplastic marrow within the area of a single section. The first changes consist of the appearance of large venous sinusoids, the opening to the circulation of the extensive network of intersinusoidal capillaries, and the hypertrophy and hyperplasia of the endothelium lining the capillaries. At this phase the openings from the intersinusoidal capillaries into the venous sinusoids can be easily detected. In a later stage the precursors of the erythrocytes appear inside the intersinusoidal capillaries, and the histologic picture is consistent with the concept that they are derived from the endothelium of the intersinusoidal capillaries. The earliest islands of marrow cells are composed of a few megaloblasts attached to endothelial cells or free within the capillary spaces. Larger cell islands usually contain more mature types of the erythrocyte series (erythroblasts and normoblasts) and there is a general tendency for the immature cells to be adherent to one another at the periphery of the group and for the mature cells to be free and independent in the center. As the cellular areas increase in size the picture becomes complicated by the appearance of other cell types, and in this advanced stage of hyperplasia the evidence that the erythrocytes develop within capillaries which are in direct communication with the venous sinusoids becomes much more obscure. There are, however, indications that the intracapillary formation of erythrocytes persists even in highly cellular marrows, and this relation suggests the general method by which young red blood cells enter the circulation.

The histology of the type of bone marrow hyperplasia which has been described can be readily analyzed on the basis of the work of Sabin, Doan and Cunningham, and this study of human tissue is offered in support of their conceptions.

I am greatly indebted to Miss Lillian M. Leavitt for the preparation of the serial sections of bone marrow, and to Miss E. Piotti for her beautiful and accurate drawings.

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DESCRIPTION OF PLATES

PLATE 91

FIG. 1. General character of material described. Aplastic marrow above; marked hyperplasia below; and intermediary stages in development of hyperplasia in the center. × 50.

FIG. 2. Drawing to illustrate hypertrophy and hyperplasia of endothelium of intersinusoidal capillaries lying between two venous sinusoids. × 500.

FIG. 3. Drawing of normal bone marrow from human femur, showing elongated nuclei of collapsed intersinusoidal capillaries. × 500.

FIG. 4. Hypertrophy of endothelial cell of intersinusoidal capillary. Note relation of endothelial cell to fat cell. × 1000.

FIG. 5. Two hypertrophied endothelial cells of intersinusoidal capillary. × 1000.

PLATE 92

FIG. 6. Earliest stage of marrow hyperplasia. Large venous sinusoids and engorgement of intersinusoidal capillaries with red blood cells. × 80.

FIG. 7. Drawing of intersinusoidal capillaries, filled with blood, opening into a venous sinusoid. × 500.

FIG. 8. Drawing of intersinusoidal capillaries, filled with blood, surrounding a fat cell. × 500.

FIG. 9. Drawing of a transitional capillary. Note hypertrophy and hyperplasia of endothelium of intersinusoidal capillaries. × 500.

FIG. 10. Drawing of intersinusoidal capillaries filled with blood and opening into a venous sinusoid. Note nuclei of endothelial cells lying on the floor of the opening. × 500.

PLATE 93

FIG. 11. Drawing of the openings of two intersinusoidal capillaries into a venous sinusoid. Note the incurving of the endothelium of the sinusoid to meet and form the wall of the capillary. The drawing indicates the funnel-shaped character of the openings and the two following photographs confirm this appearance. × 500.

FIG. 12. Photograph of the opening shown on the left in Fig. 11. × 1500.

FIG. 13. Photograph of the opening shown on the right in Fig. 11. × 1500.

FIG. 14. Drawing of hypertrophied endothelium of intersinusoidal capillary and three megaloblasts in close relation to the endothelial cells. × 500.

FIG. 15. Endothelial cells of intersinusoidal capillary, with two megaloblasts. One megaloblast in mitosis. × 1250.

FIG. 16. Two megaloblasts in close association with fat cell (in position occupied by endothelium of intersinusoidal capillary). Endothelial cell, next to a fat cell, shown indistinctly below. × 1000.

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FIG. 17. Drawing of hypertrophied endothelial cells of intersinusoidal capillaries with megaloblasts and erythroblasts developing in the capillaries. × 500.

FIG. 18. Drawing of erythroblasts and normoblasts in intersinusoidal capillary. Note endothelial cell lining the capillary spaces, above. × 500.

FIG. 19. Drawing of larger cell group near a venous sinusoid. Many normoblasts, a few leucocytes, and two clasmatocytes which have phagocytized red cells. × 500.

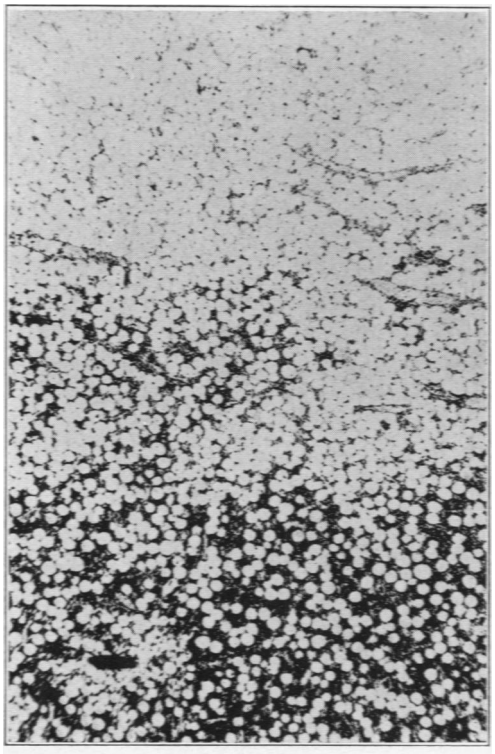
FIG. 20. Photograph of same field as Fig. 17. × 1000.

FIG. 21. Megalokaryocyte lying between fat cells, in position of intersinusoidal capillary. × 1000.

PLATE 95

FIG. 22. Drawing of a group of cells developing between and compressing fat cells. The flat endothelial cell along the upper fat cell and the hypertrophied endothelial cell along the upper left fat cell suggest that the group of cells is inside an intersinusoidal capillary which has become greatly distended. Note megaloblasts, one of which is in mitosis, in center. × 500.

FIG. 23. Drawing of a larger group of cells. In several places elongated or vesicular nuclei of endothelial cells, lying closely attached to fat cells, suggest that the cell island is developing within a space lined with endothelium. Note further decrease in size of fat cells. × 500.



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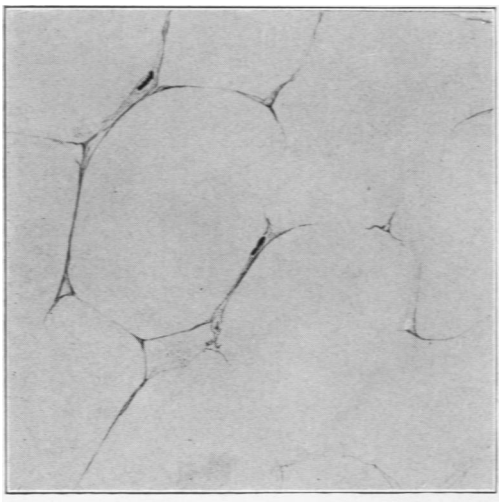

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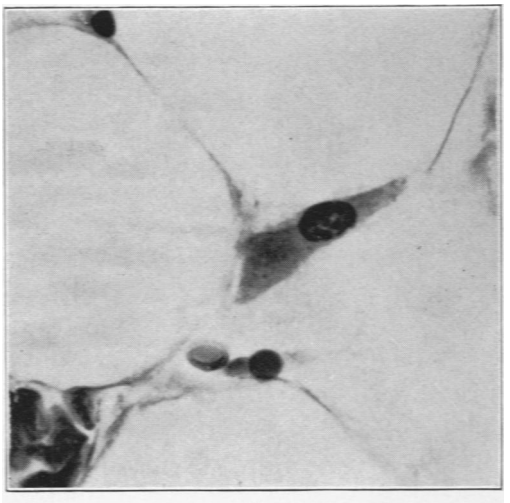

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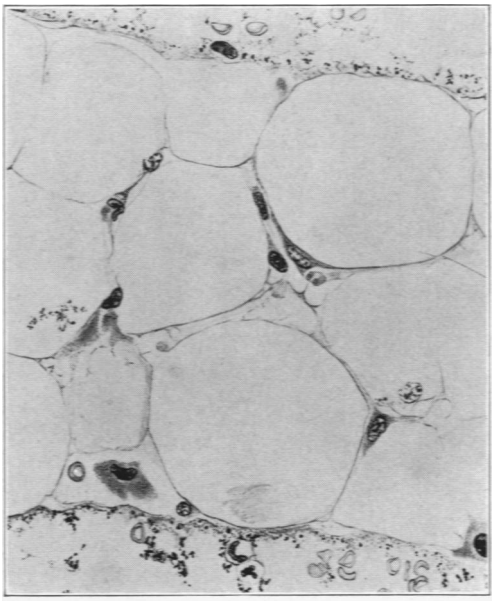

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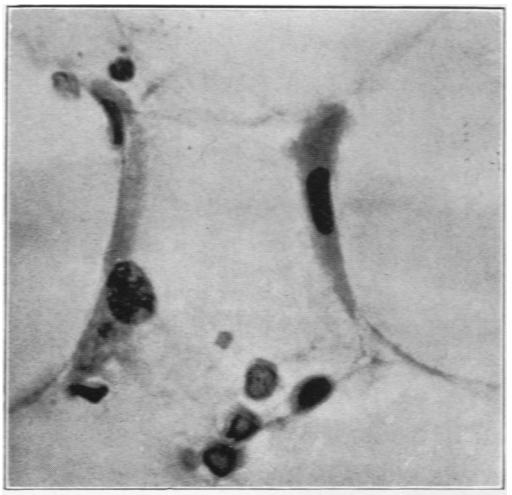

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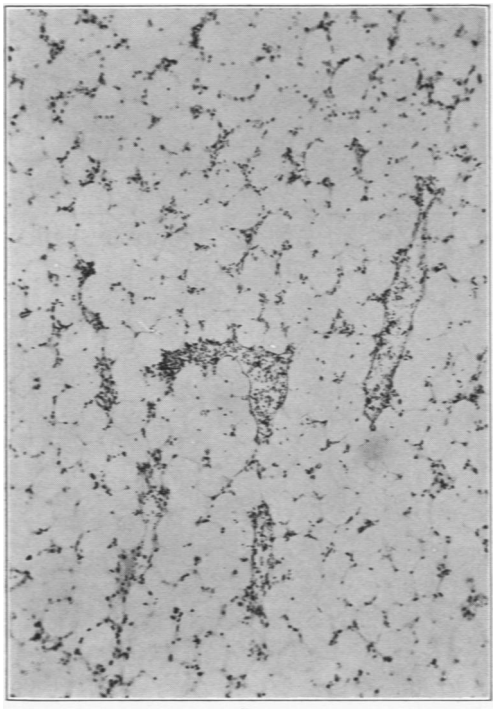

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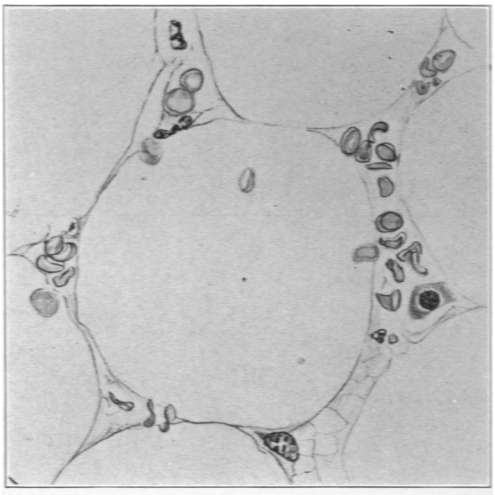

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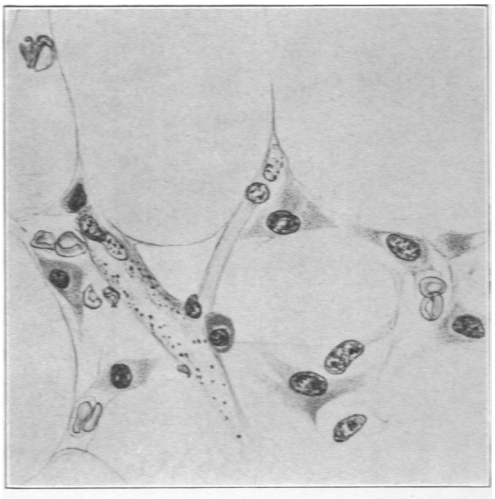

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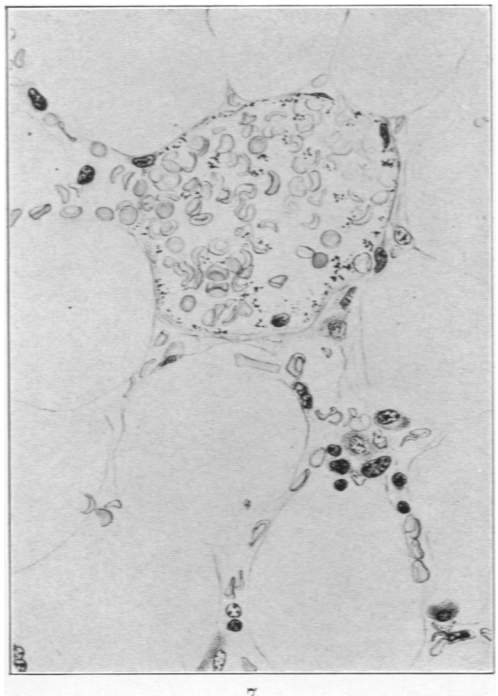

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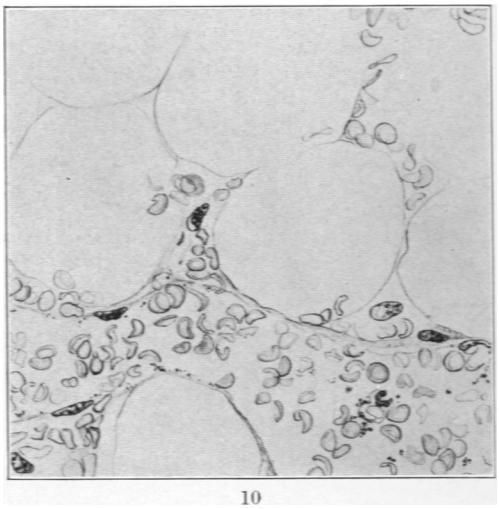

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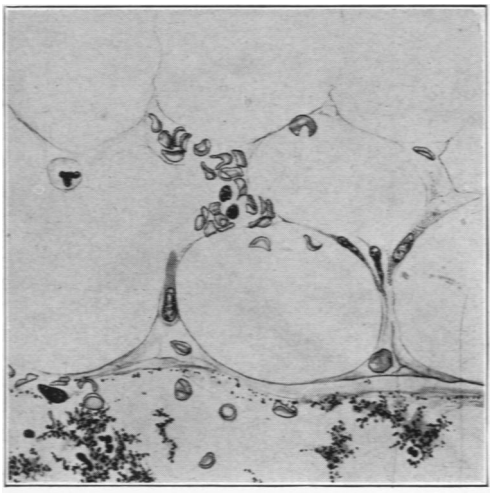
Peabody

Hyperplasia of Bone Marrow in Man



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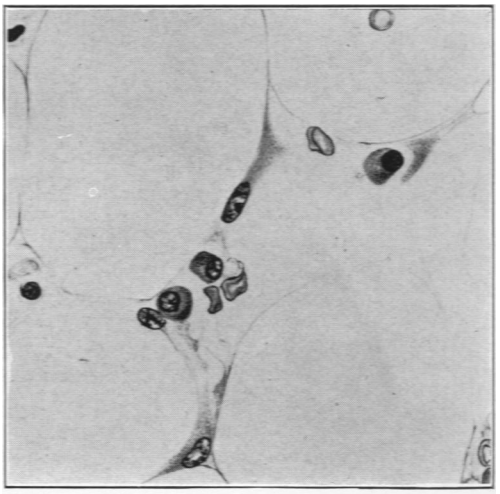

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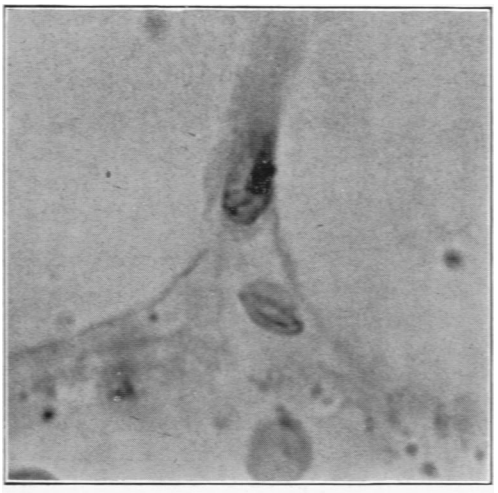

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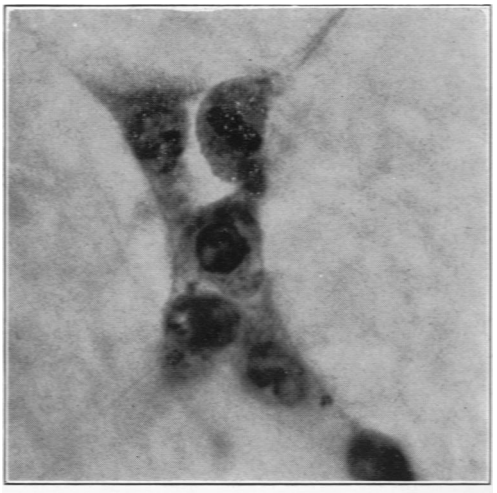

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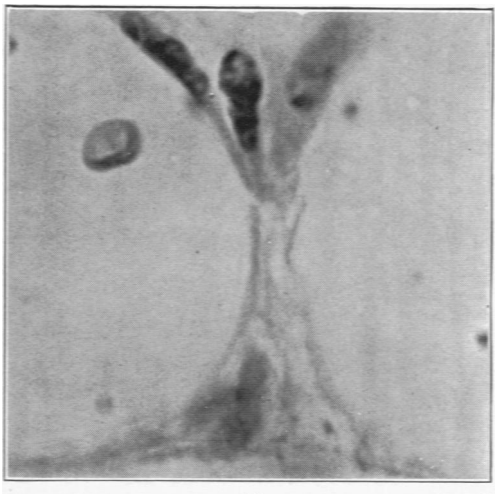

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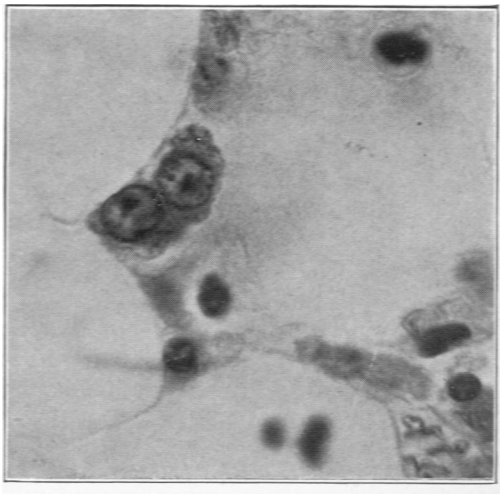

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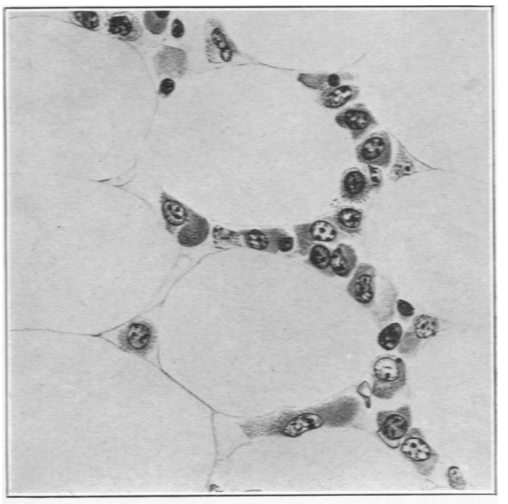

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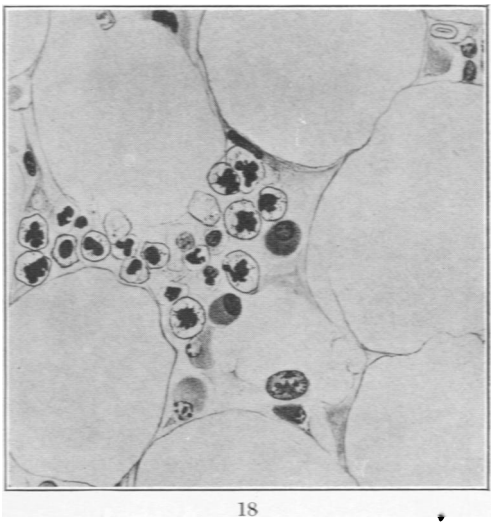

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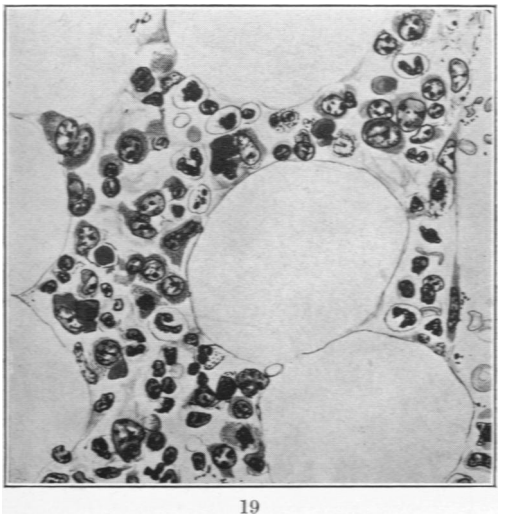

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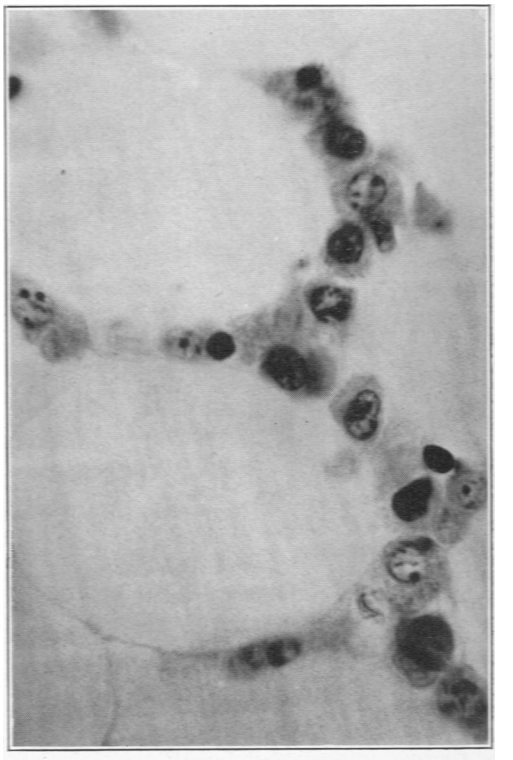

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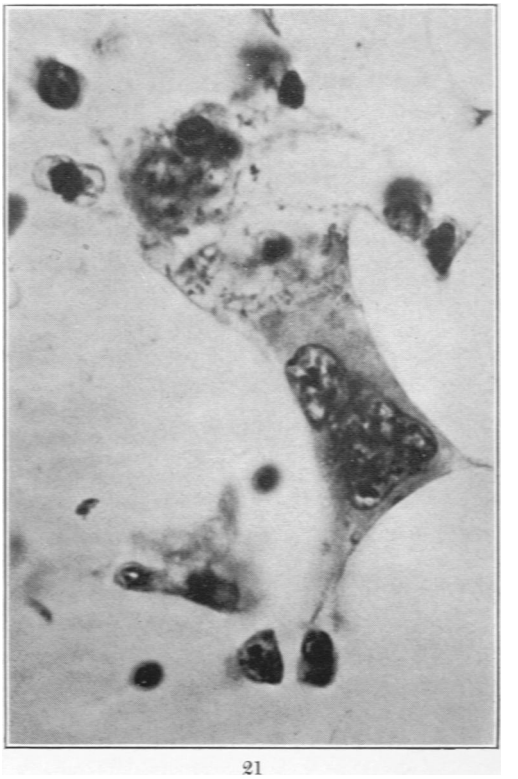

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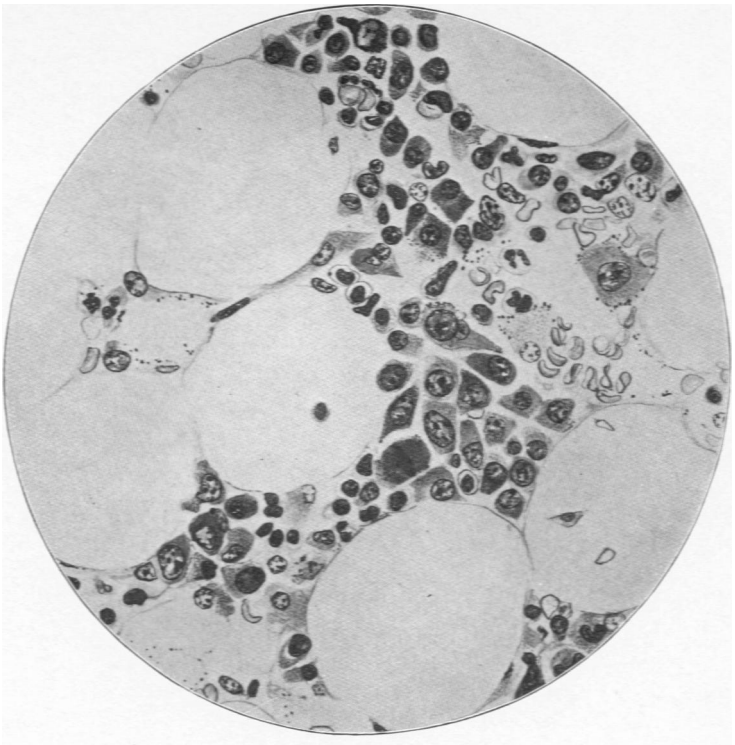

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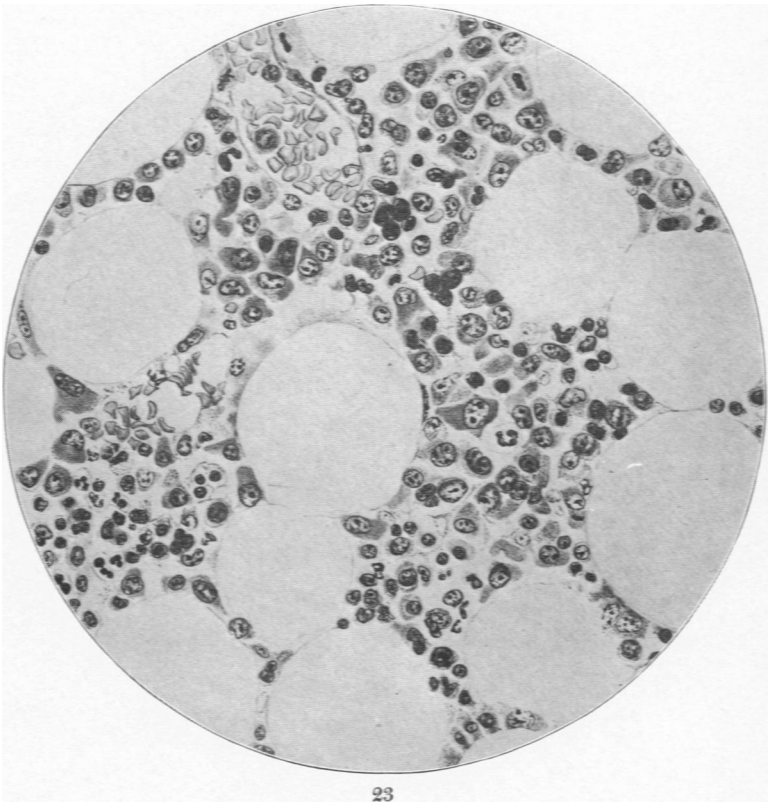

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