A HISTOLOGICAL STUDY OF TYPHOID FEVER.*

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PLATES LIV-LXI.

The object of this paper is to throw some light on the primary, essential lesion of typhoid fever, and also on certain secondary lesions which result therefrom.

Little or nothing can be added to the classical descriptions by Hoffmann, Orth and others of the gross lesions occurring in typhoid fever. On the other hand, the descriptions of the histology of these lesions, of the cell changes in the various organs and of their relation to the general pathological process peculiar to typhoid fever, leave much to be desired.

The essential points which have been discovered in the histology of typhoid lesions can be summed up briefly.

In 1848 Virchow believed and taught that the swelling of the intestinal lymphoid tissue and of the mesenteric lymph nodes was due to a simple exudative process. Later, however, he convinced himself that the swelling was due entirely to hyperplasia of the cells of the lymphoid tissue, and vigorously opposed the view held by the Vienna school that it was caused by an albuminous exudation. He also considered that the swelling of the spleen was essentially hyperplastic in origin.

In 1857 Friedreich called attention to certain small circumscribed collections of cells in the liver and kidneys from a case of typhoid fever.

In 1860 and 1861 Wagner described more fully similar small grayish nodules which were found in the liver and kidneys, and subperitoneally over the ileum, cæcum and appendix in several cases of typhoid fever. Since his time the term "lymphoid nodules" has been applied to these collections of cells.

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In 1861 Billroth and Grohe, working independently, described certain very large multinucleated cells occurring in the mesenteric lymph nodes in typhoid fever. Both regarded them as examples of endogenous cell formation.

In 1862 Billroth called attention to the presence of these same large cells in the blood-vessels of the spleen and in the portal circulation. He traced the cells into the liver and concluded, after measurements both of the cells and of the liver capillaries, that it was possible for the cells to pass through the liver and reach the lungs. He suggested the possibility that the cellular foci of the liver described by Friedreich and Wagner might be due to emboli of these cells.

In 1869 Hoffmann observed these same large multinucleated cells in Peyer's patches and in the solitary follicles of the intestine in early cases of typhoid fever.

In 1875 Klein described them again in the intestine and mesenteric lymph nodes, with wonderful accuracy considering the technical disadvantages under which he labored, but he drew wrong conclusions from what he saw. He called attention to the large cells filled with red blood globules present in the spleen in typhoid fever.

In 1895 Reed claimed that the term "lymphoid nodules" applied to the focal lesions in the liver was incorrect, because these lesions were really areas of focal necrosis of liver cells invaded by polymorphonuclear leucocytes.

In recent years the histology of typhoid fever has been neglected for the typhoid bacillus and the serum reaction. Text-books on pathology pay little attention to the microscopic appearances of the early lesions of typhoid fever. The best, that of Orth, says that the essential cause of the swelling or new growth in the intestine is an accumulation in and around the lymph nodules of large cells, only in part of the character of ordinary lymph cells, and often containing many nuclei and occasionally red blood globules.

The latest views in regard to typhoid fever are those expressed by Ribbert in his Lehrbuch der pathologischen Histologie, published in 1896. He claims that the primary swelling in the intestine and mesenteric lymph nodes is due to the typhoid bacilli getting into the lymph sinuses and causing an acute inflammatory exudation of serum and leucocytes into the outer portion of the lymph nodules and the adjoining tissue. After a certain length of time the exudation disappears and is followed by an intense proliferation and desquamation of the endothelial cells lining the reticulum of the lymph spaces. These cells are occasionally phagocytic. The real lymphoid nodules of the lymphatic apparatus,

according to him, play no part in the process. Later, necrosis and sloughing of the newly-formed tissue occur, and repair by granulation tissue follows from the base of the ulcer.

A pathological lesion can be fully understood only when every step in its development, and especially its beginning, can be followed and studied. Where lesions can be produced experimentally this is a comparatively simple matter. For the lesions of typhoid fever, however, we are dependent on material obtained from post-mortem examinations, and we rarely have the fortunate combination of an early case of the disease and an early post-mortem examination, an absolute necessity for the perfect study of the lesions of the intestine. Other requisites are exact fixation of the nuclei, protoplasm and red blood globules, and a staining method which shall clearly differentiate the various tissue elements met with. For the fixation of the tissues Zenker's fluid has been found to give by far the best results, while for staining eosin followed by Unna's alkaline methylene-blue solution has afforded the clearest pictures.

During the past year I have been able to collect and to study histologically 19 cases of typhoid fever, 11 from the Boston City Hospital, 3 from the Massachusetts General Hospital through the kindness of Dr. J. H. Wright, and 5 from other sources. The duration of the disease in the cases examined varied from 10 days to 4 weeks.

The starting point of this investigation into the histogenesis of typhoid fever was a case of the disease in a girl eleven years old, who died at the Children's Hospital on the tenth day after the appearance of the first symptoms. The post-mortem examination was made one hour after death. The Peyer's patches and the solitary lymph nodules of the intestine showed marked swelling, and occasionally small yellowish foci due to necrosis, especially at the lower end of the ileum, but no macroscopic evidence of ulceration. The mesenteric lymph nodes were much enlarged and hyperæmic, and the spleen was considerably larger than normal, firm to the touch and dark in color. Portions of the intestine ware put at once, without washing the surface, into alcohol, Zenker's and Orth's fluids, and sections of the various organs were preserved in the same fixatives.

Although no other case was obtained so early in the disease or so

soon after death, yet it was possible in seven other instances to trace the whole development of the intestinal lesions, partly because the cell changes in typhoid fever are comparatively slow, and partly because all of the swollen Peyer's patches usually do not undergo necrosis and sloughing.

In the following histological descriptions of the various lesions in typhoid fever the different organs, beginning with the intestine, will be considered separately.

INTESTINE.

The lymph nodules of the intestine consist of masses of lymphoid cells lying in the meshes of a delicate connective-tissue reticulum. Lining this reticulum are certain large cells with vesicular, lightly staining nuclei, usually looked upon as the cells of the reticulum, but regarded by Ribbert and some others as endothelial cells intimately adherent to the reticulum, which is said to have a few spindle-shaped, deeply staining nuclei of its own. Owing to the close relationship between endothelial and connective-tissue cells embryologically and pathologically, and to the fact that the endothelium of newly-formed blood-vessels has been shown in the organization of thrombi to produce connective tissue, it is doubtful if these two varieties of cells can ever be sharply differentiated. In the lesions to be described, however, the large cells of the reticulum of the lymphoid tissue behave in all respects like the endothelial cells of the lymph and blood-vessels. This fact might be used as an argument, therefore, in favor of their being endothelial rather than connective-tissue cells. In the following pages these cells will be spoken of as endothelial cells.

Under the influence of the toxic product of the typhoid bacilli these larger endothelial cells increase in number (Plate LV, Fig. 4). The new cells are epithelial in character, with round or oval, vesicular nuclei surrounded by a considerable amount of protoplasm, which is always sharply outlined and is stained pink by the staining method employed. The proliferation of these cells may take place diffusely throughout the lymph nodule (Plate LIV, Fig. 2), but may also start in the centre (Plate LIV, Fig. 1) or at the periphery.

The cells increase not only in number but also in size, and soon

begin to incorporate (Plate LV, Fig. 5) and to digest the neighboring lymphoid cells. In a short time the only lymphoid cells left are those in that part of the lymph nodule where the endothelial cells have not proliferated. As these cells increase in size the nuclei lie eccentrically, usually near the periphery, and almost invariably become irregular in shape, either curved or variously indented. The cells are generally spherical in shape, but through pressure are often rendered irregular or elongated. Only rarely is a form seen that suggests amœboid movements on the part of these cells which probably do not change their relative positions, although they must have some power of motion in order to incorporate the cells found within them. Occasionally these large cells have two or more nuclei of their own.

These newly-formed cells all show to a marked degree the property of phagocytosis. Often 10 to 20 or more lymphoid cells in various stages of digestion will be found within one of the large cells (Plate LV, Fig. 6). As the lymphoid cells undergo digestion the nuclei shrink a little, become homogeneous in appearance and stain very deeply with nuclear stains. They usually dissolve irregularly and may become hollowed out into crescentic forms or break into fragments. As a rule, the incorporated cells can be seen to lie within digestive vacuoles. Occasionally red blood globules, more rarely plasma cells and polymorphonuclear leucocytes, are taken up by these large cells and digested in the same manner as the lymphoid cells. Outside of the lymphoid nodules, the less clearly defined lymphoid tissue shows an irregular, more or less diffuse formation of large cells with properties similar to those already described. The same cells are found in large numbers in the dense fibrous tissue of the submucosa, both beneath the patches of Peyer and the solitary lymph nodules, and also for some little distance peripherally beyond the limits of the lymphoid tissue. The cells are usually elongated, owing to pressure, and show marked phagocytic properties.

Orth has called attention to the swelling of the mucous membrane of the intestine, especially in the lower part of the ileum, in typhoid fever. Microscopic examination shows that the swelling is due largely

to the same cell changes that are found in the lymph nodules. They are most marked in the mucous membrane covering and adjoining the patches of Peyer, but also occur to a moderate degree everywhere in the mucous membrane of the lower part of the ileum. The changes are always found more marked between the glands of Lieberkühn (Plate LV, Fig. 3) than in the villi, and consist of proliferation of the endothelial cells in the fibrillar reticular connective tissue, the meshes of which in this situation contain usually more plasma than lymphoid cells and also a fairly large number of eosinophiles. The newly-formed cells do not differ in character from those already described.

Proliferation of the endothelial cells is shown by mitosis in all of the situations in which these cells are found (Plate LV, Figs. 3 and 4). While not abundant, it is sufficiently frequent to account for all of the new cells formed.

Besides these cells derived by proliferation from endothelial cells and characterized by marked phagocytic properties, there are certain other cell changes which have to be taken into consideration. The epithelial cells in the glands of Lieberkühn are in a state of very active proliferation, as shown by numerous mitotic figures present in every gland. How much more abundant, if at all, the cell division is than in the normal intestine it is impossible to say. Occasionally a gland of Lieberkühn is dilated and filled with polymorphonuclear leucocytes. Mitosis is also very frequent in the lymphoid cells remaining in the lymphoid tissue and in the mucous membrane. The mitotic figures can be differentiated from those of the endothelial cells because they are smaller and by the fact that their protoplasm is very granular and stains deeply with methylene-blue. Many of the lymphoid cells have changed or are changing into plasma cells characterized by small, round, coarsely granular, deeply staining, eccentrically situated nuclei and finely granular protoplasm which stains deeply with methylene-blue. Besides the lymphoid and plasma cells originally in the tissues or derived from them, others are added to them by emigration from the blood-vessels (Plate LVI, Fig. 14), Large multinucleated plasma cells are found occasionally. Irregu-

larity of shape, due to amœboid movements, is shown by many of the lymphoid and plasma cells.

In the muscular coats of the intestine the cellular increase is most noticeable along the lymphatic vessels. The cells consist in part of infiltrating lymphoid and plasma cells, but principally of large phagocytic cells in the lymph vessels and spaces around and near the blood-vessels. Similar cells are also found between the smooth muscle fibres and are generally elongated in shape in consequence of pressure. Mitotic figures can occasionally be found, and the cells often occur in small clumps.

Subperitoneal collections of cells are usually found only beneath the patches of Peyer. As in the muscular coats, they consist of collections of phagocytic cells derived by proliferation from the endothelial cells around the blood-vessels. Occasionally fairly large clumps of cells are formed.

LYMPHATICS.

The terminal lymphatics of the mucous membrane of the intestine by the tenth day of the disease are distended and filled with large phagocytic cells derived from the lining endothelium (Plates LV, Fig. 3, and LVI, Fig. 8). Along with them is usually a small number of lymphoid and plasma cells. In consequence of their distention with cells, it is easy to follow the lymphatic vessels into and all through the submucosa (Plate LV, Fig. 7). The cellular contents vary to some extent in the relative number of phagocytic and lymphoid cells, but as a rule the large cells predominate.

BLOOD-VESSELS.

Microscopic examination of the distended blood-vessels of the mucous membrane and submucosa shows a surprising absence of polymorphonuclear leucocytes. In their stead are occasional lymphoid and plasma cells, which not infrequently divide by mitosis in the blood current, and very numerous, large cells with lightly staining, vesicular, curved or indented nuclei (Plate LVI, Fig. 10). Many of these cells are phagocytic and contain red blood globules, less often lymphoid and plasma cells or polymorphonuclear leucocytes.

The number of cell inclusions is usually small and is limited chiefly to red blood globules. The large cells are evidently derived from the vessel walls, because examination of the lining endothelium of the capillaries and veins of the mucosa and submucosa shows mitotic figures to be quite numerous (Plate LVI, Figs. 9 and 12). During mitosis the cells are usually adherent to the wall but may be somewhat loosened. Much more rarely these large cells divide by mitosis when free in the blood stream.

The lesions thus far described are proliferative in character and probably mark the limit reached by the typhoid process in many of the agminated and solitary lymph nodules in mild cases of the disease. Even in severer cases some of the patches of Peyer do not undergo necrosis with sloughing and ulcer formation. Instead, the large newly-formed phagocytic cells rapidly undergo fatty degeneration and disappear. When the typhoid process has been more severe, however, certain changes take place which lead to obstruction of the lymphatics and to the obliteration of many of the blood-vessels, thereby causing necrosis of the tissue in which they lie.

Virchow thinks that the necrosis is due to a form of caseation much like that occurring in tuberculosis, while Orth is of the opinion that the necrosis is due to pressure exerted on the blood-vessels in consequence of the great hyperplasia of the cells. Careful study leads me to the view that possibly some of the capillaries may become occluded by proliferation of their endothelial cells, but the truth of this view or of Orth's is difficult to demonstrate. By far the most common method of occlusion of the blood-vessels, and perhaps the only one, takes place in the following way:

The first regressive changes in the intestinal lesions of typhoid fever are shown in the large phagocytic cells in the lymphatic vessels. The cells degenerate and an abundance of fibrin soon binds them together. The outlines of the cells disappear and the nuclei become more irregular than before. In this way thrombi are formed which occlude the vessels, so that it is difficult to believe that much, if any, circulation can take place in them under such circumstances.

Beneath the lining endothelium of the large and smaller veins,

much more rarely of the larger lymphatic vessels, accumulations of cells take place in what must be a lymph vessel or lymph space. The cells consist in part of lymphoid and plasma cells, in part of large phagocytic cells derived by proliferation from the cells lining this lymph space (Plate LVII, Fig. 15). The cell accumulations, which project more or less into the lumina of the veins, may be large or small, focal in character or spreading out for some distance around or along the vessels. Necrosis of the large phagocytic cells takes place very frequently in these collections of cells beneath the endothelium and furnishes the starting point for a very abundant formation of fibrin which often extends for some distance along the vessel (Plate LVII, Fig. 16). The nuclei of the large cells undergoing necrosis usually become more irregular in shape than normally before they lose the property of staining and disappear. The lining endothelium of the vessel is generally preserved intact (Plate LVII, Fig. 19), at least for a time, over such a collection of cells, but often by necrosis becomes the starting point for the formation of fibrin which reaches out into the lumen and by extending along it may divide it into two or more channels. The cells in the blood current get caught in this fibrin and thrombi are soon formed which completely occlude the vessel (Plate LVII, Fig. 17). From these primary foci the fibrin formation extends along the vessels and into the capillaries, thereby occluding them. So far as can be ascertained by a careful study of serial sections, these masses of fibrin, which are often very numerous beneath the lining endothelium of veins before any other regressive changes have taken place anywhere in a Peyer's patch, always start from the protoplasm of degenerating phagocytic cells. The fact that these large cells do form beneath the lining endothelium of the veins is best seen in the larger vessels of the spleen (Plate LXI, Fig. 34) and liver. The areas thus deprived of their blood supply by occlusion of the veins and capillaries soon show evidence of undergoing necrosis. The outlines of the cells become indistinct and more or less fused, owing to the formation of fibrin which is not always very abundant. The nuclei become even more irregular in shape than normally and finally disappear. The included, partially digested cells break up into fine particles which after a while refuse to stain.

The inflammatory exudation which takes place in consequence of the necrosis of the tissue consists almost wholly of serum in which abundant fibrin forms. Polymorphonuclear leucocytes are rarely found. The exudation, as is usual in the intestine, collects in greatest quantity in the deeper layers of the submucosa. The earliest necroses seem to take place generally in the lymph nodules which were first affected. The mucous membrane also, which is very thin over them, quickly undergoes necrosis. The upper portions of these necroses soon macerate and slough off. In this way small superficial ulcerations are formed, along the edges of which numerous bacteria quickly collect. Sometimes, however, the mucous membrane over a Peyer's patch is fairly well preserved when necrosis in the submucosa is already well advanced. In the small necroses polymorphonuclear leucocytes are very uncommon, but in the large necroses they usually occur in considerable numbers, not along the edge of the necrotic tissue, but nearer the surface where the various bacteria of the intestinal tract are invading the necrotic tissue. The irregularity of the necrosis and ulceration of a Peyer's patch depends, of course, on the fact that all of the veins usually do not become occluded. Even when the necrosis is quite marked there is generally a little tissue immediately around the arteries supplying the affected areas which does not undergo necrosis, at least at first, because the arteries, unlike the veins, do not become thrombosed.

MESENTERIC LYMPH NODES.

The lesions occurring in the mesenteric lymph nodes do not differ in character from those found in the lymph nodules of the intestine. In fact the mesenteric lymph nodes offer the very best tissue for studying the essential lesion of the typhoid process in all its stages, because they are not so freely exposed to invasion by various organisms as is the intestine the moment its lining epithelium is injured.

In the lymph nodes the lymph sinuses are always more affected than the nodules and cords of lymphoid cells. They become widely dilated and filled with large phagocytic cells containing mainly lymphoid and plasma cells, but also occasionally red blood globules. Besides

the large cells, numerous lymphoid and plasma cells are also present in the sinuses. The large cells are unquestionably derived in part, if not entirely, from the endothelial cells lining the loose reticulum of the sinuses.

In the lymphoid tissue between the sinuses a proliferation of the large cells lining the reticulum takes place just as in the intestine. Sometimes it is most marked centrally, sometimes diffusely or peripherally. Mitosis of the endothelial cells of the reticulum of the sinuses and lymphatic tissue is fairly frequent. Necrosis in the lymph nodes, when it occurs, is always most marked and most extensive in the lymph sinuses. An abundant formation of fibrin takes place, binding the cells together. The nuclei of the large cells become very irregular in shape and finally disappear.

In the lymph nodules the necrosis seems to depend largely on the same lesions of the blood-vessels that are found in the intestine, namely, collections of phagocytic and lymphoid cells beneath the lining endothelium, necrosis of the large cells and fibrin formation with extension into the vessel and occlusion of the lumen.

The typhoid process often extends outside of the lymph nodes into the adjoining fat tissue, where many large phagocytic and plasma cells are found between the fat cells. These areas also may become necrotic.

In many cases some at least of the lymph nodes do not undergo necrosis; instead, resolution takes place; the cells rapidly show signs of fatty degeneration and disappear. Apparently resolution can occur even when fairly extensive necrosis with fibrin formation exists in the lymph sinuses. What the exact changes are which take place when a whole lymph node becomes necrotic I have not been able to follow. Certain it is, however, that the necrotic tissue ordinarily shows very little or no infiltration with polymorphonuclear leucocytes.

SPLEEN.

I wish to speak next of the spleen, because the cell changes which take place in it have an important bearing on the lesions of the liver.

As a rule the lymph nodules of the spleen do not show any marked change in typhoid fever. In certain cases, however, some or all of

the nodules show to a greater or less extent the same formation of phagocytic cells from the endothelial cells of the reticulum that is found in the lymphoid tissue of the intestine.

The most marked changes of the spleen are those found in the blood-vessels and spaces of the pulp. They are much dilated and filled with large phagocytic cells containing principally red blood globules, usually in very large numbers, but also lymphoid and plasma cells and polymorphonuclear leucocytes. These phagocytic cells are derived chiefly or entirely by proliferation and desquamation from the endothelial cells lining the vessels. Occasionally mitosis takes place in the cells lying free in the blood. Sometimes the blood-vessels and spaces become occluded by masses of these large cells, which degenerate and become bound together by a meshwork of fibrin.

Besides this general proliferative process we get, as in the intestine, numerous plasma cells in the veins and in the splenic pulp. Many of them show amœboid shapes and not infrequently mitosis.

In some of the splenic veins, especially the larger ones, the lining endothelium is lifted up by masses of large phagocytic cells, and of lymphoid and plasma cells (Plate LXI, Fig. 34). In places these cells degenerate and fibrin forms between and around them.

LIVER.

Two varieties of focal lesions, to both of which probably the term "lymphoid nodule" was applied originally, are often found in the liver in typhoid fever. One is confined to the small amount of connective tissue around the portal vessels, that is, it lies outside of the lobules and in no immediate relation to the liver cells; the other may occur anywhere within the lobule among the liver cells. The two forms of lesion often adjoin each other. It is important to separate them sharply because they arise in different ways.

The lesion around the portal vessels consists to some extent of an increase of lymphoid and plasma cells, due in part to proliferation, in part, probably, to immigration. The chief part of the lesion, however, is formed of large cells with phagocytic properties derived by proliferation from the endothelial cells around the portal vessels. The

phagocytic cells do not differ from those found in the intestinal lesions and in the mesenteric lymph nodes, except that the cell inclusions are not so numerous and are confined almost entirely to lymphoid cells. Very rarely a giant cell is formed in this situation, apparently by fusion of the endothelial and other cells in a lymph vessel.

In order to understand the origin of the second form of focal lesion in the liver—that occurring somewhere within the lobule among the liver cells—it is necessary to refer to the lesions of the intestine and spleen. In these organs we found that fairly abundant mitosis of the endothelial cells of the capillaries and veins took place, that these cells desquamated into the blood current, and in the intestine could be followed into the large veins of the submucosa. They were distinguished from the nucleated cells ordinarily found in the blood by their size, the irregular shape and eccentric position of their nuclei, and especially by their marked phagocytic properties. The last feature was most prominent in the cells in the veins and blood spaces of the spleen, where the circulation is probably slower. From these organs many of the large cells are carried directly to the liver. Billroth observed large multinucleated cells in the splenic and portal veins in 1861 and traced them to the liver. As already mentioned, he thought they might be the source of the lymphoid nodules in the liver described by Wagner. He does not seem to have recognized the fact that the large cells often contained red blood globules.

Examination of the livers of the cases that came to post-mortem examination within the first two weeks of the disease shows in many of the branches of the portal vein, numerous large phagocytic cells containing usually many red blood globules or undigested portions of them, less frequently lymphoid cells, and rarely polymorphonuclear leucocytes (Plate LVIII, Fig. 21). These same cells are found in the capillaries all through the liver, often closely crowded together. Mitosis may take place in them either in the large vessels or in the capillaries (Plate LVIII, Fig. 23). The cells often assume irregular and elongated shapes, evidently from the pressure to which they are subjected in passing through the narrow vessels. Occasionally these cells undergo necrosis, as is shown by the fact that the

various stages in the cell changes leading up to the picture presented by complete necrosis can be followed, and in these earlier stages the cells can be definitely recognized by the inclusions in the protoplasm.

Occasionally some of these large cells stick fast in the capillaries. At least four causes favor this condition, viz.: the general swelling of the liver cells from parenchymatous degeneration leading to narrowing of the capillaries, the very large size of many of these phagocytic cells in consequence of the great number of their inclusions, the swelling and phagocytosis of the endothelial cells lining the liver capillaries, and finally, mitosis of the capillary endothelium (Plate LVIII, Fig. 20).

When by obstruction of a capillary a focus of cells is formed, other cells are added to it, partly, it would seem, from mechanical causes owing to interference with the circulation at such a point, partly from cell division as is shown by mitosis, so that soon a number of liver cells are completely surrounded by these large cells (Plate LVIII, Figs. 22 and 25). Then the included liver cells, presumably on account of the interference with their nutrition, quickly undergo necrosis, as is shown by the deeper stain of their protoplasm with eosin (Plate LIX, Fig. 27). The nuclei at first stain deeply (Plate LIX, Fig. 27), then they and the protoplasm break down into granular detritus and disappear (Plate LX, Fig. 29). Sometimes the cells which block up the capillaries undergo necrosis before the liver cells (Plate LX, Fig. 28).

Pressure on the surrounding liver cells, making them narrow and elongated, is often exerted peripherally by these clumps of cells owing to the proliferation in them. It is possible that some of the foci in the liver may arise solely from the proliferation of the endothelial cells lining a capillary. The cells within the focal areas usually do not contain many inclusions, probably because those which they may have taken up in the circulating blood have been more or less digested, and because the newly-formed cells in the foci do not have the same opportunity for getting hold of other cells. Mingled with these large cells in the focal areas are often a few lymphoid and plasma cells, and occasionally red blood globules.

Sooner or later necrosis of these large cells in the focal areas takes place, possibly not always, for it is presumable that at least the smaller collections of cells may undergo fatty degeneration and disappear as in the intestine and mesenteric lymph nodes. The necrosis begins in the centres of the areas; the protoplasm loses its sharpness of outline, fibrin usually appears between the cells and binds them together (Plate LIX, Fig. 26), the nuclei of the large cells become still more irregular in shape and finally disappear. Invasion of the necrotic areas in the liver with polymorphonuclear leucocytes even as late as the fourth week is infrequent and slight. What becomes of the areas after this time could not be ascertained owing to the lack of appropriate material in which to trace the process.

This form of focal lesion, accidental in its location in a liver lobule and leading to the destruction of a limited number of liver cells, is not confined to typhoid fever, but occurs in other infectious processes. It may also result from cell emboli derived from malignant growths. The same variety of lesion can be produced experimentally in 24 to 48 hours by injecting a sterile suspension of carmine in normal salt solution into a mesenteric vein of a guinea-pig.

There is a form of primary necrosis of liver cells which occurs in many acute infectious processes, and is due apparently to some strong, diffusible toxine. It follows practically the same distribution as that seen in chronic passive congestion, *i. e.* the necroses are confined fairly definitely to the centre of every lobule. The capillaries remain pervious, the necrotic liver cells are quickly invaded by polymorphonuclear leucocytes. It was produced experimentally by injecting a dose of diphtheria toxine sufficiently large to kill a rabbit in three days. The muscles all over the body showed intense fatty degeneration and the centre of every lobule of the liver was necrotic. No example of this type of lesion was found in any of the cases of typhoid fever.

Many of the phagocytic cells pass through the capillaries of the liver and get into the lungs, where they can be found in the larger and smaller blood-vessels and in the capillaries (Plate LXI, Fig. 33). They do not seem to cause any obstruction, but pass along into

the general arterial circulation. Sections of the pale clots of blood from the right ventricle of the heart in a case that died on the fourteenth day of the disease showed numerous large phagocytic cells among the normal cells of the blood. Sections of a clot from the left auricle showed them present there also in about equal numbers (Plate LXI, Fig. 32). There is no question, therefore, about these cells getting into the general arterial circulation. Examination of the pale watery fluid in the thoracic duct in this same case showed an occasional large phagocytic cell containing numerous lymphoid cells. It is evident, therefore, that cells also get into the general circulation through the thoracic duct (Plate LXI, Fig. 30). The cells derived from the lymph vessels show almost nothing but lymphoid cells as inclusions, while those that come from the portal circulation contain chiefly red blood globules.

It is difficult to explain why these large cells have not been found in the ordinary blood examinations during the second and third weeks of typhoid fever, when they are most abundant, except on the ground that the dried cover-slip method of examining blood breaks up cells of this type. In 1874 Eichhorst reported finding from 2 to 4 large cells each containing 2 to 5, rarely as many as 7, red blood globules in every drop of blood drawn from the tip of the finger of a typhoid patient. This condition was present for five days during the second week of the disease, after which time the large cells suddenly disappeared. Slight pressure upon them caused these cells to break up and set the globules free. I have found them on careful examination in the blood-vessels of the heart, kidneys and brain. So far as can be judged from the sections of the clots in the heart, the phagocytic cells may form at least from 1 to 2 per cent of the nucleated cells in the circulation.

The kidney is the only organ in which the phagocytic cells in the general circulation seem to give rise to any lesion.

It has been shown by Dr. W. T. Councilman* that when the lymphoid and plasma cells increase in number in the general circulation, they filter out into the veins in the pyramids of the kidneys, and

* *Journal of Experimental Medicine*, iii (1898), 393.

may often be there in great numbers. Under certain conditions these cells emigrate from the vessels and give rise to focal collections of cells. In typhoid fever the large phagocytic cells filter out in the same way and crowd the vessels along with numerous lymphoid and plasma cells. Occasionally the large cells occlude several adjoining blood-vessels, and by cutting off the circulation lead to necrosis of the intervening tubules. To complicate the picture, emigration of the lymphoid and plasma cells also present may take place, and hæmorrhage is not infrequent.

The heart was examined in two cases, but in only one was the examination at all thorough. In both cases occasional small foci of lymphoid and plasma cells were found similar in character to the areas often seen in the heart in diphtheria. Besides this form of lesion, phagocytic cells were found here and there in the lymph spaces, especially beneath the pericardium and along the larger blood-vessels. In some of the lymph vessels they were quite numerous. Occasionally a lymph vessel would be occluded by them and then the adjoining lymph spaces would usually also be crowded with them. In this way foci of considerable size would be formed. In one place the lining endothelium of the endocardium was lifted up by a group of large cells (Plate LVII, Fig. 18). In none of these areas was necrosis found. In one brain a single focal lesion was found, but the tissue had been hardened in alcohol and the character of the cells could not be determined. In two cases an occasional phagocytic cell was found in the lymph spaces of the pia-arachnoid.

Examination of the testicles in two cases showed complete cessation of spermatogenesis. One case showed nothing else. In the other the blood-vessels were dilated. Everywhere in the connective tissue between the tubules were numerous large cells in the lymph vessels and spaces. The cells were large and had irregular nuclei and abundant protoplasm; they were often phagocytic and occasionally showed mitotic figures. Sometimes the large cells were clumped together, apparently in connection with the large lymph vessels. In this same case there were numerous fairly large foci of lymphoid cells with a certain proportion of large phagocytic cells among them. Plasma

cells and polymorphonuclear leucocytes were rare. Scattered diffusely in the tissue were numerous Mastzellen.

The bone-marrow from the femur was examined in two adult cases, in both of which it was found quite red at the post-mortem examination. The cell changes closely resembled those in the spleen. In the blood-vessels were many large cells containing red blood globules, much less frequently lymphoid cells and polymorphonuclear leucocytes. The large cells also occurred diffusely in the lymph spaces among the other cells of the bone-marrow and around the fat cells. Occasionally clumps of these phagocytic cells were found undergoing necrosis and bound together by fibrin. So far as could be determined, the areas arise by occlusion of blood and lymph vessels by these large cells.

The bladder examined in one case was negative, while the wall of the gall-bladder was infiltrated with numerous lymphoid and plasma cells, and occasionally showed phagocytic cells.

Summing up the lesions thus far described, we have as the essential lesion of typhoid fever a diffuse proliferation of endothelial cells giving rise to large epithelioid cells characterized by the possession of marked phagocytic properties. This proliferation is most marked in the lymphoid tissue of the intestine, in the mesenteric lymph nodes, in the spleen, bone-marrow and liver, but may also be found to a varying extent in the lymphatic vessels all over the body, as shown by examination of the lymphatics of the heart, lungs, testicles and pia-arachnoid.

In regard to the typhoid bacillus I have very little to say and nothing new to add. It was obtained in cultures from most of the organs of the cases studied. Histologically it was rarely found, but it must be confessed that no exhaustive search for the organism was made. Occasionally the characteristic colonies were found in the mesenteric lymph nodes and in the spleen, but not in any case that came to post-mortem examination very soon after death. In the earliest case, in which the post-mortem examination was made one hour after death, no bacteria were found microscopically except along the edges of the beginning ulcerations of the intestine, and in that

situation it is of course impossible to differentiate the typhoid from the colon bacillus. Certain it is that when the typical colonies of the typhoid bacillus are found in the different organs they bear no intimate relation to the lesions present.

It would be exceedingly interesting to know whether the typhoid bacillus gains access to the lymphoid tissue of the intestine before any lesion is produced and before the lining epithelium is injured, or whether the lesion is caused primarily by absorption of a toxic substance eliminated by the bacilli which at first are within the intestinal canal only and which gain an entrance into the tissues later.

Unfortunately the line of experimental work so successfully carried out with the diphtheria bacillus and its toxine seems to be out of the question with the typhoid bacillus owing to the immunity in respect to this organism enjoyed by the lower animals. We have to depend, therefore, as yet, for our views in regard to the typhoid bacillus and the lesions produced by it on such deductions as may be drawn from the study of the gross and histological lesions occurring in man.

The following facts favor the view that the intestinal lesions are due primarily to an absorption of a toxic substance secreted by typhoid bacilli in the lumen of the intestine. The lesions diminish in intensity from the ileo-cæcal valve upwards, and are along the line of absorption. The lesions are diffuse. This characteristic is shown in three ways: (*a*) all of the lymphoid tissue for a given distance is generally, although not equally, affected; we do not get here and there a patch of Peyer swollen while the intervening patches remain normal; (*b*) the whole of each patch of Peyer affected shows about the same degree of swelling; (*c*) the mucous membrane in the lower part of the ileum shows diffuse proliferation. In judging of the above points it is necessary to take early cases in which the lesions are in the stage of swelling, because the ulcers, as already shown, depend on more or less accidental causes, which may lead to ulceration of half of a patch of Peyer while the other half undergoes resolution, or to complete ulceration of one or more patches while the others return to normal conditions.

This view that the intestinal lesions are due primarily and perhaps

chiefly or entirely to a toxine originating in the intestinal lumen is favored by the character of the lesions occurring elsewhere in the body. They all lie along the lines of absorption through the lymphatics and of distribution through the circulation; they vary in intensity and are always diffuse; an organ, such as the spleen or a mesenteric lymph node, shows practically the same degree of cell change throughout its whole extent. The focal lesions in the liver and other organs all depend on accidental causes.

If the lesions depend on the immediate presence of the typhoid bacillus, then we have to assume that multiple infections of the lymphoid tissue of the intestines take place within a very short time, extend from the ileo-cæcal valve upward and spread uniformly throughout each patch of tissue affected; also that the organism gets into the circulation and reaches the spleen and other organs in the very beginning of the process.

Ribbert bases his opinion that the typhoid process begins with an acute inflammatory exudation on the fact that he finds among the large cells in early cases a little fibrin and an occasional leucocyte which he regards as the remains of the exudation. In view of the lesions above described, it seems more reasonable to regard this evidence of inflammation as the beginning rather than the end of the inflammatory process which is secondary to degeneration of the proliferated cells. Neither can his view that the newly-formed cells are of a reparative nature be accepted; for these cells do not produce any intercellular substance, or form blood-vessels or connective tissue as endothelial cells do in the organization of thrombi and in other reparative processes; instead they either undergo fatty degeneration as in resolution, or extensive necrosis (for which he gives no explanation), followed by ordinary granulation tissue.

The multinucleated lymphoid cells of the early observers are for the most part the phagocytic cells with their inclusions, produced by the action of the typhoid toxine. A very few of them, however, are multinucleated plasma cells.

The typhoid process in the various organs, especially the intestine, spleen and bone-marrow, is to a slight degree complicated by the form-

ation of plasma cells from lymphoid cells, by proliferation of lymphoid and plasma cells, and by their migration into and out of blood-vessels and in the tissues. These lymphoid elements never reach anything like the number present in cases of diphtheria and rarely give rise by emigration to the focal and diffuse collections of cells so often found in that disease, particularly in the kidneys. It is a question whether their increase is due to the direct action of toxic substances or is to be regarded as reparative in nature and dependent on other causes.

This formation by proliferation of phagocytic cells from endothelial cells is not peculiar to typhoid fever except in regard to location, extent and degree. The fact that toxic substances derived from various sources may produce at least two effects on cells, the one degenerative, the other proliferative, and also that they may act focally or diffusely, seems generally to have been overlooked. The staphylococcus pyogenes aureus is a good example of an organism that produces necrosis focally. The toxine is strong and is but slightly diffusible. The tubercle bacillus on the other hand produces proliferation focally. The diphtheria bacillus acts both focally and diffusely and produces, according to the strength of its toxine, either proliferation or necrosis, or the one process following the other. The typhoid bacillus produces a mild toxine that acts diffusely and causes proliferation.

Taking this view of the action of the typhoid bacillus, that it causes proliferation of endothelial cells by means of a diffusible toxine, how are the cases of meningitis, of pneumonia and of abscess formation in bones, the spleen and other organs, reported to be due to the typhoid bacillus, to be explained?

In the spleen of one of the cases studied there were two yellowish nodules, one the size of a pea, the other of a marble. On section the larger nodule was opaque and yellowish white in one-half, while the other half contained thick pus. The smaller nodule was firm except near the centre, where a little pus was present. Bacteriological examination showed only the typhoid bacillus present both in the abscesses and elsewhere in the spleen. On microscopic examina-

tion numerous small areas of large phagocytic cells undergoing necrosis and imbedded in abundant fibrin were found all through the spleen. In the neighborhood of the nodules just mentioned some of the large veins were thrombosed by masses of fibrin and degenerating phagocytic cells. The firm portions of the nodules consisted of necrotic tissue in which in places degenerating phagocytic cells could still be distinguished. The softened portions of the nodules contained polymorphonuclear leucocytes. Typhoid bacilli were present in moderate numbers in the form of colonies in the necrotic tissue, and scattered diffusely in the softened portions. In the latter situation many of them were within the leucocytes. This case suggests that possibly the typhoid bacilli, which happened to be in the necrotic area produced through occlusion of blood-vessels by phagocytic cells, may have found more favorable surroundings for growth than they ordinarily do in living tissue, just as the tubercle bacillus grows most luxuriantly in old cavities of the lung or in softened, broken down lymph nodes. It is also possible that the post-typhoid abscesses of bones may owe their origin through obstructed blood-vessels to primary foci of necrosis, in which, as in the necroses in the spleen, the typhoid bacillus finds favorable surroundings for growth.

One of the cases of typhoid fever was complicated with typical fibrinous pneumonia of the whole of the right lower lobe in the stage of gray hepatization. The post-mortem examination was made in a hurry, at night, three hours after death, and unfortunately cultures of the lung were not made. Microscopic examination of the exudation showed serum, fibrin, fairly numerous polymorphonuclear leucocytes, occasionally lymphoid and plasma cells, rarely an eosinophile. There were also present, however, great numbers of large phagocytic cells with irregular, vesicular nuclei situated peripherally (Plate LXI, Fig. 31). The inclusions consisted almost entirely of polymorphonuclear leucocytes, of which usually one or two, but occasionally several, were within a single cell. More rarely the inclusions consisted of red blood globules. The number of phagocytic cells varied considerably in different parts of the lobe, but in many of the alveoli this was almost the only cell present. Microscopically, pneu-

mococci were present in very small numbers, while a bacillus, morphologically like the typhoid bacillus, occurred more abundantly and usually within leucocytes. The perivascular and peribronchial lymph vessels and spaces contained lymphoid, plasma and phagocytic cells in small numbers. There are of course three possible sources for these phagocytic cells within the alveoli of the lung. They may have emigrated from the blood-vessels or have been derived by proliferation from the epithelium lining the alveoli or from underlying endothelial cells after destruction of the epithelium. The third view seems the preferable one. No evidence of emigration or of active amœboid motion on the part of these cells has ever been observed. On the other hand very numerous mitotic figures were found in large cells lining the alveoli. It is of course impossible to deny that the proliferating cells may be epithelial, but in view of the marked phagocytic properties shown by them, it seems more reasonable to assume that they have the same origin as the other phagocytic cells already described. This is assumption, however, not proof.

The simplest explanation of the presence of these phagocytic cells in such large numbers (for they can be found not infrequently in ordinary cases of pneumonia) is that we have here a case of lobar pneumonia complicated by the action of typhoid bacillus of which the toxine has caused a proliferation of certain cells in the wall of the alveoli. How the typhoid bacilli get into the lung I do not pretend to explain beyond suggesting that they may have been brought from the blood-vessels by the emigrating leucocytes. These two cases, the abscesses in the spleen and the lobar pneumonia, certainly suggest that careful bacteriological and histological study of the various complications of typhoid fever, and especially of cases of meningitis claimed to be due to the typhoid bacillus alone, may throw additional light on the character of the lesions produced by the typhoid bacillus.

In view of the lesions described in the blood-vessels of the intestine, liver and spleen, and beneath the lining endothelium of the heart, it seems fair to suppose that the thrombi which sometimes occur in typhoid fever, rarely in the heart but rather frequently in the veins of the lower extremities, may owe their origin to similar lesions.

Remlinger has recently claimed to have produced typical typhoid lesions in a certain proportion of rabbits and guinea-pigs by feeding them every day on vegetables soaked in bouillon cultures of typhoid bacilli. A series of experiments was carried on to confirm, if possible, these results, but without success, although in one case 30 cc. gradually increased to 100 cc. of a bouillon culture were introduced each day for ten days directly into the stomach of a rabbit by means of a stomach tube. The virulence of the organism used may of course have much to do with the success of such experiments.

By injecting 1.5 cc. of a thirty-hour-old bouillon culture of the typhoid bacillus into the peritoneal cavity of a guinea-pig and gradually increasing the amount every day up to 3 cc. on the fifth day, there were obtained on the sixth day an enlarged spleen in which were many large cells filled with red blood globules, and a number of small yellowish foci irregularly distributed in the liver.

Rabbits and guinea-pigs are, however, poor animals in which to study the possible effects of the typhoid toxine for the reason that under what must be considered normal circumstances many phagocytic cells containing the more or less digested remains of lymphoid cells are present, often in abundance, in the lymphoid tissue of the small and large intestine. Attention was first called to these cells by Flemming. Besides these lesions in the intestine, pigmented cells in the mesenteric lymph glands and spleen, and small areas of necrosis in the liver are not infrequent. They are entirely distinct from lesions caused by coccidia, and strongly suggest an origin due to absorption of toxic substances from the intestinal tract. The lesions in the liver are probably embolic in origin, but focal lesions in the liver of these animals are much more difficult to fathom, partly because the capillaries are very narrow and easily occluded, but principally because it is difficult to get perfect preservation of the various cell elements and of the red blood globules, a difficulty due in part at least to the large amount of glycogen present in the liver cells.

CONCLUSIONS.

The typhoid bacillus produces a mild diffusible toxine, partly within the intestinal tract, partly within the blood and organs of the body.

This toxine produces proliferation of endothelial cells which acquire for a certain length of time malignant properties.

The new-formed cells are epithelioid in character, have irregular, lightly staining, eccentrically situated nuclei, abundant, sharply defined, acidophilic protoplasm, and are characterized by marked phagocytic properties.

These phagocytic cells are produced most abundantly along the line of absorption from the intestinal tract, both in the lymphatic apparatus and in the blood-vessels.

They are also produced by distribution of the toxine through the general circulation, in greatest numbers where the circulation is slowest.

Finally, they are produced all over the body in the lymphatic spaces and vessels by absorption of the toxine eliminated from the blood-vessels.

The swelling of the intestinal lymphoid tissue of the mesenteric lymph nodes, and of the spleen is due almost entirely to the formation of phagocytic cells.

The necrosis of the intestinal lymphoid tissue is accidental in nature and is caused through occlusion of the veins and capillaries by fibrinous thrombi, which owe their origin to degeneration of phagocytic cells beneath the lining endothelium of the vessels.

Two varieties of focal lesions occur in the liver: one consists of the formation of phagocytic cells in the lymph spaces and vessels around the portal vessels under the action of the toxine absorbed by the lymphatics; the other is due to obstruction of liver capillaries by phagocytic cells derived in small part from the lining endothelium of the liver capillaries, but chiefly by embolism through the portal circulation of cells originating from the endothelium of the blood-vessels of the intestine and spleen. The liver cells lying between the occluded capillaries undergo necrosis and disappear. Later the foci of cells degenerate and fibrin forms between them. Invasion with polymorphonuclear leucocytes is rare.

Many of the phagocytic cells pass through the liver and lungs, and get into the general circulation. A few come from the abdominal lymphatics through the thoracic duct.

Focal lesions may arise in the kidneys by occlusion of the veins of the pyramids by emboli of these phagocytic cells.

Focal collections of phagocytic cells may occur in the heart and testicle by occlusion of lymph vessels.

The various sequelæ of typhoid fever deserve more careful bacteriological and histological examination, as shown by the study in one case of abscesses of the spleen where these seemed to arise in previously necrotic tissue, and of a case of pneumonia due to the pneumococcus, but complicated by the presence of the typhoid bacillus, in which great numbers of phagocytic cells were found in the exudation.

The thrombi which occur in the heart and in the veins of the lower extremities in the course of typhoid fever probably owe their origin to the same sort of lesions that cause occlusion of the vessels in the intestine.

Histologically the typhoid process is proliferative and stands in close relationship to tuberculosis, but the lesions are diffuse and bear no intimate relation to the typhoid bacillus, while the tubercular process is focal and stands in the closest relation to the tubercle bacillus.

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DESCRIPTION OF PLATES LIV-LXI.

PLATE LIV.

Fig. 1.—Lymph nodule and adjoining tissue from a patch of Peyer showing the centre of the nodule occupied by large phagocytic cells.

Fig. 2.—A solitary lymph nodule showing diffuse formation of phagocytic cells.

PLATE LV.

Fig. 3.—Mucous membrane of intestine showing diffuse formation of phagocytic cells; also a dilated lacteal filled with phagocytic cells.

Figs. 4, 5 and 6 show details from Fig. 1.

Fig. 4.—From periphery of lymph nodule, showing a large cell of the reticulum in mitosis.

Fig. 5.—From near the periphery of lymph nodule, showing newly-formed cells beginning to incorporate the lymphoid cells.

Fig. 6.—From centre of lymph nodule, showing the newly-formed cells filled with more or less digested lymphoid cells. Several red blood globules have also been incorporated.

Fig. 7.—Lymphatic vessel of mucous membrane containing phagocytic, lymphoid and plasma cells.

PLATE LVI.

Fig. 8.—Terminal lymphatic (lacteal) of mucous membrane dilated and filled with phagocytic cells.

Fig. 9.—Mitosis of endothelial cell of capillary in mucous membrane.

Fig. 10.—Phagocytic cells in large vein of submucosa.

Fig. 11.—Plasma cell in mitosis inside phagocytic cell in a large vein in submucosa.

Fig. 12.—Mitosis of endothelial cell lining large vein in submucosa.

Fig. 13.—Giant cell in submucosa.

Fig. 14.—Two plasma cells migrating through wall of vein in submucosa.

PLATE LVII.

Fig. 15.—Endothelium of vein shoved forward by a swollen plasma cell, two lymphoid and two large cells; the last are degenerating.

Fig. 16.—Another section of the same vessel showing fibrin forming around large, degenerated cells.

Fig. 17.—Vein occluded by a mass of fibrin.

Fig. 18.—Large phagocytic cells beneath endocardium of heart.

Fig. 19.—Mass of fibrin and degenerating cells beneath lining endothelium of a large vein in the submucosa. Mitosis of large cell at one end.

PLATE LVIII.

Fig. 20.—Mitosis of endothelial cell in capillary of liver.

Fig. 21.—Phagocytic cells in a portal vein in the liver.

Fig. 22.—Phagocytic cells occluding capillaries in the liver.

Fig. 23.—Mitosis of a large phagocytic cell containing a red blood globule in portal vein in liver.

Fig. 24.—A giant cell formed apparently in a capillary in the liver.

Fig. 25.—Phagocytic cells occluding capillaries of liver. Beginning necrosis of included liver cells.

PLATE LIX.

Fig. 26.—Focal area of phagocytic cells in capillaries of liver showing beginning degeneration with formation of fibrin.

Fig. 27.—Focal area in liver due to phagocytic cells in the capillaries. Necrosis of many of the included and adjoining liver cells.

PLATE LX.

Fig. 28.—Phagocytic cells undergoing necrosis in capillaries between trabeculæ of liver cells.

Fig. 29.—Large focal area in liver consisting of phagocytic cells. The included liver cells have entirely disappeared.

PLATE LXI.

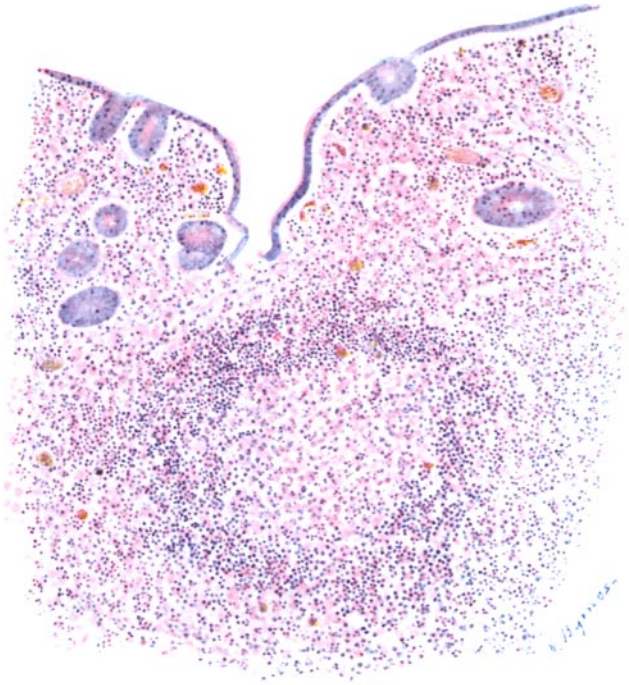
Fig. 30.—Large phagocytic cell in renal vein: judging from its inclusions it probably reached the general circulation through the thoracic duct.

Fig. 31.—Phagocytic cells in the exudation in the lung; from a case of lobar pneumonia complicating typhoid fever.

Fig. 32.—Group of cells in clot from left side of heart.

Fig. 33.—Phagocytic cells in a pulmonary blood-vessel.

Fig. 34.—Lining endothelium of large vein of spleen lifted up by phagocytic, lymphoid and plasma cells.



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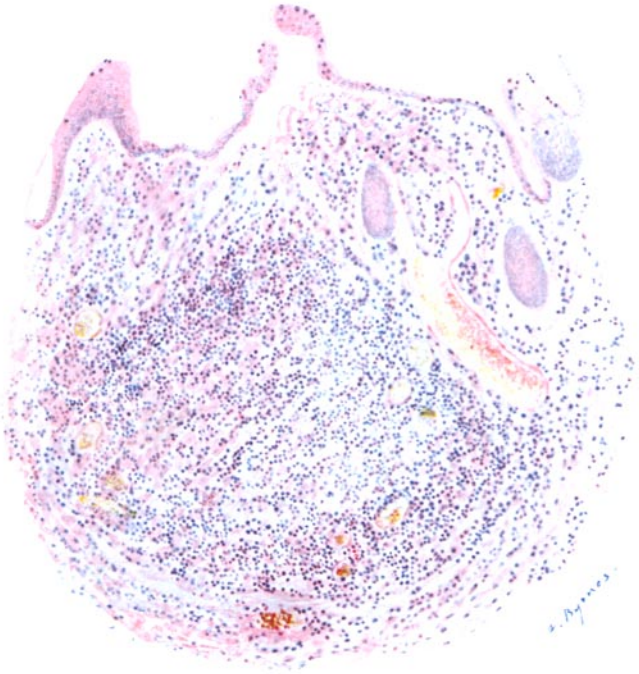

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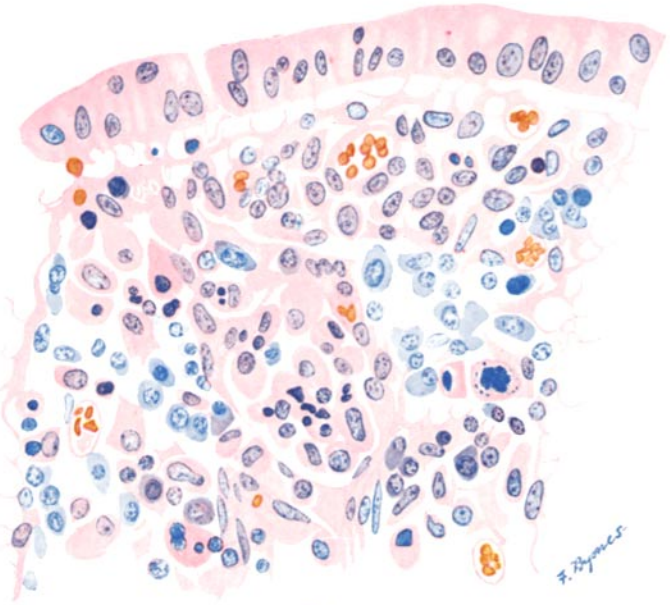

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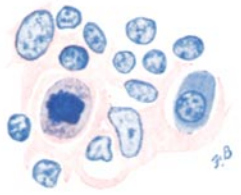

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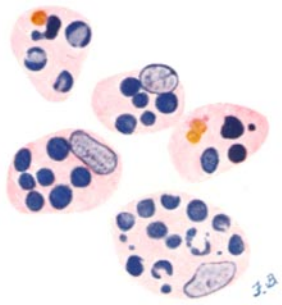

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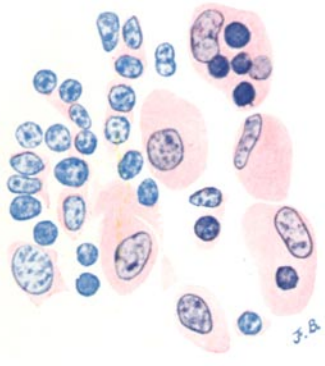

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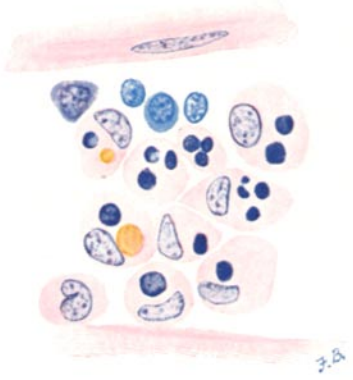

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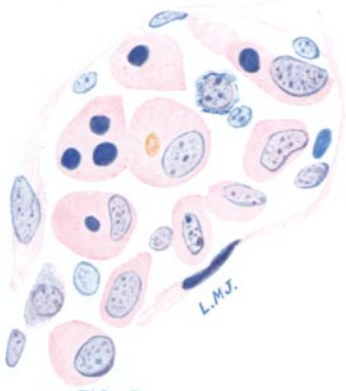

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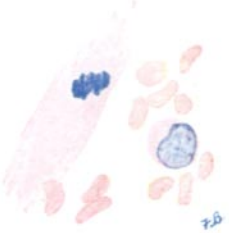

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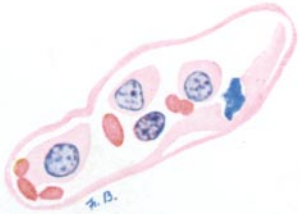

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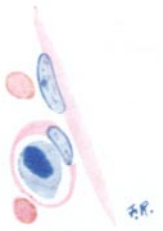

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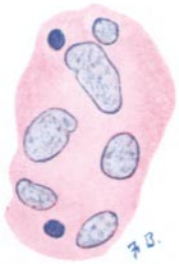

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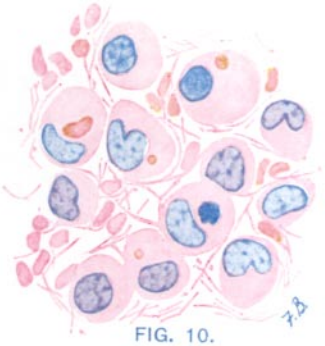

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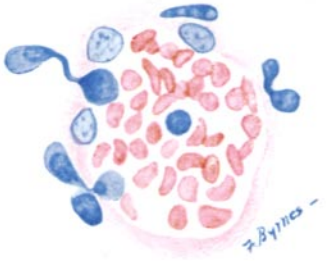

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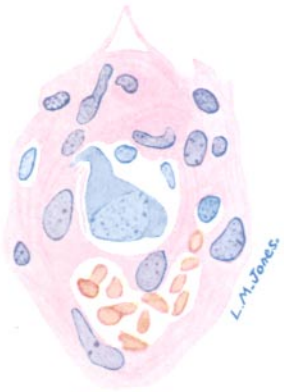

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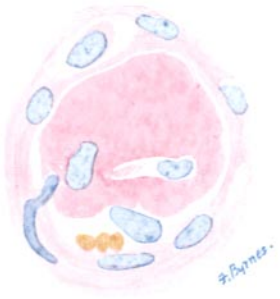

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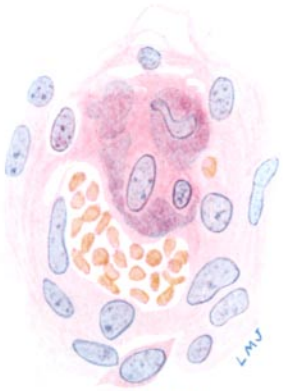

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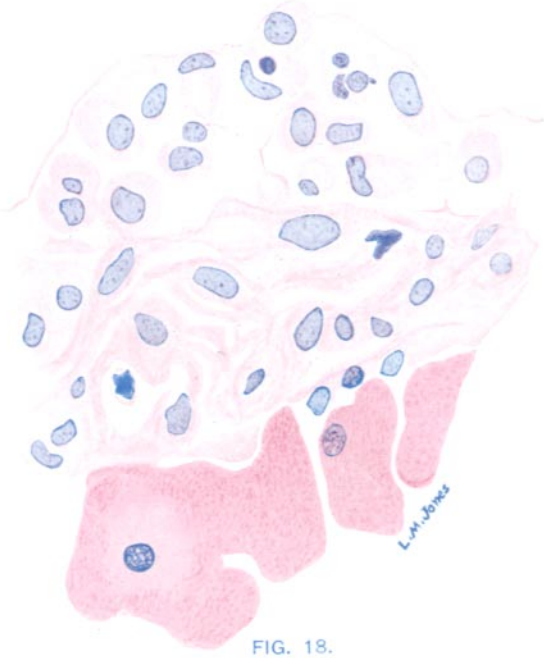

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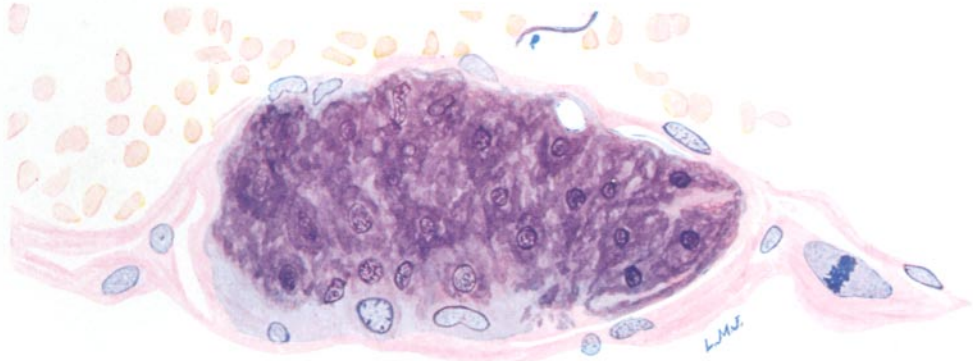

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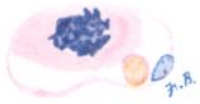

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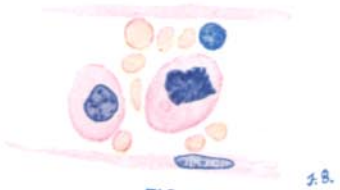

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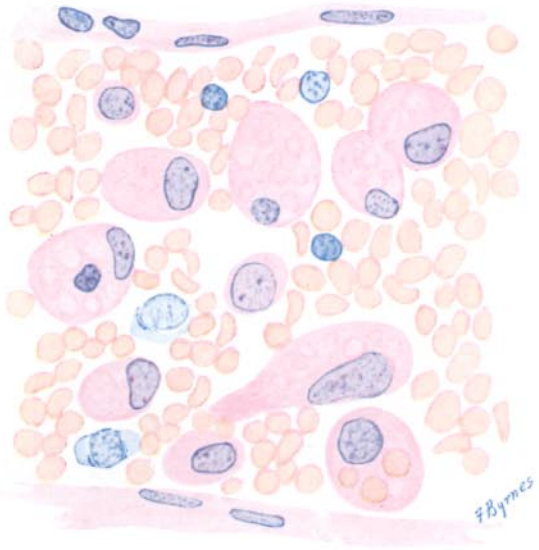

FIG. 21.

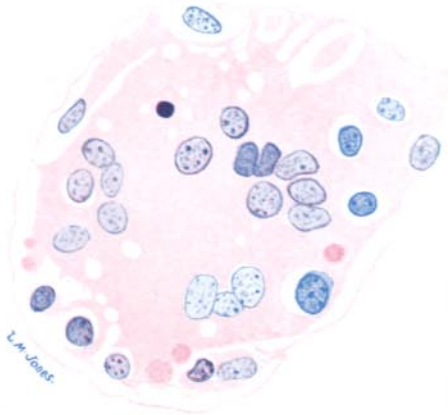

FIG. 24.

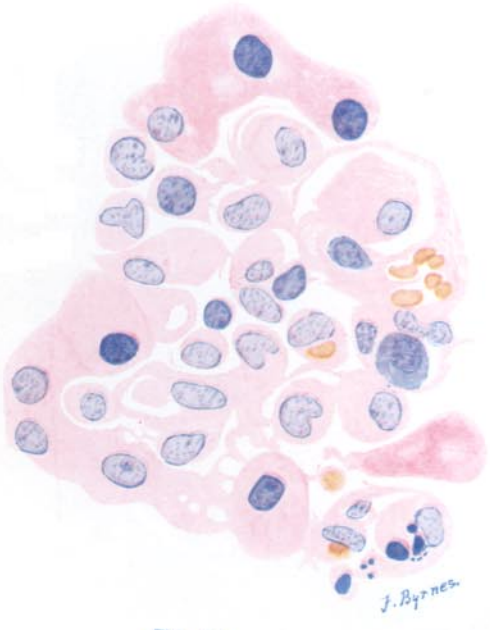

FIG. 22.

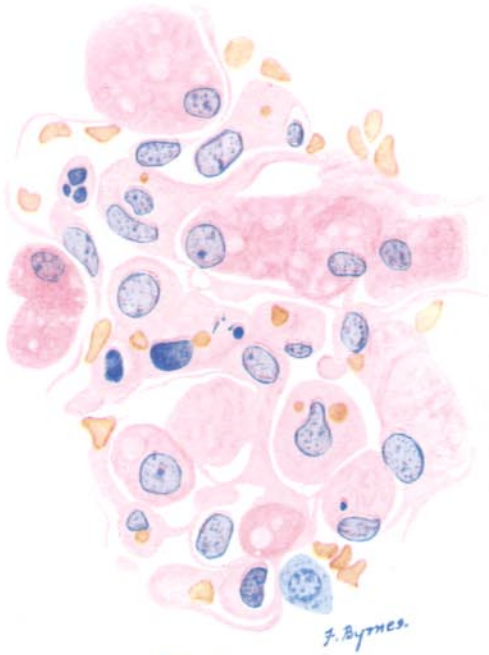

FIG. 25.

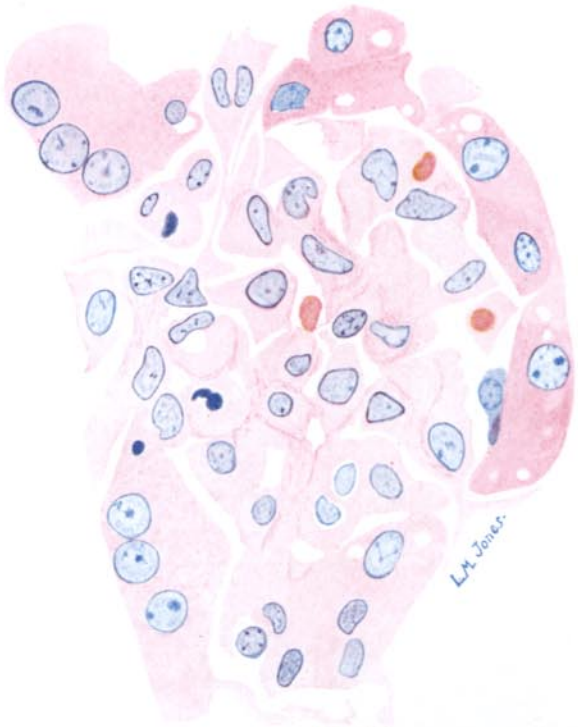

FIG. 26.

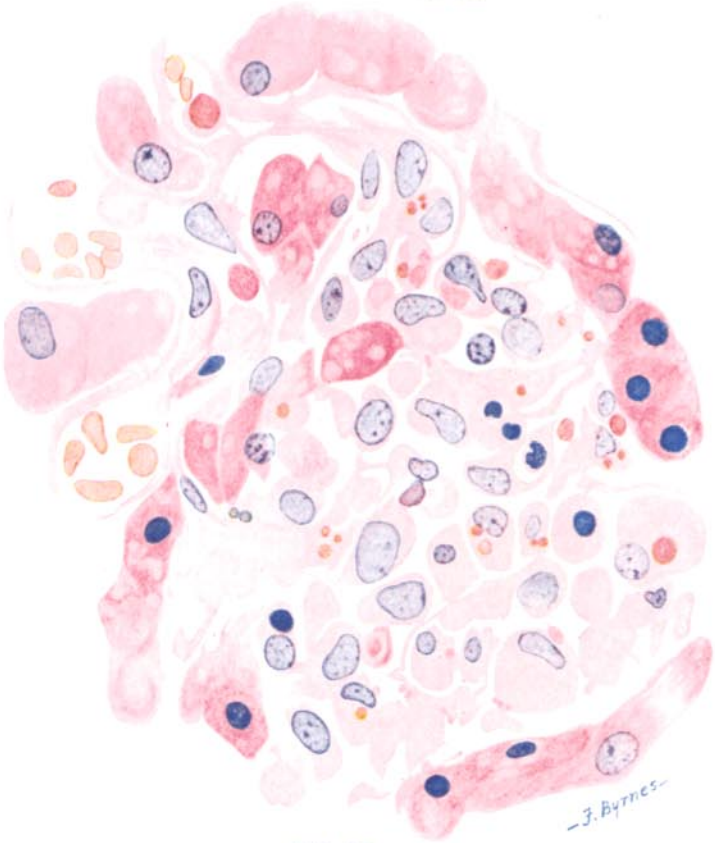

FIG. 27.

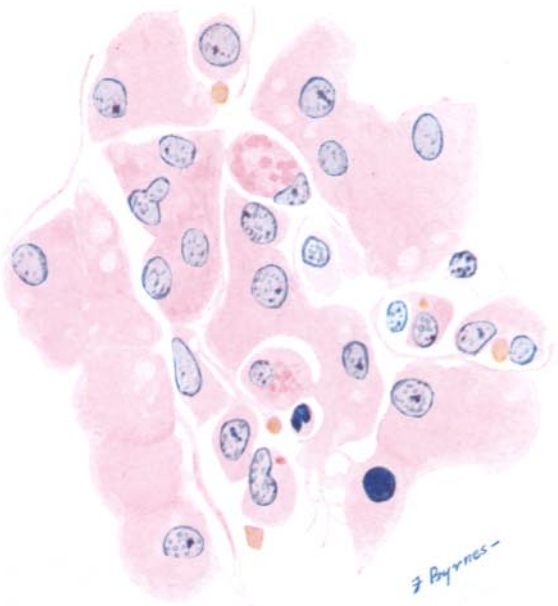

FIG. 28.

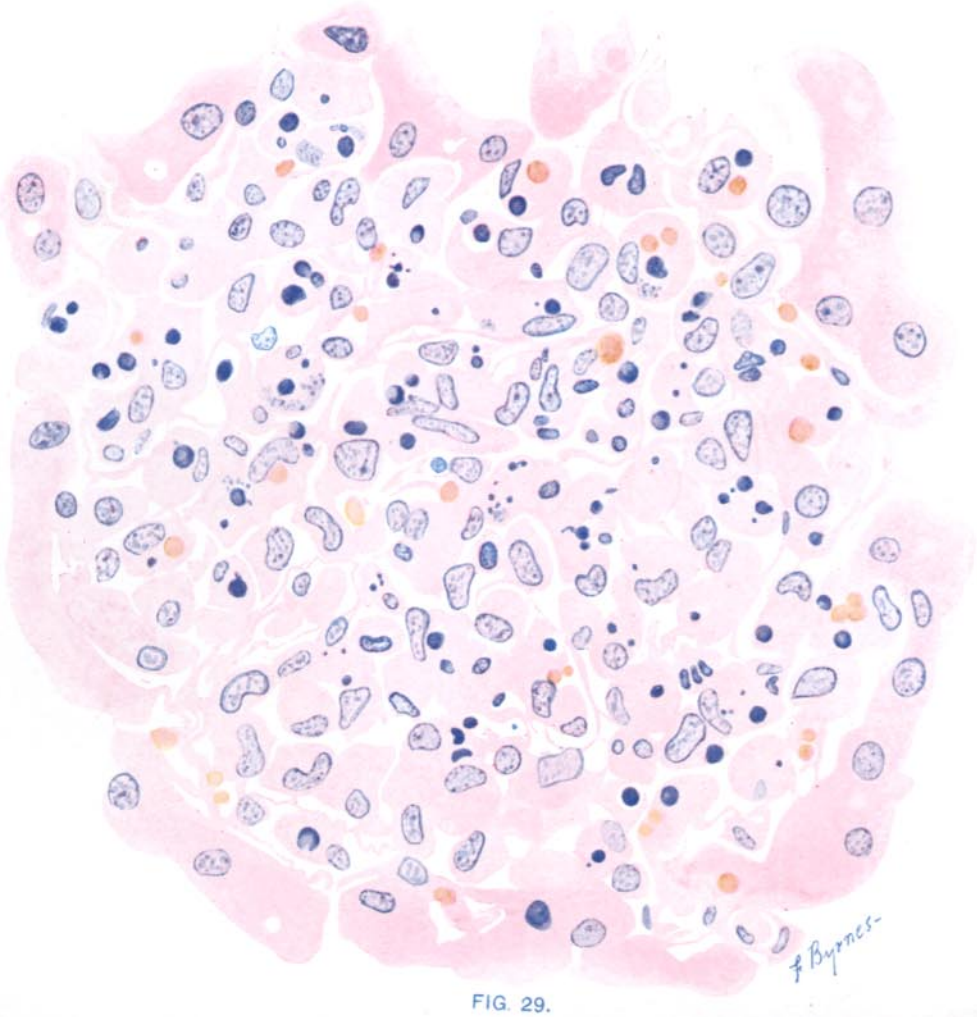

FIG. 29.

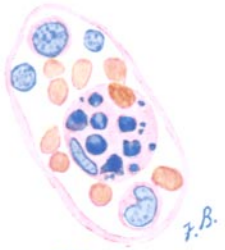

FIG. 30.

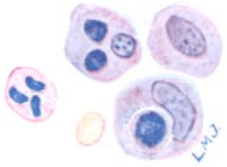

FIG. 32.

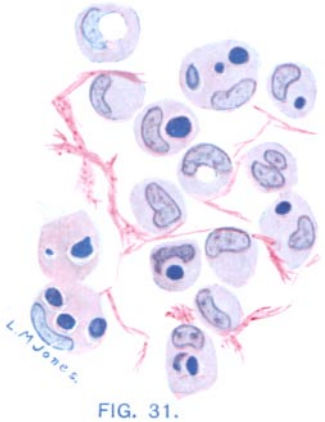

FIG. 31.

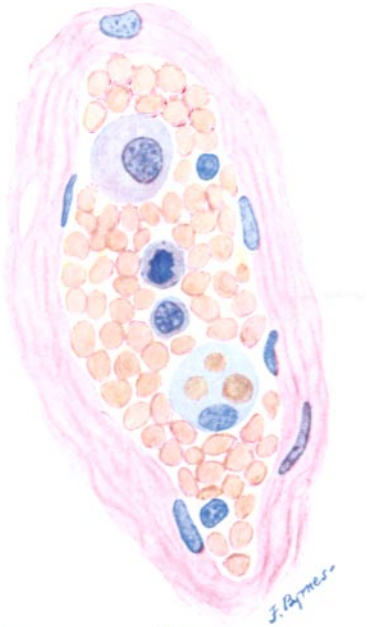

FIG. 33.

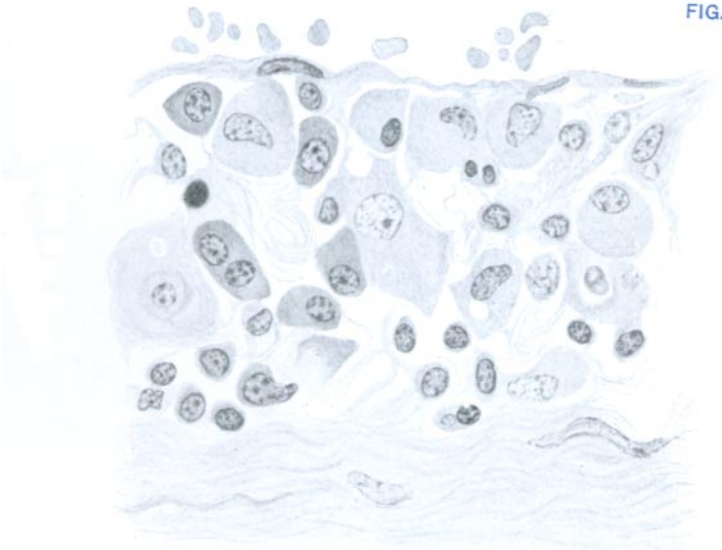

FIG. 34.