EXPLANATION OF PLATE XXXIV.

FIG. 1.—Normal Mesentery of Rabbit, Showing Size of Small Artery, Vein, and Capillaries. The artery curves across the vein, giving off a capillary; a capillary also enters the vein. 8 mm. Zeiss.

FIG. 2.—Artery, Veins, and Capillary Network of Rabbit One Hour after Injection of One-per-cent. Nitrate of Silver. Intense congestion with abundent diapedesis from veins and capillaries. 16 mm. Zeiss; half magnification of Fig. 1.

FIG. 3.—Acute Salpingitis, Showing Infiltration of Leucocytes in Tissue of the Papillæ of Fallopian Tube. 8 mm. Zeiss.

FIG. 4.—Edge of Eschar in Cornea after Forty-eight Hours, Showing Infiltrating Leucocytes in Corneal Tissue between the Fibrillæ. 16 mm. Zeiss.

FIG. 5.—Small Vein in Mesentery of Rabbit Four Hours after Injection of Water at 52° C., Showing Rapid Emigration.

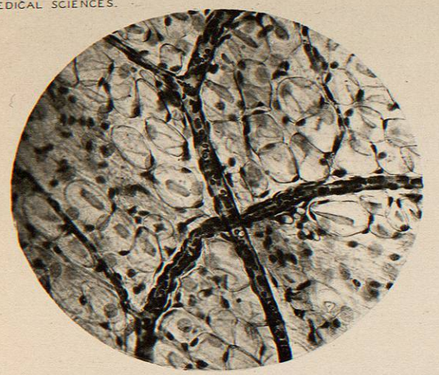

FIG. 1.

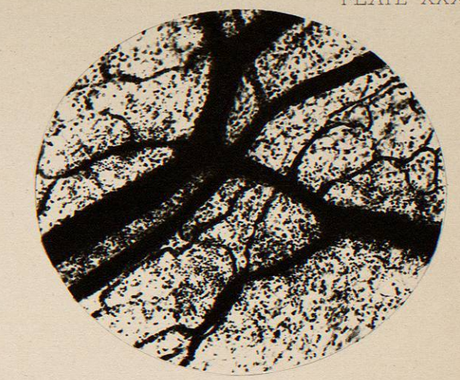

FIG. 2.

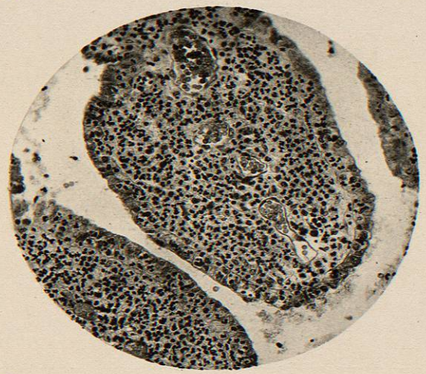

FIG. 3.

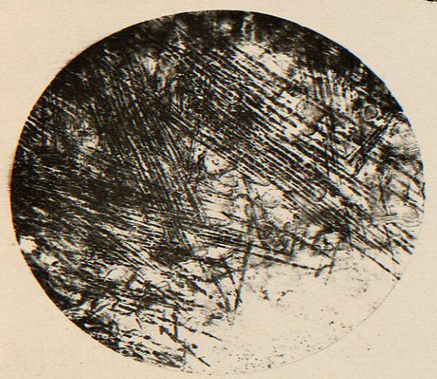

FIG. 4.

FIG. 5.

ACUTE INFLAMMATION.

clear leucocytes. These have not such power of amœboid motion nor such capacity for penetration. Ordinarily but little degeneration is seen in the lymphoid cells in the tissues, and these seem to undergo degeneration chiefly when in large masses and under the influence of strong toxins. The intensely stained solid nuclear fragments to which they give rise are very conspicuous. The fragments very often have a distinctly crescentic shape.

The red corpuscles in the exudation vary greatly in number, this depending in normal tissues chiefly on the character of the injurious agent used. In the cornea it is not possible to produce any considerable hemorrhagic exudation, although in most cases a number of red corpuscles will be found in the tissue around the vessels. In the mesentery an abundant hemorrhagic exudation may be produced by the injection of nitrate-of-silver solution into the peritoneal cavity. (Plate XXXIV., Fig. 2.) The red corpuscles are found chiefly around the vessels from which they have come, but they may be washed to a distance by the lymph streams. In the cornea they may be found in the cell spaces at quite a distance from the periphery. In diphtheria I have often found them between the epithelial cells of an intact mucous surface. As they have no amœboid power of their own they must be carried passively by the lymph stream, and their presence in such places gives an indication of the force and the amount of the lymph stream. The red corpuscles, like the leucocytes, may undergo fragmentation, and in the inflamed mesentery I have found the red corpuscles around the vessels broken up into round fragments.

Do the blood platelets take any part in inflammation? I do not believe that these exist as such in the normal blood. For a long time I have been examining the blood in normal vessels to determine this point and have never found them. The view of Arnold that they are formed from red blood corpuscles is probably correct. In the inflamed mesentery of the rabbit I have occasionally found numbers of them in the small veins and in the adjoining tissue. It cannot be decided whether they emigrate from the vessels or whether they are formed *in situ*.

Along with the cells there is a considerable amount of fluid exudation from the vessels, and the swelling of the tissue is chiefly due to this. The fluid passes into the tissue, distending first the lymph spaces and then saturating the tissue itself, forcing apart the connective-tissue fibrillæ. In the cornea the cell spaces and passages are thus made larger than normal. Occasionally a beautiful demonstration of the fibres of the cornea is given in specimens of the inflamed tissue stained with nitrate of silver. The fibres are all separated and the thin space between any two adjacent fibres is stained brown by the silver. The fibres are all of the same size and each plane is composed of a single thickness of parallel fibres. A very thin flat section of the cornea contains a number of these planes of fibres. In the mesentery also, in spite of the ease with which the fluid can pass to the surface and away, spaces may be seen between the fibrillæ. In the rabbit's ear the fluid chiefly collects in the connective tissue on the outside surface, and all the fibres are separated so as to form a loose meshwork. The passage of the fluid from the vessels begins before either the diapedesis of the red corpuscles or the emigration of the white, and continues much longer. An abundant fluid exudation may take place on a very slight injury to the tissue and without any cellular exudation. If a blunt instrument be drawn over the inner surface of the forearm making considerable pressure, a slight swelling becomes perceptible in a few minutes. In a circumscribed area of inflammation this exudation takes place in the border zone where the effect of the injury has not been sufficient to produce the cellular exudation. The amount of the fluid exudation and the relation between the fluid and cells depend upon the situation of the inflamed area. If this is deep down in the tissues so that the fluid cannot escape, but remains in the tissues, there will be relatively few cells present. If it is near the surface, the fluid may escape easily either to the surface of the body or into a cavity, and most of the cells may be left entangled in the tissue. In inflammation of the lung the fluid and cells also pass without trouble from the thin walls into the air spaces. In inflammation of the pleura or peritoneum the fluid passes into the large cavities and collects there; more leucocytes, however, are held back in the tissues than is the case in the lung. The skin offers a marked resistance to the passage of fluids through it. The exudation collects chiefly in the loose subcutaneous tissue distending the spaces, but it may pass through the lower layer of the epidermic cells, forcing up the horny layer in the form of vesicles filled with fluid. If the vesicle is ruptured the exudation may pass through to the surface, but this is usually prevented by the drying of the exudation and the formation of a scab. The smallpox vesicle differs from the ordinary vesicles; it is not produced by the collection of an exudation beneath the horny layer, but is formed deeper down in the epithelium, its formation being preceded by a degeneration of the epithelial cells. In some cases the entire epidermis may be elevated by the exudation. Most mucous surfaces, even when lined with stratified epithelium, offer little opposition to the outward passage of the exudation. As we have said, the exudation seems to pass with considerable force, for cells are swept along by it and may be carried into situations where they could not arrive by their own activity. Not only is the presence of red corpuscles in the upper layers of the epidermis to be accounted for in this way, but the force of the exudation is probably an important factor in the movement of the leucocytes. An excellent example of an almost pure serous exudation is given in sunburn. In this condition the subcutaneous tissue may be greatly distended with such an exudation, and examination of the fluid of the vesicles will show very few leucocytes. Such an exudation represents the reaction following the slighter forms of injury.

If inflamed tissues are carefully examined a varying amount of fibrin will be found in nearly all. It will be absent in slight degrees of inflammation and in the severer forms of suppurative inflammation. The amount, situation, and character of the fibrin vary in different cases and the factors which influence these conditions are not definitely known. The fibrin is formed from the fluid exudation after it has left the vessels. The conditions for its formation are present when the exudation comes in contact with necrotic cells. These may be either the cells of the tissue or broken-down leucocytes. The fibrin is formed by the fibrinogen of the serous exudation in the presence of a ferment produced by the degenerated cells. When it is not formed under such conditions or when its formation is extremely feeble, as in the suppurative inflammation, this is due to the presence of substances which prevent the chemical reaction by which it is formed, or lead to its solution when it is formed. The fibrin appears under the most varying forms. It may take the form of a network of the finest filaments or the filaments may be broad and hyaline. Within the tissues it may appear in stellate figures, the filaments radiating from a centre. In the centre a small stained body is often seen which represents the remains of the nucleus of a degenerated cell. Such stellate fibrin figures are found in great numbers in the subcutaneous tissue of the inflamed ear of the rabbit and in the submucous tissue in diphtheria. The fibrin is also found on inflamed surfaces where it forms connected masses. On the surface of the pleura it may be present as a layer 1 cm. or more in thickness, or it may be in such small amounts as to constitute only a faint granulation. New interest was given to fibrin formation some years ago by the statement of Neumann that it is formed not on but in the serous surfaces, and that most of what are regarded as fibrin filaments really are connective-tissue fibrillæ which are transformed into fibrin. A careful study of the process has shown that there is a relation between the connective-tissue fibrillæ and fibrin formation. The fibrillæ are not converted into fibrin, but fibrin is deposited upon and probably in them. Under such conditions the fibrillæ become swollen, refractive, and hyaline, and give the microchemical reactions of fibrin. This fact may be

more easily demonstrated in diphtheria than in any other process. The membrana propria beneath the false membrane on the trachea may show patches of this, and extending from it into the tissue beneath there are swollen hyaline fibres which may be shown by appropriate stains to be continuous with unaltered connective-tissue fibrillæ. On serous surfaces Ribbert has shown that the first appearance of the fibrin takes the form of small projections between the endothelial cells. The great mass of fibrin is on the surface and is a true exudation, but there may be a slight fibrinoid metamorphosis of the tissue, and the fibrin formed in this way may be connected with the membrane on the surface. The relation of the endothelium to the fibrin formation varies. Usually no trace of this layer will be seen, or small areas of intact endothelial cells may be found. In a case of fibrinous peritonitis following amœboid dysentery the endothelium was found almost everywhere beneath the false membrane, the cells being greatly swollen and proliferating. In rare cases larger or smaller spaces lined with large cells of a typical epithelial character may be found in the false membrane on serous surfaces. These are connected masses of the surface endothelium which have been lifted off by the exudation coming from beneath and have become enclosed in the fibrin mass. On mucous surfaces the fibrinous exudation may form dense elastic membranes which may be in some cases stripped off in large pieces, while in others the membrane clings more closely and can be removed only in fragments. In situations where the membrane has been formed on a dense membrana propria the separation is easy. It is due to the presence of a membrana propria that in the trachea the false membrane formed in diphtheria is easily removed, while in the pharynx where there is no membrana propria it adheres. On mucous surfaces the formation of the false membrane is due to a combination between the exudation coming from below and necrosis of the surface epithelium. Microscopically it is easy to distinguish two definite forms of pseudomembrane. In both there is a reticulum, but in one case the spaces are small and the reticulum is broad and highly refractive, and in the other the spaces are larger and the reticulum has the character of fibrillar fibrin. Even macroscopic differences in the membrane can be seen. The first, which may be distinguished as the hyaline membrane, is formed on mucous surfaces covered with stratified epithelium. The epithelial cells remain and are converted into fibrin very much in the same way as in the fibrinoid metamorphosis of the connective tissue. In a case of membrane formation in the œsophagus it was possible to trace the formation of fibrin around necrotic cells and the conversion of these into the membrane. In the trachea the epithelium is cast off and takes no part in the fibrin formation other than supplying by its necrosis the necessary fibrin ferment. In many cases the membrane shows a peculiar architecture, the fibrin being arranged in definite arches and pillars, the latter being attached to the tissue beneath by a broad foot or connected with the fibrinoid connective tissue. Large numbers of both white and red corpuscles may be found in the membrane, the dark color which it sometimes shows being due to the presence of the latter. When once formed, the fibrin may extend over an intact epithelial surface and areas of completely healthy epithelium may be found beneath it. In the intestinal canal a perfect fibrinous exudation is rarely met with. What appears macroscopically as fibrin is composed of necrotic cells and tissue, with but slight admixture of fibrin. The best examples of fibrinous exudation in the digestive tract are found in the stomach. It is probable that the formation of fibrin is influenced by the character of the fluid which comes from the vessels, its varying richness in fibrinogen, and conditions which this exudation meets in the tissues. We know very little about the character of the exudation fluid as it comes from the vessels. Analyses have shown that it contains about the same amount of salts and is richer in proteids than the blood serum; it is, however, no longer as it came from the vessels, but is a tissue fluid, and it may have been modified by conditions it met with in the tissues. In the tissues it differs greatly in concentration and probably in other ways, as is shown by the character of the coagulum formed in rapid hardening. In some cases there is a dense granular coagulum, in others scarcely any coagulum is found.

The exudation may be converted into a hyaline mass without a trace of structure. Such hyaline masses may be found in the alveoli of the lung in various forms of pneumonia but particularly in tuberculous pneumonia. In this the hyaline material is most apt to be found in the anterior borders of the lung. To what extent the hyaline masses found in the tubules of the kidney in various forms of renal disease represent a metamorphosis of an albuminous exudation is not known. We know that these casts are certainly formed by the coalescence of hyaline drops which are formed in the degeneration of epithelium, but this may not be the only mode of formation. They are most frequent in those forms of renal disease in which hyaline epithelial degeneration is common, as in the amyloid kidneys and in some forms of acute nephritis, but they are also found when hyaline epithelial degeneration is not conspicuous. It is not known whether such changes in the exudation are due simply to its becoming more concentrated or whether there is a further chemical change.

Suppurative inflammation is a special form in which an exudation is produced which is especially rich in cells, and in which there is a strong inhibition to the formation of fibrin. (Plate XXXIV., Fig. 3.) It differs from other forms of inflammation also in its etiology. Varying degrees of injury of the tissue, even when produced by the same agent, may give a serous, a hemorrhagic, or a fibrinous inflammation, but without the addition of a specific cause the inflammation will not result in suppuration. In this the exudation may form for itself a cavity in the tissues, called an abscess, in which it is confined. The content of the abscess is called pus. Probably without exception, under natural conditions suppurative inflammation is produced by the action of bacteria. A great number of bacteria may produce pus, but certain micro-organisms are so generally found in connection with suppuration that they are known as the pyogenic or pus-producing bacteria. The most common of these is the Staphylococcus aureus. Exactly what the conditions are under which certain bacteria, which ordinarily act in an entirely different manner, produce suppuration is not known. This action may be due to some condition in the tissues affected or it may be due to some peculiar change in the character of the organisms. Certainly we do not know any distinct varieties of either the typhoid or the tubercle bacillus which are associated with suppuration. Even such an organism as the pneumococcus or the diphtheria bacillus, with whose action we are accustomed to associate a fibrinous exudation, may—the former not infrequently—produce suppuration. Experimentally an inflammation closely resembling suppuration may be produced by croton oil. After injection of this into the subcutaneous tissue or muscle there is formed in it a cavity which contains pus, that is, a fluid containing great numbers of polynuclear leucocytes, but without fibrin. The various steps in the formation of the abscess can be followed experimentally by injecting staphylococci into the tissues or inoculating the cornea with them. After injecting staphylococci into the ear vein of a rabbit abscesses are found in the organs in large numbers. It is difficult to explain the situation of these abscesses. They are found most frequently in the kidney, and next in frequency in the heart and in the anterior abdominal wall; they are very rarely found in other situations, although the organisms must be carried everywhere by the blood. The formation of abscesses in these situations is probably to be accounted for by the conditions of the circulation favoring the accumulation of the bacteria in the vessels. The early stages are more easily seen than the fully developed abscesses, for in most cases the animal dies before these are actually formed. The first thing in the production of the abscess is the collection of a mass of the cocci,

occluding a small vessel, usually a vein. It is not probable that this large mass is brought to the tissue as such, but single organisms lodge in the wall of the vessel and this becomes filled by their gradual growth. The immediate effect of the presence of the bacteria is the production of an area of necrosis around them. The extent of this area of necrosis varies slightly according to the size of the occluded vessel and the number of micro-organisms. The necrotic area appears macroscopically as a small white speck. The elements of the tissue are obscured but can be distinguished. The nuclei no longer stain, but do not generally undergo degeneration or break up into chromatin fragments. The capillaries in the area are not visible; they are not occluded by fibrin but appear to be compressed by the swollen tissue. No leucocytes are present. There is simply necrosis of the tissue. This is well shown in the cornea. After central inoculation with virulent staphylococci a white speck is formed which under the microscope is seen to be composed of central masses of cocci in the corneal spaces around which is an area of necrotic corneal tissue. The necrosed corneal corpuscles are contracted into irregular clumps but can be distinguished. Either around the necrotic area or just within it there are large numbers of leucocytes closely packed in the tissue and forming a definite wall. The surrounding blood-vessels are congested, show a mural arrangement of leucocytes, and emigration takes place rapidly. In most cases the leucocytes are exclusively polynuclear. We are rarely able to trace the beginning of abscess formation in man, as we can experimentally in animals, for the abscesses are usually met with in a later stage of formation. In man we very frequently find, particularly in the liver, but also in the kidneys and spleen, masses of staphylococci in the vessels without necrosis or any evidence of reaction around them. I have also occasionally found in the kidneys and in the heart small abscesses similar in all respects to those produced experimentally in the rabbit.

The next step in the formation of the abscess is the softening of the necrotic tissue and its invasion by leucocytes. In an early stage there is no invasion. The wall of leucocytes is perfectly definite and they may form a complete circle with the bacteria in the centre. There is produced by the bacteria something which repels the leucocytes in the beginning while the necrotic tissue attracts them. It is probable that the bacteria in the centre may produce a toxin which paralyzes the amœboid activity of the leucocytes. Some are certainly destroyed, but in most of them no evidence of degeneration is seen. I have never been able to follow microscopically the various steps in the softening, but it seems to be a complete liquefaction of the tissue. In the cavity thus formed the leucocytes and bacteria become free and the latter are then taken up by the leucocytes in numbers. To no one who is acquainted with the degenerative process in leucocytes can there be any question that the process is a true phagocytosis. Perfectly unchanged leucocytes will be found with great numbers of bacteria within them. The polynuclear leucocyte is essentially phagocytic for the pus organisms and pneumococci, but I have never found these enclosed within either the large mononuclear leucocytes or the eosinophiles. It is not possible to be certain with regard to other bacteria. Large numbers of leucocytes are destroyed in the pus, and even those in the surrounding tissues may be destroyed. They seem to undergo the same sort of destruction as those in the mesentery, but the process cannot be so easily followed. The destruction is recognized chiefly by the fragments of chromatin. Certain organisms seem to exercise an especially destructive action on the leucocytes. In glanders, masses of fragmented polynuclear leucocytes may be found in tissue which shows but little degeneration. In the contents of the muscle abscess formed in human glanders not a single normal leucocyte may be found. These abscesses are also characterized by the complete absence of the regenerative processes in the surrounding tissue; of this I shall speak later.

The process of abscess formation after the injection of croton oil is very similar in most respects to that produced by staphylococci. The tissue which is immediately acted on by the oil is destroyed. If the injection has been made into the muscle and the latter is examined after forty-eight hours, a sharply circumscribed area is found in which the tissue closely resembles the necrotic area around bacteria. The muscle fibres are swollen and hyaline, the nuclei do not stain, and neither vessels nor cells can be recognized. Immediately around this area of complete necrosis is the enveloping wall of leucocytes. In the midst of the leucocytes and on the side toward the normal tissue there may be numerous single necrotic fibres, which become filled with leucocytes, but there is not complete necrosis of all the elements of the tissue. It seems that here also the leucocytes are attracted to the necrotic tissue, but there is something in the central mass which repels them. The softening of the tissue takes place first in the area of intense leucocytic infiltration around the necrosis, and the necrotic mass may remain in the cavity as a sequestrum, or it may become softened and disintegrated. I have found the central necrotic mass produced by a turpentine injection remain in the tissue as a foreign body and undergo slow absorption by granulation tissue. A definite abscess cavity is not always formed in purulent inflammation. Certain tissues, especially loose connective tissue, undergo softening more easily than the denser tissue, and the softening may extend along these connective-tissue septa leaving the denser tissues. In this way the muscles may be dissected out. This result is favored by the course of the lymphatics by means of which the infectious agents may extend. In a racemose gland the suppuration may extend along the ducts and connective-tissue septa dissecting up the gland tissue proper. In some cases there may be a general purulent infiltration of the part with but little tendency to softening. In such cases small foci of leucocytes are found in the tissue. There is a great difference in tissues relative to the ease with which softening takes place. Elastic tissue is very resistant and may be found unchanged, cartilage is not softened. In a case which I recall of extensive abscess formation in an amyloid liver, the amyloid material was dissected out by the softening process and lay unchanged in the abscess contents. The absence of fibrin is generally considered one of the most characteristic features of purulent inflammation, distinguishing it from other forms of inflammation. Yet there may be considerable fibrin present in some situations, especially in suppuration occurring on serous surfaces.

The pain in inflammation is due to the pressure exerted on the nerves in and around the swollen tissue. The severity and the character of the pain are influenced by a great many conditions. Parts which are not ordinarily sensitive, such as the peritoneum, may become intensely so in inflammation. As a rule the denser the tissue, the less able it is to be distended by the exudation, the greater will be the pressure exerted on the nerves within it and consequently the greater the pain. It is for this reason that inflammation of the periosteum is usually intensely painful. In an acute inflammation the pain is often throbbing, there being exacerbations which correspond with the systole of the heart. This is due to a sudden increase of tension produced in the part by the blood driven into it by each heart beat.

So far we have spoken only of the exudation, the cells and fluids which are derived from the blood. But the tissues also participate in the process and the changes which take place in them are not secondary in importance to the circulatory disturbances. All the phenomena of inflammation are due to an injury of the tissue which is produced by the action of the causative agent. It cannot be due to injury exerted on the vessels alone, for these cannot be injured without injury to the tissue at the same time. The attempt has been made to regard all the phenomena as the result of vascular disturbance and to explain them partly on a physical basis. It is not always possible to estimate the degree of influence exerted on a tissue by an injurious agent. We can detect those injuries which lead to complete destruction and