NECROSES OF THE LIVER.

F. B. MALLORY.

This paper is based in part on the routine histological examination of the livers in 1,190 consecutive autopsies at the Boston City Hospital, in part on the study of lesions produced experimentally in the livers of guinea-pigs and rabbits. The work was suggested by the study of the lesions which occur in the liver in typhoid fever.[1] So much of it as refers to diphtheria in human beings has already appeared.[2]

In the livers from autopsies two types of necroses were found; the one diffuse in that it affected every lobule in the liver; the other focal, occurring irregularly both in the liver and in the lobule. To the diffuse form of necrosis the term *central necrosis* will be applied because the lesion occurs in the centres of the lobules and spreads peripherally. Reference has already been made to its characteristic location.[1] The second form of necrosis has received the name of *focal necrosis*.[3]

In all cases the tissues were fixed in Zenker's fluid, but for certain purposes other fixatives were also used. Eosin followed by Unna's alkaline methylene blue solution gave the best differential stain; no other method brings out the necrotic cells in such sharp contrast to the normal tissue. Alum hematoxylin either alone or followed by eosin gave less differentiation, but was generally more useful for photographic purposes. Another exceedingly useful stain, second only to eosin and methylene blue, was the aniline blue connective-tissue stain[4], because it brought out with great sharpness the reticulum lining the liver capillaries, and therefore clearly defined their walls. The stain was also very useful from a photographic standpoint.

CENTRAL NECROSES.

Lesions of this type were found in ninety-five cases. They occurred in a wide variety of diseases, but chiefly in

acute infectious processes; for example, in diphtheria, fourteen times; in acute endocarditis, twelve times; in lobar pneumonia, eight times; in acute peritonitis, six times; in epidemic cerebro-spinal meningitis, twice; and in a variety of other acute and chronic processes, once or twice each. Forty-five of the cases (47 per cent.) were complicated with cardiac lesions such as chronic endocarditis, chronic myocarditis, or mural thrombi.

Age was of no significance; the cases varied from two to ninety years.

The bacteriological examinations are not complete, but are extremely instructive so far as they go. In twelve cases cultures were not made; in seventeen cases they were negative. In the remaining sixty-six cases the streptococcus pyogenes alone was present in one or more organs (often as a septicemia) nineteen times; the diplococcus lanceolatus, four times; the staphylococcus pyogenes aureus, five times; the bacillus diphtheriæ, twice; the diplococcus intracellularis meningitidis, twice; the bacillus mucosus capsulatus, once.

Alone or combined with other pathogenic bacteria the streptococcus pyogenes was present forty times; the diplococcus lanceolatus, fifteen times; the bacillus diphtheriæ, twelve times; the staphylococcus pyogenes aureus ten times.

With the exception of a few of the last cases studied the central necroses were not recognized macroscopically. The size and weight of the liver are not characteristic; they vary within rather wide limits. The markings of the lobules are usually very distinct owing to congestion of the central and middle portions of the lobules. The picture presented is often that of a nutmeg liver, but the centres of the lobules are not depressed, the surface is rather dry, and on pressure blood usually does not flow from the capillaries in the congested centres. Sometimes the centres of the congested areas present a yellowish color; this is rendered more prominent by washing the surface; then the yellow centres stand out more sharply and are surrounded by a reddish zone. But a case of chronic passive congestion of the middle zone of the lobule with fine fat drops in the liver cells (but with

no evidence of necrosis) in the centre of the lobule gave the same picture.

The histological changes found in the different livers vary greatly. In the most marked cases the necroses surrounding the central vein of every lobule extend to within three or four cells of the portal vessel (Plate XV., Figs. 1 and 2); but in only one case, the most marked of all, were any liver cells immediately adjoining the portal vessels ever found to be necrotic. In other cases the necroses do not reach more than a third or a half of the way to the peripheries of the lobules. In the less well-marked cases the necroses are sometimes arranged fairly regularly around each central vein, but in other cases small areas of necrosis adjoin the central vein at one or more points, or are in its immediate neighborhood; that is, they are present in the central portion of the lobule, never adjoining the portal vessels.

When chronic passive congestion of the liver exists the necroses adjoin the congested areas, forming a ring of necrotic cells or appearing as small necrotic areas, in the middle zone.

In the earliest cases of central necrosis the protoplasm of the liver cells in the centres of the lobules for a varying distance up to about two-thirds of the way towards the peripheries shows a tendency to stain more or less deeply with eosin. It usually becomes homogeneous, but sometimes is finely granular. Rarely the protoplasm breaks up into small hyaline globules which stain intensely with eosin. At the same time that the protoplasm becomes distinctly acidophilic the chromatin granules of the nuclei enlarge and the nuclei stain deeply; later the nuclei stain homogeneously and intensely and then gradually fade away. Fragmentation of the nucleus sometimes occurs, but is not common.

In a majority of the early cases the protoplasm of the liver cells contains numerous small and large vacuoles in which are single small hyaline globules; single, sometimes multiple, coarse, and fine threads (Plate XVI., Fig. 1; Plate XVII., Fig. 1); and occasional networks, all of which stain deeply with eosin and with Weigert's fibrin stain. With other stains also they react exactly as fibrin does. The hyaline

globules are not threads cut across; whether they really are fibrin is difficult to prove. They often seem to precede the formation of the threads and networks of fibrin.

In a certain number of cases the cells apparently undergo direct necrosis without any evidence of an inflammatory exudation collecting within them, while in still other cases the necrosis seems to be preceded by fatty degeneration.

The necrotic cells are often invaded by polynuclear leucocytes, less often by endothelial cells. The polynuclear leucocytes penetrate the liver cells, frequently in large numbers, and disintegrate them; the endothelial cells more often form a layer around the necrotic cells, dissolving them from the outside, but sometimes invade them.

In the older lesions the nuclei of the liver cells have disappeared entirely and the cells appear as hyaline masses, often invaded by polynuclear leucocytes and endothelial cells, or are more or less completely disintegrated. In some cases all trace of the liver cells has disappeared and their place is occupied by polynuclear leucocytes and endothelial cells.

At the same time that the liver cells are undergoing necrosis a serous exudation appears between the liver cells and the walls of the capillaries (Plate XVII., Fig. 1), separating them more or less widely. At the same time the liver cells may be separated from each other. The exudation often contains polynuclear leucocytes (Plate XV., Fig. 4) and endothelial cells; rarely fibrin is present. In a considerable number of cases the exudation consists in part or largely of blood. This hæmorrhagic type of lesion (Plate XV., Fig. 3; Plate XVII., Fig. 2) was very well marked in thirteen cases. At first sight the centres of the lobules seemed markedly congested, but careful study and especially the use of the aniline blue connective-tissue stain showed perfectly definitely that the blood lay almost entirely between the liver cells and the capillary walls.

In most of the cases of central necrosis the capillaries between the necrotic cells are narrowed, at least in places, to partial or complete occlusion by the extra-capillary exudation and by the swelling of the cells. In a few cases the

vessels are more or less congested, at least in places. Fibrin is almost always found in the capillaries (Plate XVI., Fig. 1; Plate XVII., Fig. 2) in the necrotic areas. Rarely it is in the form of a slight or abundant network of fibres which extend in all directions throughout the capillaries in the centres of the lobules. Much more frequently the fibrin occurs as irregular hyaline masses here and there in the vessels, completely occluding the lumina. So far as can be made out from a study of the earliest cases, the fibrin forms in the capillaries opposite those cells which first undergo complete necrosis, and then by obstructing the circulation, aid, along with the exudation within the cells, and between the cells and the capillary walls, in hastening the necrosis either in small separate areas or uniformly throughout the whole centre of the lobule.

It seems probable that this type of necrosis is due to the action of strong toxines in the circulation, more often to that of the streptococcus pyogenes than of any other bacterium. To say why the centre of the lobule is affected more than the periphery is not easy. Possibly the cardiac lesions present in such a large number of the cases may have some bearing on the question, but on the other hand just as perfect cases of central necrosis occurred where there was no cardiac or other lesion to cause congestion of the liver. A second and more reasonable suggestion is that the liver cells in the centre of a lobule are not so well nourished as those in the periphery; even in the most marked cases of central necrosis the cells immediately adjoining the portal vessels show little or no marked degenerative change.

In proof of the toxic origin of this form of necrosis is the fact that the earlier stages of central necrosis were produced in two rabbits by the injection of enough diphtheria toxine to kill the animals on the third and seventh days respectively. The three-day case was the better. In both cases a well-marked fatty degeneration of the different organs and muscles was present. In the livers the protoplasm of the cells in the central third to two-thirds of every lobule stained more or less deeply with eosin. The nuclei stained deeply and homo-

geneously, or occasionally were fragmented. Many of the liver cells, either singly or in small groups, were completely necrotic and in part invaded by polynuclear leucocytes, in part surrounded by endothelial cells. Many of the cells in places contained threads or small networks of fibrin within vacuoles in the protoplasm. Some of the liver cells had entirely disappeared and their places were occupied by endothelial cells. Occasionally there was a serous, rarely a hemorrhagic, exudation between the necrotic cells and the capillary walls. In a few places fibrin was found in the capillaries opposite the necrotic cells.

It seems probable that some of the cases of central necrosis recover. In many of the lesions the necrotic liver cells were disappearing; the spaces formerly occupied by them were filled with exudation. In the hemorrhagic form of lesion this condition was confusing, because at first sight it seemed as if the capillaries were much dilated, when in fact they were almost completely closed. The process of repair could not be followed, but in this same series of autopsies eight cases of well-marked increase of the connective tissue in the centres of the lobules were found. The liver cells in the centres were partially or completely absent; the connective tissue around the central vein was much thickened, and coarse fibres radiated out a third or a half of the way to the periphery of the lobule. In two cases congestion of the liver was absent, in two it was moderate, while in the other four chronic passive congestion was well marked. In one of these cases there was well-marked necrosis in the middle zone just outside of the area of central congestion and cirrhosis.

It is possible that the marked increase of connective tissue present in the liver in some cases of chronic passive congestion really is due, in part at least, to a previous central necrosis following an acute endocarditis or other acute infectious process.

The necroses of the liver described by Smith and Kilbourne in their study of Texas fever [5] probably belong to this same type of lesion, but no other reference to it in literature has been found.

Central necroses may occasionally be combined with focal necroses: for example, in four cases of typhoid fever slight central necroses were present in addition to the characteristic focal lesions of the disease.

FOCAL NECROSES.

Aside from tuberculosis, focal lesions and necroses were found in this series of livers fifty-one times. Twenty-eight occurred in typhoid fever. Of the remaining twenty-three five were in connection with acute peritonitis, three with diphtheria, two with lobar pneumonia, and the others with a variety of acute infectious processes. In fourteen cases the streptococcus pyogenes alone was present, almost always as a septicemia; in one case the streptococcus pyogenes was associated with the diplococcus lanceolatus; in one the diplococcus lanceolatus occurred alone; and in one the staphylococcus pyogenes aureus. Of these twenty-three cases three were remarkable and deserve especial mention; in the remaining twenty the lesions were few in number and were recognized microscopically only.

So far as can be made out, focal necroses of the liver can arise in at least three different ways: (A) around bacteria, that is, in direct relation with them; (B) by occlusion of the capillaries by large phagocytic endothelial cells; and (C) by occlusion of capillaries by fibrin thrombi. It is not possible to classify definitely all of the above-mentioned twenty-three cases, owing to the fact that many of the lesions were so advanced that the manner of their origin could not be traced; but the positive cause of some and the probable origin of others can be given.

A. *Necroses around Bacteria.* — Ordinarily the tubercle bacillus produces proliferation of endothelial and connective-tissue cells, resulting in the formation of miliary tubercles composed of epithelioid and giant cells. Occasionally, however, the lesions are chiefly degenerative and exudative and show little else than necrotic cells and fibrin. This exudative form of lesion closely resembles the focal necroses of the liver produced in other ways, and in some instances can be dis-

tinguished from them only by a knowledge of the lesions elsewhere in the body or by staining for the tubercle bacillus.

Less commonly necroses may be formed around other micro-organisms. In this series of cases necroses were found in direct connection with bacteria eight times. In four of these cases the streptococcus pyogenes was obtained in pure culture from the liver and other organs, and could be demonstrated microscopically in direct relation with the lesions. In a fifth case the staphylococcus pyogenes aureus was present in pure culture in abscesses of the liver and could be demonstrated microscopically in areas of necrosis not yet invaded and softened down by polynuclear leucocytes. In the three other cases the cultures were not pure; in two of them the bacteria present in the lesions seemed microscopically to be the streptococcus pyogenes.

One of the streptococcus cases (B. C. H., '01.46, female, 46 yrs.) was quite unusual. The chief lesions at autopsy were acute salpingitis, pelvic abscess, acute peritonitis, and necroses of the liver. The streptococcus pyogenes was present in abundance in the various exudations on cover-slip examination and was obtained in pure culture from the heart's blood and the different organs. The liver weighed 2,320 grams; surface smooth, of a yellowish color finely mottled with red. On section, centres of lobules bright yellow surrounded by a reddish zone. Consistence somewhat diminished. Histologically the lesions were distributed with great regularity, forming often a perfectly definite zone in the outer third of the lobule, but not reaching to the periphery by a layer of from two to three cells. In some of the lobules, however, the lesions were irregularly distributed and reached to or surrounded the central vein. The necrotic cells were finely vacuolated, the protoplasm granular and deeply stained with eosin; the nuclei had disappeared. The cells were invaded and surrounded by polynuclear leucocytes and endothelial cells; a few of the latter were phagocytic. Considerable fibrin had formed around and between the cells. The capillaries in the congested areas were for the most part dilated and filled with blood. Very rarely fibrin thrombi were

found in the vessels. Mitosis of liver cells in or adjoining the necrotic areas was frequently observed. Masses of streptococci were found throughout the liver, chiefly in the necrotic areas, but also to some extent in the more normal tissue; they were largely within the capillaries, but occasionally extravascular. The tissue around the portal vessels contained numerous leucocytes, and a few were also found within the bile ducts. It seems probable that the lesions were due to the immediate action of the micro-organisms present and not to a toxine brought by the circulation; but it is possible that the lesions should be classed in Group C. The curiously regular arrangement of the lesions in the lobules is difficult to account for.

B. *Necroses due to Occlusion of Capillaries by Cells.* — The best examples of this type of lesion are furnished by typhoid fever. The twenty-six cases in this series all showed the characteristic lesions; as these have been fully described elsewhere (1) it is not necessary to consider them here. In a case of malaria a few small areas of necrosis of liver cells were found, due as far as could be made out to occlusion of the capillaries by large pigmented endothelial cells. In no other case was it possible to demonstrate that the focal lesions were caused by occlusion of capillaries by cells, although, as will be seen later, experimental lesions show that such an origin is easily possible in guinea pigs.

C. *Necroses due to Occlusion of Capillaries by Fibrin Thrombi.* — Fibrin thrombi form in the capillaries under at least two conditions, namely, adjoining necrotic liver cells, and around endothelial or other cells which have undergone necrosis within the capillaries. In the livers of five cases, two of lobar pneumonia and three of streptococcus septicemia, numerous single necrotic liver cells were found scattered throughout the organ, often to the number of a dozen or more in a section through a single lobule. The lesion closely resembles that described by Councilman as occurring in the early stages of yellow fever;[6] whether the further development is the same, it is impossible to say. Occasionally two to four cells in close proximity were necrotic. Some of

them were invaded by from one to six polynuclear leucocytes or by endothelial cells. In the capillaries adjoining these cells, hyaline masses of fibrin had often formed, sometimes completely occluding the lumen. In this way small focal lesions had arisen, and the liver cells adjoining them were beginning to show the early changes of necrosis, such as an eosin stain of the protoplasm and vacuoles containing fibrin threads.

One case (B. C. H., '98.46; male, 3 years; diphtheria, streptococcus septicemia) evidently represented a later stage of this same process. Focal necroses were present in great numbers; they were usually of the size of miliary tubercles or less. No bacteria could be demonstrated in connection with them. The lesions consisted of small areas of necrotic cells invaded by polynuclear leucocytes; in a few areas there was marked invasion with endothelial cells, some of which were phagocytic. Many of the nuclei were fragmented. The liver cells surrounding these areas often contained two to ten nuclei, and a few nuclei were seen in the process of direct division. The capillaries were often filled with blood, but in places were narrowed, and many were completely occluded by hyaline masses of fibrin.

Another case (B. C. H. '97.144; child, 5 years; scarlet fever, diphtheria, streptococcus septicemia), which probably also owes its origin to occlusion of the vessels by fibrin thrombi, has already been reported.[7] The liver contained great numbers of focal lesions (Plate XVI., Fig. 2) the size of miliary tubercles, and a little larger. They were usually rounded, and very sharply limited. Many of the lesions adjoined or even surrounded the portal vessels. The areas stained very deeply with eosin. They consisted of hyaline necrotic liver cells invaded and surrounded by polynuclear and endothelial cells. The aniline blue connective-tissue stain showed that the capillaries were much narrowed; in many places they were completely occluded by hyaline thrombi; the polynuclear leucocytes and endothelial cells were almost entirely extravascular.

It seems probable that the other cases of focal necrosis

owe their origin also to occlusion of capillaries by thrombi. It is impossible, however, to demonstrate that fact. They may have been due, in part at least, to occlusion of the capillaries by phagocytic cells or to the immediate presence of bacteria which later died out.

A large number of experiments were made on guinea-pigs, partly to see if any light could be thrown on the origin of focal necroses in the human liver, partly to substitute if possible some definite explanation in place of the theories advanced by Flexner to explain the origin of focal necroses in the livers of guinea-pigs in particular, and of necroses in the liver and other organs of man in general. Our work on diphtheria[2] in man had shown that the so-called focal necroses of the spleen and lymph nodes were due primarily to the endothelial cells lining the reticulum of the lymphoid tissue proliferating and becoming phagocytic, ingesting and destroying the surrounding lymphoid cells. Experimentally I have been able to reproduce exactly the same lesions in guinea-pigs by the injection of the diphtheria bacillus or of its toxin. It therefore seemed reasonable to expect that some definite cause existed for the focal lesions in the liver.

Into a mesenteric vein of one animal was injected 1 cc. of a sterilized suspension of carmine in water; in a second case lycopodium (Plate XVI., Fig. 3); in a third case pulverized animal charcoal (Plate XVI., Fig. 4) were used. When examined at the end of twenty-four hours the livers were found studded with great numbers of necroses; with the charcoal they were all small; with the carmine and lycopodium they had often coalesced into large areas. The histological pictures were practically identical. The areas varied from a few cells to many. As a rule the lycopodium was confined to the intralobular vessels, as the spores were too large to enter the capillaries of the lobules. Necroses seemed to occur only when fibrin formed around the lycopodium. The carmine and charcoal penetrated all parts of the lobule, and were sometimes taken up by the lining endothelium. They too seemed to cause necrosis only when fibrin formed around them. The necroses were all of an early stage. The cell

protoplasm stained intensely with eosin; the nuclei were homogeneous and stained deep blue. Some of the cells were invaded by polynuclear leucocytes. Many of the necroses adjoined the portal vessels, but others reached to or even surrounded the central vein. The large necroses seemed to be due entirely to confluence of small areas.

The diphtheria bacillus was inoculated subcutaneously into guinea-pigs six times; in five of the cases necroses were found in the liver. Diphtheria toxin was injected subcutaneously seven times, and necroses obtained in six. In both groups of cases the necroses varied from a few to many; they were usually small, 1 to 2 mm. in diameter, but occasionally embraced a number of lobules. In one case 1 cc. of diphtheria antitoxin was injected; when the animal was killed after three days, numerous necroses were found in the liver and some of them were quite large. In an experiment with abrin numerous necroses were obtained, while a single experiment with ricin was negative. In the above experiments the animals died or were killed all the way from twenty-four hours to thirty-seven days after inoculation.

Histologically lesions of every stage of development were found. The earliest lesions were due almost entirely to obstruction of the capillaries by large phagocytic and usually pigmented cells (Plate XVII., Fig. 3). Similar cells were often present in considerable numbers in the capillaries throughout the liver; occasionally they were found projecting into or within the central vein, so that there is no question but that some of them pass through the liver and get into the general circulation. The blood taken fresh from the portal vein of a guinea-pig killed two days after subcutaneous injection with diphtheria toxin contained a few phagocytic cells filled with red blood corpuscles and pigment. Another experiment with a guinea-pig killed eight days after subcutaneous inoculation with the diphtheria bacillus showed many similar cells in the portal vein. In all cases fresh examination of the spleen showed the presence of many phagocytic cells containing red blood corpuscles and pigment.

Some of the necroses were due to occlusion by fibrin of

one or more capillaries running in from the portal veins at the periphery of the lobules. So far as could be made out, the fibrin always formed around phagocytic cells which had undergone necrosis. Sometimes fibrin threads were seen inside of vacuoles within these necrotic cells; in other instances the necrotic cells were invaded by polynuclear leucocytes. Around or on one or more sides of the masses of fibrin formed in this way the liver cells were beginning to show the early signs of necrosis.

The way in which focal necroses are formed can be made out only in the very earliest lesions; as soon as the necrosis is at all advanced the phagocytic cells and fibrin change to hyaline masses and are lost among the necrotic liver cells.

As the lesions grow older they are surrounded by endothelial and connective-tissue cells and the necrotic material is gradually removed.

As the adult guinea-pigs under what are ordinarily considered normal conditions contain in the blood sinuses of their spleens phagocytic cells in which are red blood corpuscles and pigment, it occurred to me that it might be possible to set free these cells mechanically from the spleen and in this way cause necroses in the liver. The experiments succeeded beyond all expectation. In eight cases the spleen was gently massaged for three to five minutes by pressing in the lax abdominal wall over it. In a ninth case the lower half of the abdomen, and in a tenth case the liver on the right side, were massaged in the same way. In all ten cases necroses were found in the liver. In eight cases they were small, rarely over 2 mm. in greatest diameter, but in the other cases there were besides the small necroses two or three larger areas, one extending vertically through a lobe. Some of the necroses were very distinct, others but faintly visible, especially in animals killed two to four hours after the experiment.

Although in gross these lesions resembled those already studied, the chance of direct mechanical injury to the liver was considered, and the possibility of obviating it tried. A Faradic current was passed interruptedly for five minutes

transversely through the body of a guinea-pig, taking in the spleen and liver, with the hope of causing the smooth muscle fibres of the capsule and trabeculæ of the spleen to contract. Eight necroses were found in the liver; the repetition of the experiment in another gave twenty-four necroses; in a third animal where the current was passed vertically through the spleen so as to avoid as much as possible the liver, thirteen necroses were found. In two guinea-pigs through which a strong direct current was passed several times in the course of one or two minutes, four and six necroses respectively were present. These fifteen consecutive experiments, ten with massage and five with electricity, seemed to show conclusively that necroses of the liver could be produced in guinea-pigs at will. There were, however, certain disturbing features. The animals were killed from two to twenty-four hours after the experiments. Many of the necroses were as well marked at the end of two hours as at the end of twenty-four. In some of the lesions repair had already begun. Finally two animals were killed which had had massage of the spleen twice and the Faradic current passed through each once; both livers were absolutely free from necroses.

All of the animals used in this entire series of experiments came from three different sources: (a) from the Harvard Medical School, (b) from Maine, (c) from the Convalescent Home of the Boston City Hospital; lots (b) and (c) were both bred and raised in the country under the best hygienic conditions. Sixteen normal animals from these three lots were killed, with the following results: seven livers were negative; two contained one necrosis each; one contained two; two contained three; one contained four; one contained five; one contained eleven; one contained over a hundred, the liver was speckled with them. The necroses varied from pin point to 2 or 3 mm. in diameter. Histologically they did not differ in any way from those found in the previous cases. In the liver which contained the most necroses the lesions were well on in the stage of repair; many of them showed little beyond the remains of necrotic liver cells surrounded by endothelial and connective-tissue cells.

Sex seemed to have no influence; on the other hand, age is perhaps of importance: the very young animals had no necroses and their spleens contained almost no phagocytic or pigmented cells.

It is difficult to draw any very positive conclusions from the experiments except the one that the guinea-pig is wholly unsuited for the scientific study of necroses of the liver, because normally it so often contains them.

On the other hand, there seems to be no question but that certain toxic substances, such as the diphtheria toxin, may give rise to necroses. The number of phagocytic cells in the blood sinuses of the spleen is increased in number and many of them are carried to the liver, where, as careful study of very early lesions shows, they give rise to necroses by blocking up the very narrow capillaries. However, if this line of reasoning is true for toxic substances, the same claim can be made for mechanical and electrical irritation of the spleen. For example, in the liver from one of the guinea-pigs massaged for five minutes and killed at the end of two and three-quarters hours, besides small and early but definite necroses, in certain areas numerous single liver cells and small groups of them were surrounded by phagocytic, usually pigmented, cells and were undergoing necrosis (Plate XVII., Fig. 4). It is possible of course that the animal was killed at a time when the necroses were forming under what might be considered normal conditions, and that they were not due to the mechanical setting free of the phagocytic endothelial cells in the spleen, but such a coincidence seems hardly probable.

One other conclusion seems perfectly justifiable, namely, that the focal necroses of the liver in the guinea-pig, whatever the exciting cause, are due to occlusion of the capillaries partly by phagocytic and pigmented endothelial cells brought to the liver from the spleen by the portal circulation, partly to fibrin thrombi which have formed around necrotic cells. The cells around which the fibrin forms are chiefly the phagocytic cells from the spleen, but it is possible that endothelial cells of the liver capillaries or liver cells themselves may occasionally prove the starting point. The focal necroses

must be regarded as miliary infarctions, due in one class of cases to cell emboli, in the other to capillary thrombosis. The large necroses are due to confluence of small areas.

A point that needs settling is whether really normal guinea-pigs contain phagocytic and pigmented cells in the spleen and in the mucous membrane of the intestinal tract. If they do, then the apparently normal necroses of the liver might be explained as due to rough handling or possibly even to too active exercise. It seems much more likely, however, that both the cells and the necroses to which they give rise are due to some infectious disease common among these animals.

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DESCRIPTION OF PLATES.

PLATE XV.

Fig. 1. The light areas are the necrotic liver cells in a case of marked central necrosis; the dark areas are the living liver cells around the interlobular vessels.

Fig. 2. Periphery of a lobule from the same case under high power.

Fig. 3. Hemorrhagic type of central necrosis; the light zone is the living liver tissue in the periphery of the lobule; the dark area shows the necrotic liver cells surrounded by red blood corpuscles which are almost entirely extravascular.

Fig. 4. Trabeculæ of liver cells from a case of central necrosis: an exudation of serum and polynuclear leucocytes lies between the necrotic liver cells and the capillary walls.

PLATE XVI.

Fig. 1. From an early case of central necrosis; shows fibrin threads within vacuoles in the protoplasm of liver cells, and also a fibrin thrombus in a capillary.

Fig. 2. Focal necroses from Case B. C. H., '97.144, described in the text; the single lesion adjoins the interlobular vessels.

Fig. 3. A small necrosis (infarction) in the liver of a guinea-pig due to the injection of lycopodium into a mesenteric vein.

Fig. 4. A small necrosis (infarction) in the liver of a guinea-pig due to the injection of pulverized animal charcoal into a mesenteric vein.

PLATE XVII.

FIG. 1. Serous exudation between necrotic liver cells and the adjoining capillary walls; threads of fibrin in vacuoles within the necrotic liver cells.

FIG. 2. Hemorrhagic type of lesion; space between the necrotic liver cells and the capillary walls filled with red blood corpuscles; fibrin thrombus in a capillary.

FIG. 3. Early necrosis due to the occlusion of capillaries by pigmented endothelial cells from the spleen: from a guinea-pig killed three days after the injection of diphtheria toxine.

FIG. 4. Early necrosis due to occlusion of capillaries by pigmented endothelial cells from the spleen: from a guinea-pig killed two and three-quarters hours after massage of the spleen.

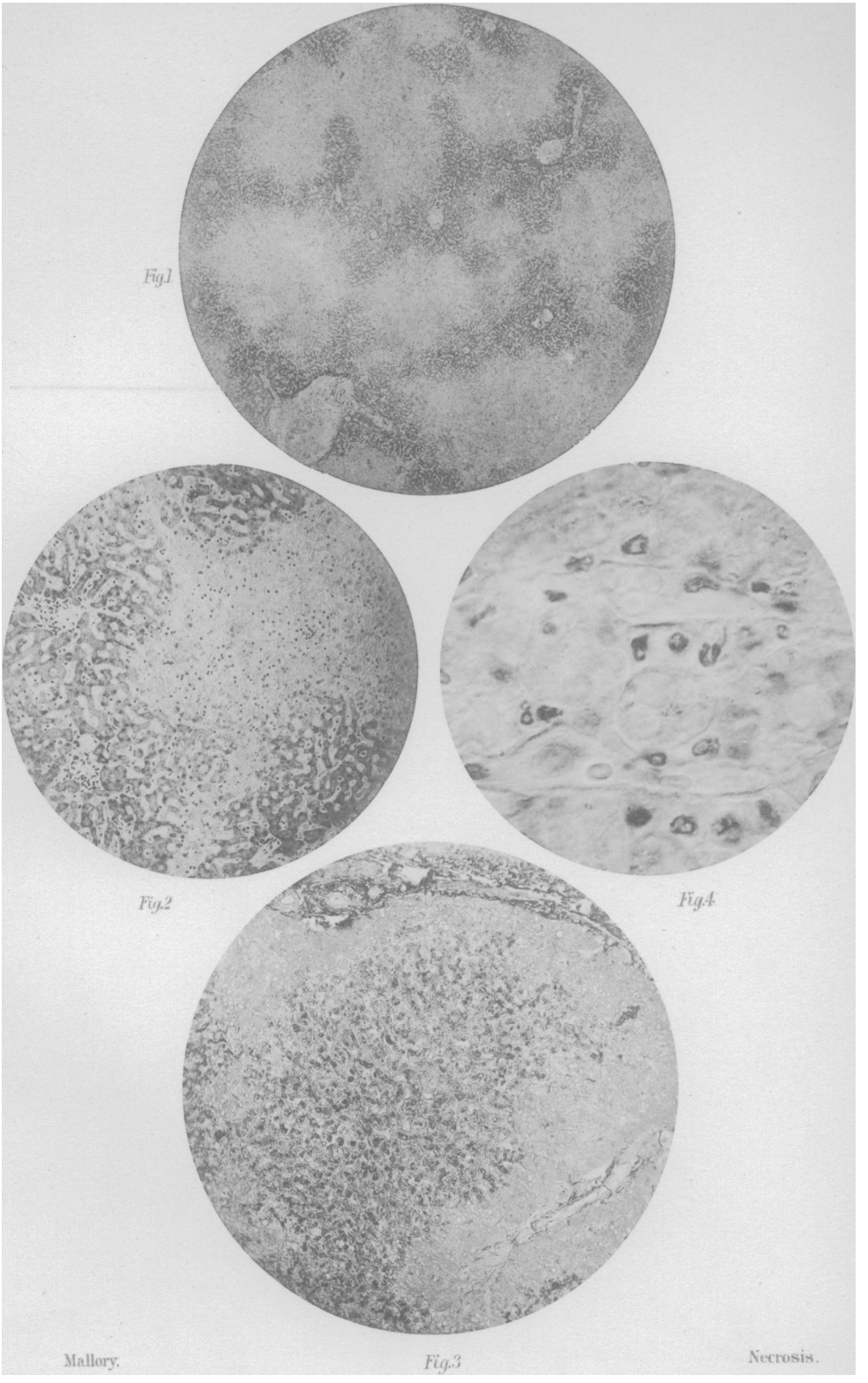


Fig.1

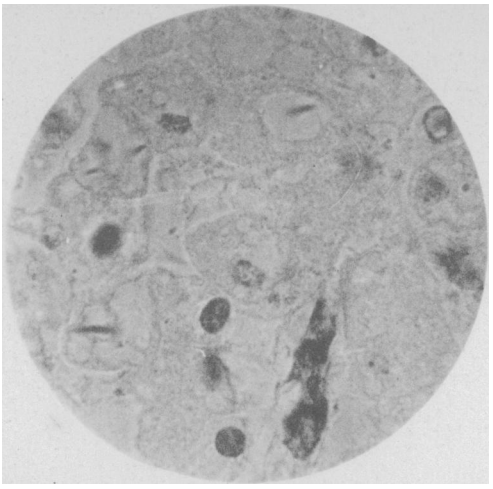
Fig.2

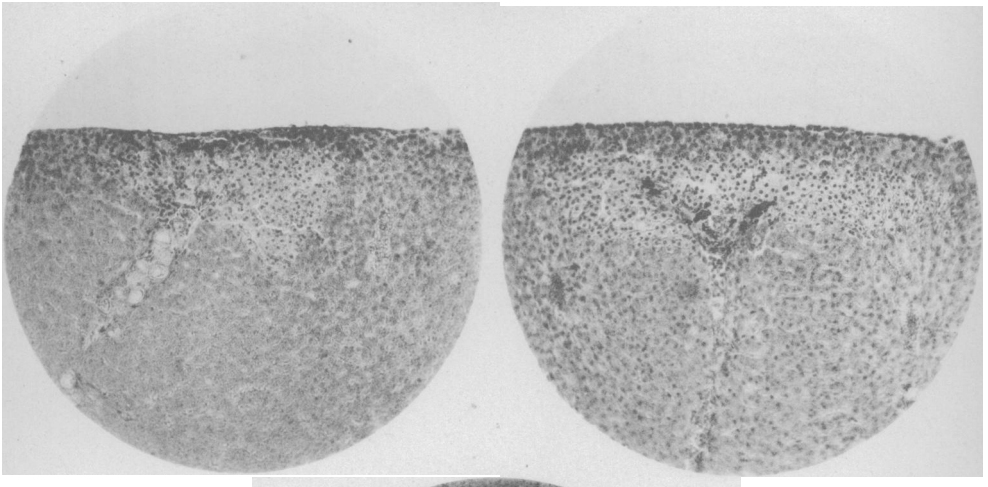
Fig.4

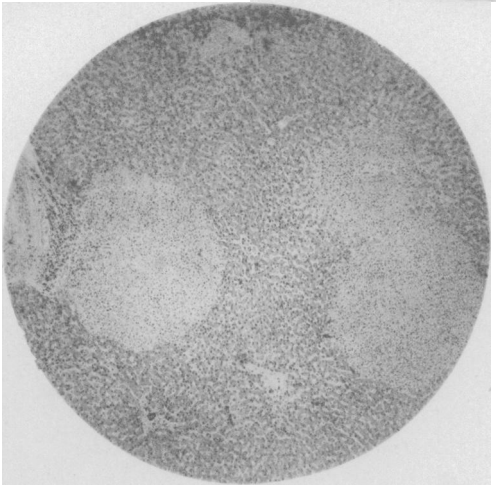
Fig.3

Mallory.

Necrosis.







Mallory. Necrosis.

Heliotype Printing Co.

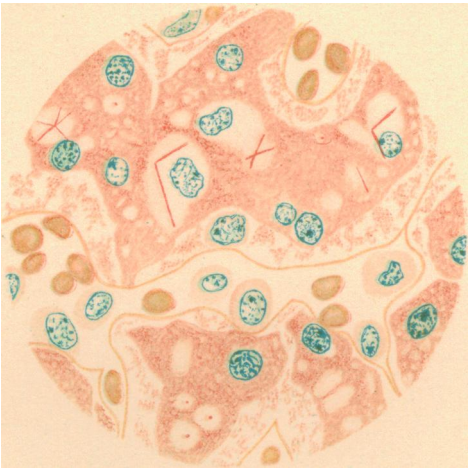


Fig. 1.

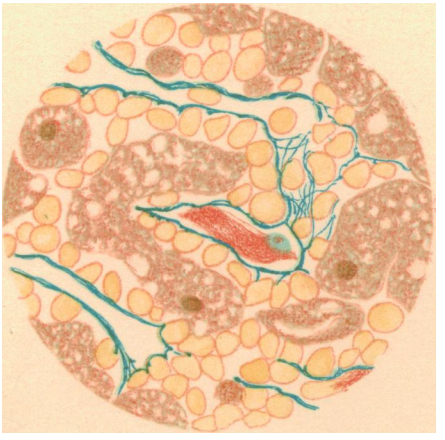


Fig. 2.

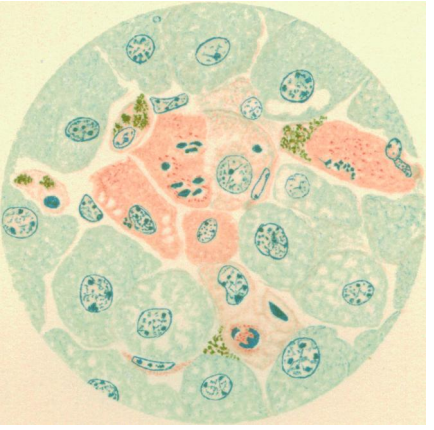


Fig 2.

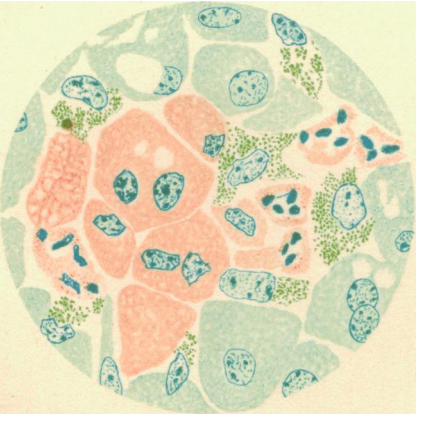


Fig 1.