

NECROSES OF THE LIVER.¹

By JOHN McCRAE, M.B.(Tor.), M.R.C.P.(Lond.), *Lecturer in Pathology, McGill University, and Associate in Medicine, Royal Victoria Hospital, Montreal*; and OSKAR KLOTZ, M.B. (Tor.), M.D. (McGill), *Lecturer in Pathology, McGill University, and Assistant Pathologist, Royal Victoria Hospital.*

From the Pathological Laboratory of the Royal Victoria Hospital, Montreal.

WE have examined with some care the material from 1350 autopsies at the Royal Victoria Hospital to determine the conditions of occurrence of necroses of the liver, especially those of the focal type. This involved the examination histologically of material from about ninety cases, from which we take those that have given us a positive result, and we make mention also of those classes of cases that gave a uniformly negative result.

The views as to the causation of focal necrosis of the liver are rather at variance: some hold that it is caused by a diffusible toxin; others that it is the result of vascular stoppage, in other words, infarction; others consider that a combination of these two factors is necessary.

Material is available from eight cases of eclampsia which occurred in advanced pregnancy, four being at full term and two at the seventh month; in four the seizure was of twenty-four hours' duration; one lasted fifty-five and one seventy-two hours; the ages varied between 17 and 40 years, and all had nephritis, as proved at autopsy. One case of 35 years of age, with nephritis, showed no necroses, but the other seven showed peripheral necroses, while two of them showed also middle zone and central necroses.

The macroscopic examination indicated the condition in one, and in three others hæmorrhagic spots were seen, but the focal necroses were not definitely recognised. The case above referred to was so striking as to merit description.

The liver was enlarged, weighed 1780 grms., was icteroid, and the upper two-thirds were dotted by small purple hæmorrhagic spots; it was soft, swollen, and on section the lower part showed yellow areas or islands of necroses, measuring from 0.4 to 1 cm. in diameter, of irregular shape, of an opaque

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appearance; these were very definitely demarcated from the surrounding brown liver tissue, in which the lobules could not be distinguished. Microscopically, these areas of necrosis showed tissue in which the general appearance of the lobules was retained, but in which no living liver cells were present. Here and there a narrow margin of living liver parenchyma bordered the portal vessels. In places the necrosis was complete, and the liver cells had melted together. Around some of the gross areas of necrosis, comprising numerous lobules, there was a very definite boundary of leucocytes, much more sharply defined on the inner than on the outer aspect, with hæmorrhage in the outer zone. On examination with a high power the necrosed areas were seen to contain a fair number of leucocytes, and at times the liver-cell nuclei could be seen, but generally they had quite lost their ability to take up a nuclear stain. The necrosed areas were not definitely central or peripheral. The liver cells, as a whole, were very fatty, but with Sudan III. the necrotic areas showed practically no fat.

Just at this point we might instance a case of quite a different kind, but of very similar appearance.

In a case of endocarditis and empyema there were noted, macroscopically in the liver, small grey areas, looking like tiny abscesses; on section these proved to be well-defined areas of necrosis, with the liver structure preserved, but with the cells dead. The artery lay in the centre of the necrotic area, and was thrombosed by a hyaline mass; a moderate infiltration was present, and the necrotic areas appeared to cover indiscriminately all parts of the lobules. A single area might include several lobules. This sounds and looks very like the eclamptic necroses we have just discussed, and it is a case of thrombosis of the hepatic artery.

The first cited case was the most extreme case of the series. The average microscopic appearance of the other cases was as follows:—

In the peripheral, more rarely the mid or central zone, are large necroses, which are yet considerably smaller than a lobule itself; at the outer edge the capillaries are dilated, and in these lie masses of fibrin, which is not, however, necessarily confined to the capillaries. These large masses of fibrin may be seen to encircle undestroyed liver cells; leucocytes are numerous, but not crowded. Actual disintegration of liver cells has occurred, and fibrin replaces them. Hæmorrhage occurs into and around the necroses, and is probably purely a secondary manifestation, as it can be found at one side of an area of necrosis, while the other side shows none.

In a general view of these seven cases the necroses were not circular, were frequently not so sharply demarcated as in typhoidal necroses; the inflammatory reaction was intense in two, and moderate or slight in four. In every one there was a deposit of fibrin-like material, matted together so as to form a kind of matrix. This does not give the fibrin reaction with Weigert's stain, so it may not be fibrin, but a mass of debris which has its origin in the dead tissue cells.

In all cases, too, however fatty the liver cells in the unaffected areas, the necroses were free from fat. Hæmorrhage into or around the necroses was noted in four cases, and had been noted macroscopically in two others. The distortion of the liver cells, which we have referred to as "jumbling," which is seen in acute yellow atrophy and lesser grades of hepatitis, was not seen in these cases.

We had been under the impression that severe cases of vomiting of pregnancy and other forms of hyperemesis would be likely to show focal necroses of a character similar to those found in eclampsia, and consequently examined the liver tissue of seven cases of hyperemesis, where this had been a prominent symptom—in fact, in several of the cases the chief symptom; of these cases, five had had long periods of severe vomiting, up to six and a half weeks. In two cases there was pregnancy, and there had been anaesthesia in four of them. In spite of all these factors no focal necroses were found. In two cases of protracted vomiting necroses were found, but one of these proved to be finally a case of eclampsia, and is included in that series; the other case was subjected to repeated anaesthesia, and will be discussed under another heading. If we remove these two cases we are yet left with five cases of long-continued vomiting, complicated by pregnancy and anaesthesia, without any necroses. Considering the effect of phosphorus upon the liver, we examined the livers of four cases of lead poisoning, two of arsenic, and one of carbolic acid, but found no necroses in any of them; in all the livers were intensely fatty.

In the eclamptic cases the point that seems to us the most striking is the similarity in structure to cases of undoubted infarct of the hepatic artery.

In conditions other than those already dealt with we found focal or other necroses in the liver thirty-five times; so often was it an accompaniment of typhoid fever that it is somewhat remarkable. In eighty-two autopsies upon cases dead of that disease we found the necroses twenty-two times, a percentage of slightly less than twenty-seven. Of the twenty-two, thirteen were cases of typhoid with no attendant conditions, six were cases of typhoid with peritonitis, of which two had operations, and supposedly anaesthetics; two were typhoid with pneumonia, one typhoid with meningitis. Of the cases other than typhoid, three were infective endocarditis, two were cases of pneumonia; two septicæmia with peritonitis and pregnancy, and in one case each the following conditions were found, pyæmia, pulmonary tuberculosis, meningitis and otitis, pyelitis with operation, syphilis with hepatic vein obliteration, and crush of the femur, with death in thirty-six hours. It will be seen that in all of these, save perhaps the obliteration of the hepatic vein, we are dealing with a known general bacterial infection of an acute kind, or with bacterial infections in sites other than the liver; in the apparent exception we cannot prove at this time whether infection was present or not. These twenty-two cases strongly point in the direction of an infective origin.

Before discussing the characters of the necrotic areas we would point out that this is essentially a microscopic change; the naked eye is not of much service in the matter of deciding whether or not focal necroses are present. In the above thirty-five cases they were

recognised ten times, and in at least seven cases the macroscopic diagnosis of necroses was not borne out by the microscopic examination. Thrice miliary tubercles were thought to be necroses. Of the thirty-five cases, twenty-seven were males, eight females, and the ages varied from 10 months to 70 years, the majority being young. These observations, however, are of no moment for our present purposes.

The histological characters we have observed appear to divide our cases into three groups, namely, a diffuse form; a form which appears to be connected with dilatation of the central vein, which we have referred to as "pressure"; and lastly, a typical focal form. We shall deal with these very briefly one by one.

1. *Diffuse form*.—These are in no sense focal, but seem to us best described by the term diffuse necrotic hepatitis, and the appearance of the affected tissue is well described by the word "jumbled"; the liver columns no longer preserve their symmetry and arrangement, but appear as if broken and fragmented, and the cells have lost their continuity; cells are ill-staining, often irregularly cuboidal or cubical in shape, and some nuclei are found fragmented, though many are unaltered. This picture suggests, in an indefinable way, the jumbling that one sees to perfection in acute yellow atrophy; three cases were found. We mention these because they seem to us to link the localised slight necroses to the diffuse necroses, although they are most closely related to the latter.

2. *Pressure form*.—We recognise that perhaps this form has no place here; with central dilatation, when it is extreme, the liver cells no longer are to be seen in the central part of the lobules,—it appears as if they had been pressed out of existence, which is probably the case; in fact, that they have undergone a necrobiosis as a result of pressure. When this occurs as a direct sequence of passive congestion of the liver from cardiac disease its universality in the liver renders easy its recognition; but when it occurs to a marked extent in one lobule, and lobules side by side with the affected ones are unaffected, obviously the cause cannot be wholly a cardiac congestion. There were three cases which fulfilled this condition, but we have no explanation to offer as to their causation; suffice it to say that they resemble the pressure necroses.

3. There yet remain twenty-nine cases of *undoubted focal necrosis of the liver*.—These are generally numerous; in twelve cases they are definitely noted to have been multiple (say half a dozen at least) in a single section. Their position in the lobule is very variable, and we have not found any exact correspondence between the site and special diseases. They are oftenest found in the mid zone, that is, neither central nor peripheral; next, oftenest in the periphery, but not as a part of the Glisson's capsule, for wherever we found collections of cells that were in the direct line of the interlobular tissue

we disregarded them. Less frequent than the peripheral ones were the central ones, that reach the edge of the central vein, or are close to it. In two cases the necroses were found in any and every part of the lobule.

As to the size, the largest occupy an area that is thought to be a quarter, or perhaps a third, of a lobule, and these, which we called "large," were present in eight cases, but the remainder, a far greater number, showed only minute areas. In fifteen cases these were definitely circular, but in four they were specially noted as being irregular. They are always clear cut, and stand out against the well-stained liver lobules as lighter areas with clear-cut edges. The liver cells that border them show no histological change, unless we admit the observation of a slightly deeper staining in one or two cases with Sudan III, indicating a little more fat than have the cells that lie more remote. These clean-cut areas consist of an unstained material, which appears to represent the débris of cells, for no liver cells are distinguishable; at times cell bodies can be observed which contain pigment, and these we considered were the wrecks of liver cells; a greater or less number of leucocytes, a few larger nuclei, which appear like liver-cell nuclei, and others which were definitely endothelial cells, complete the picture, save for the more or less changed blood cells that in some cases could yet be distinguished as filling up what were once capillary spaces. Fragmented nuclei of all three sorts (as we suppose) were often seen; there is no surrounding ring of leucocytes, and in none of this series was any reaction observed close by in the liver capillaries. The degree of infiltration by leucocytes varied greatly. In eight there was no inflammatory reaction—that is, the number of nuclei observed appeared to correspond to the number of cells (or less) naturally present in an area of that size; in one there was slight, in twenty moderate, and in seven great inflammatory reaction. In the latter it will be readily understood that we were often in doubt as to whether we were dealing with a necrotic area, so called, or an abscess. Undoubtedly this whole question of inflammatory infiltration must be a question of repair, because eight of the cases did not show it; these eight might be of very recent formation, and to this we shall refer elsewhere. All the sections examined were stained by Sudan III. for fat, and in every case the fat was absent from the necrotic areas, or if a faint tint of reaction was to be seen it was always greatly less than in the rest of the liver. Once isolated cells, evidently leucocytes, carried a considerable number of fatty particles; save for this the findings were absolutely uniform.

It has been said that wherever mitoses exist they represent the efforts of the liver tissue to repair a very small lesion, but wherever mitoses, or at least very large nuclei or double nuclei, were seen we were nowhere able to correlate them with the necrotic areas, or to be

sure that they represented a stage of repair performed by liver cells alone. We never saw them in the immediate vicinity of the necroses. Lastly, in four of these cases we happened upon definite thrombosis of vessels either in or connected with focal necroses; it is difficult to say whether these are cause or effect, but in one case at least a fairly large capillary ran longitudinally, and a necrosis was perched upon it in direct continuity with its walls.

One case of necrosis in pneumonia is not included in the foregoing list, because of the peculiar nature of the change that the tissue had undergone. There were large, irregularly distributed necroses in which the cells seemed to have undergone a kind of vacuolar change; the fact that these areas were strongly reactive to Sudan III. made a distinction from the ordinary necroses. The liver cells seemed to be entirely destroyed in these areas, nevertheless. Lobules greatly affected lay side by side with lobules that showed no change; the nuclei were unchanged. We suggest that this case is one in which the circulatory disturbance occurred, but in which the diffusible toxin was not of great strength.

The salient features of these focal necroses seem to be a rapid destruction of the liver cells, which differs from inflammation in that the death of the cells is rapid, as in no case does any fat appear, which is an almost constant feature of the gradual toxic alteration of protoplasm.¹ The cells are rapidly killed, and apparently with them some of the stroma; it is true that in a short time the stroma appears to proliferate in repair, so that large endothelial cells appear. The presence of leucocytes is also presumably a reparative process, as seven of the cases noted showed few or no leucocytes, and equally the absence of proliferated endothelium. What endothelial cells are seen may be the result of remnants of stroma that still remains, or, on the other hand, we perhaps are mistaken in supposing that the stroma cells are actually destroyed. In none but the larger areas does a peripheral reaction appear, which may be due, on the one hand, to the comparative smallness of the area involved, or, on the other, to the non-infection of the area involved, or to both factors.

Under what circumstances can these necroses be formed? Is it to be supposed that these areas have a special affinity for the toxin, and are affected more than the rest?² Rather, it seems

¹ The absence of fat offers a problem of some interest: the liver after a certain duration of an infective disease shows some fat in all its parts; at the moment when the focal necrosis occurs it is fair to assume that there is fat in the area. It may be, on the one hand, that the fat enters into some soluble form or combination and is removed, or it may enter into a combination or undergo a transformation, after which it no longer reacts as fat.

² Opie states that the mid-zonal and central necroses of the hepatic lobule are caused by bacterial toxins; he illustrates his contention by the liver of a case of peritonitis of gonorrhoeal origin. We can only say that our autopsy series contains about 300 cases of general peritonitis, and we have not been able to duplicate his case, nor have we found that the bacterial toxins have any special affinity for the mid and central zones.

to us, is a relatively weak toxin at work in all parts of the liver, in witness whereof is the cloudy swelling that almost always, if not always, accompanies the necrosis. What, then, is the additional factor in the areas necrosed? Perhaps a thrombosis of the vessels supplying the part. The observation of thrombosis in four of the focal necroses goes towards the support of this, and so, in a sense, does the proved infective nature of practically all the diseases with which the necroses were associated. One might even go further and say that typhoid fever, the commonest cause in this series, is essentially a disease in which thrombosis is clinically frequent. Four of these areas with visible thrombosis form but a small percentage; yet it is to be remembered that the thrombosis may be some distance away, and that the section seen may be only a part of the area affected. If now we consider that thrombosis is the cause, it will occur in portal and in hepatic vessels alike, for any reason we know to the contrary. Portal thrombi, we know, cause little or no histological change in the liver,—hepatic thrombi, as Chiari and others have shown, a most destructive effect. If, then, we can conceive of small hepatic branches being thrombosed, the greater degree of toxicity of the portal blood in intestinal disease might be held to account for the greater frequency with which the periphery is attacked; but the facts that the other blood supply is also toxic, and that the portal supply reaches all parts of the liver, though probably with gradual loss of its toxicity, may account for the diverse situations of the lesions. It is perhaps too fanciful to suggest that the circular shape of the necroses points to a centrifugal origin, for it may be said that serial sections might prove their shape to be an entirely different one. Pearce and Winne, in microscopic studies of the experimental lesions they were able to produce by the toxins of *Bacillus typhosus* and *Bacillus cholerae suis*, found typical focal necroses with hyaline thrombi, which they consider due to fused red blood cells, fused by the effect of agglutinins. We are able to see red blood corpuscles sufficiently well in the capillaries and vessels of the necrosed areas, but we do not feel capable of distinguishing whether or not these are in a thrombotic or fused state. Pearce, in more recent work, found that hæmolytic sera, poor in agglutination power, failed to produce necroses in rabbits, but agglutinated red blood cells, which had been agglutinated by immune serum, did cause necroses; he thinks that these necroses are due to mechanical obstruction, and that the products of the associated hæmolysis play no part. He was able to support this mechanical obstruction contention by injecting into control animals ammonium carmine, and by finding that the injection was evidently mechanically prevented when the agglutinative serum had been previously used, the agglutinative serum making a “hyaline thrombus” block the capillary. We may point out that Levy shows that a great degree of hæmolysis is made in the test tube by typhoid toxin, and that

M. B. Schmidt has also shown that in typhoid fever a great hæmolysis is produced in the body; the debris of the red blood cells Schmidt found to be particularly situated in the liver and spleen; this seems to us to go far to explaining in the light of Pearce's idea the occurrence of thrombosis and subsequent necrosis in the typhoid liver.¹

Pease and Pearce examined the tissues of horses inoculated with tetanus and diphtheria toxins, and in one they found areas of necrosis corresponding to thromboses of the portal vein; but another horse showed portal thrombosis and no necrosis. Our own cases of portal thrombosis have never showed necroses of the liver, as far as our knowledge goes. These authors consider that bacterial toxins are responsible for focal necroses. Cohnheim and Litten, on the other hand, found no histological changes in liver cells as a result of obstruction of the portal vein; the affected area does, it is true, become congested, and where small interlobular branches of the portal become blocked the affected area may show focal necroses. Chiari's case of hepatic artery thrombosis gave a complete necrosis of the liver.

Our conclusions, briefly, are these:

In seven cases of eclampsia focal necroses were found in six; no necrotic changes were found in five cases of hyperemesis (pernicious vomiting), four of lead poisoning, two of arsenic poisoning and one of carbolic acid poisoning.

Thirty-five cases of different kinds, of which thirty-four were definitely infective, showed necroses; twenty-nine of these were focal, and twenty-two of these last were in typhoid fever. These necrotic changes are, we think, due to a combination of thrombosis and the action of diffusible chemical toxins; bacteria we found in them but once, and we consider the leucocytic infiltration so often seen to be an evidence of repair. Eight cases showed none such. We never found evidence of the liver cells entering into the reparative process.

The evidences we can show in favour of the thrombotic origin of focal necroses are the existence of actual thrombosis four times, the frequently circular shape, the great similarity between the focal necroses of doubtful origin of eclampsia and the infarcts of the liver, definitely proven to be such; and the constant occurrence of focal necroses in infective conditions, especially typhoid fever, which gives rise so often to thromboses.

We might point out, further, that the macroscopic recognition of focal necroses is not very reliable; that the necroses in our series are mostly peripheral, and that some change in the fat present in the tissue occurs as a result of the necrosis, so that these lesions are uniformly deprived of fat as such.

¹ Mallory's contention for a cellular thrombosis of endothelial cells from vessel walls or from spleen sinuses we have not been able to support; the thrombi are always of a granular or hyaline rather than of a cellular nature. As to whether Pearce has suggested the right origin of these hyaline thrombi we have no evidence to offer.