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SEROUS HEPATOSIS: A PATHOGENESIS OF HEPATIC FIBROSIS IN JAMAICAN CHILDREN

PRELIMINARY REPORT*

BY

K. R. HILL, M.D. KATERINA RHODES,† M.B., Ch.B.

J. L. STAFFORD, M.B., Ch.B. AND R. AUB,† M.D.

(Department of Pathology, University College of the West Indies)

[WITH SPECIAL PLATE]

The object of this communication is to report upon a disease of the liver found in Jamaican children ; because of its clinico-pathological features we have proposed the term " serous hepatosis " (Hill, 1951 ; Hill *et al.*, 1951).

In all, 150 cases have been investigated. On clinical analysis it is apparent that they can be classified as conforming to certain different types which are, however, different phases of the same disease with the same underlying pathology. Histologically, this condition resembles that described by Roessle (1930) as " serous hepatitis," or that described by Keschner and Klemperer (1936) as " hepatic oedema."

Three methods of approach were used in the study of these Jamaican children. First, a dietary survey was made ; secondly, all children were subjected to a complete examination in which were included certain biochemical tests for liver function ; and, thirdly, needle-biopsy examination was carried out on approximately 50% of cases, from some of which serial biopsies were taken.

Dietary Survey

This has been previously described by Rhodes (1951). The common background of all these children was a poor dietary history starting in early infancy. Most of them were of good average weight when born, and they were breast-fed for a period varying from four to nine months. In Jamaica, however, complete breast-feeding is stopped early and complementary feeding adopted. This means that the baby receives breast milk about twice during the night, and during the day is fed on cereals such as cornmeal, or rolled oats with or without a little condensed milk.

From the neonatal period, except in a few cases, the babies are given " bush tea," which is an infusion of leaves, flowers, or seeds of various plants. When the babies are weaned they are put on a cornmeal diet, although rolled oats and Robinson's patent barley are also used. The diet is monotonous in the extreme, and one of these highly refined cereals is given meal after meal for months and years on end.

For economic reasons, and also because of its poor keeping qualities in the Tropics, cows' milk is seldom used, and little, if any, meat, fish, and eggs is eaten. Often the children are given diluted condensed milk, one to two tins a week being shared by the whole family. Children 4 to 5 years and older live on root vegetables such as yams and sweet potatoes and, in addition, cornmeal and rice.

The dietary history as presented above implies a very low protein intake, particularly low in animal or so-called first-class protein, but an adequate calorie intake. Only a few cases of this series (7%) had a very low calorie intake in addition to a low protein consumption, and these, as shown later, presented a modified clinico-pathological picture.

Clinical Findings

The children were between the ages of 4 months and 16 years, the majority being from 1 to 3 years old. Nearly all were from poor homes, and the remainder came from lower middle-class homes in which the standard of intelligence or the knowledge of what comprises a nutritious diet is low ; possibly associated with this is the fact that the familial incidence of the disease is high. The children are predominantly of African extraction, with European, East Indian, and Chinese racial admixtures.

On examination about one-third of the cases were in the *acute* phase of the disease. About a half of these cases gave a recent history of acute illness such as tonsillitis, whooping-cough, and pneumonia before the onset of gross abdominal enlargement due to ascites and hepatomegaly. The acute illness usually preceded, or sometimes was concurrent with, the liver enlargement. These children were usually normal in physique, and in two or three weeks they recovered from the acute hepatic involvement, though often they had a residual asymptomatic enlargement of the liver. Liver-function tests showed an absolute rise in serum globulin with a reversed albumin/globulin ratio and a lowered serum cholinesterase. Recovery from the acute liver enlargement occurred whether or not treatment was given for this condition.

The other half of the patients in the acute phase had no previous history of infection so far as could be elicited. They had ascites and an enlarged firm liver. The liver-function tests generally showed a lowered serum albumin, often with a low total protein and also a low serum cholinesterase. On a high-protein diet it was two to three months

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before they improved from the acute phase. A few apparently recovered completely, but frequently they tended to lapse into the subacute or the chronic phase.

All the children in the acute phase were very ill and fretful. The liver was hard with a smooth outline and a sharp lower edge, and both the left and the right lobes were enlarged. Sometimes the liver was bulging and tender on pressure as if under tension. Occasionally the enlargement was great, up to 12 cm. below the costal margin; a varying degree of ascites was present, and on first paracentesis the protein content was sometimes as high as 2.1 to 2.8%. On subsequent tapping the protein content decreased.

Signs of vitamin deficiency were rare. The appearance of these children was in striking contrast to the usual picture of subnutrition found in the Tropics (Waterlow, 1951).

About one-third of the series were found to be in the subacute stage when first examined. They usually looked well developed, with rounded contours and adequate subcutaneous fat, although on closer examination some had flabby muscles, some were stunted, and many were underweight. The liver was often slightly or moderately enlarged and there was little or no ascites. Liver-function tests generally showed lowered serum albumin and serum cholinesterase. The results of the flocculation tests were not significant. Jaundice was absent, although not infrequently the total serum bilirubin was slightly raised. Many of these subacute cases were, however, asymptomatic, and were found only on routine examination at schools or on investigation of brothers and sisters of affected children. There was no complaint, and the child was usually happy and looked well, had no ascites, but had an enlarged liver. In a recent survey (not connected with this study) of 116 children from two villages, 55% were found to have symptomless liver enlargement.

About one-third of the series were seen in the chronic phase of the disease. They were usually older children with a long medical history. The picture was one of hepatic fibrosis with a large, nodular, or contracted liver, with sometimes an enlarged spleen and clubbing of the fingers and toes, an established collateral circulation, and occasionally jaundice. These children were retarded and of poor nutrition. Two cases have been followed from the subacute stage to the chronic stage over a period of a year.

Eleven cases in the whole series were starved babies with generalized oedema, loss of subcutaneous fat, and signs of vitamin deficiency such as angular stomatitis, depigmentation of the hair, and various dermatoses which have been described in the literature many times as part of the syndrome of kwashiorkor or fatty liver disease. These babies were on a low-calorie diet, and the usual history was loss of appetite for one to three months and subsequent feeding on sweetened "bush tea" as a home remedy. Oedema was always present and not necessarily associated with ascites, the oedema being presumably a starvation phenomenon. These cases had a high mortality, whilst in all the other cases the mortality was low, with a high and prolonged morbidity.

No case in the series showed severe anaemia, but some degree of slight or moderate iron-deficiency anaemia was often seen. Bleeding and coagulation times were normal. Sickling trait was found in 7% of the cases and 11% showed infection with *Ancylostoma duodenale, Trichuris trichiura,* or *Ascaris lumbricoides.* Malaria parasites in the blood were demonstrated in three cases.

Histology

Liver-needle biopsies were performed on 75 out of the 150 cases studied; in many cases serial biopsies were obtained. Specimens were fixed in various agents from time to time—for example, formalin, corrosive sublimate, alcohol, and Zenker's solution—but for the majority formal-sublimate solution was found to be the most suitable. Up to 80 serial sections of blocks were cut and sections were stained routinely with H. and E., periodic acid Schiff (P.A.S.), picro-Mallory connective-tissue stain, and Foote–Wilder reticulin stain; special stains for amyloid, fibrin, glycogen, haemoglobin, and fat were done when indicated.

In 25% of cases an early exudative or transudative lesion was found; this consisted of out-pouring of serous fluid into the perisinusoidal spaces of Disse and around the centrilobular veins (Special Plate, Figs. 1, 2, and 3). In some cases the lesion occupied almost the whole of the liver biopsy section under examination, but in most cases the lesion was focal and multiple, each lesion involving up to one or two lobules. The unaffected liver tissue seemed to be quite healthy, but the liver-cell columns at the site of the actual lesions appeared to be flattened. Whether or not they were in fact compressed or whether they were atrophied or shrunken it is impossible to say at the present stage of this investigation. The Kupffer cells and other endothelial cells often seemed to be swollen, increased in number, and detached.

Generally in the liver sections the sinusoids were dilated and filled with blood; alternatively, the sinusoids were wide open and empty, but this was thought to be artifact due to draining out of the blood at the time of biopsy. In about 15% of cases there were focal areas of fresh haemorrhage at the sites of recent serous exudation. This haemorrhage was thought to be due to trauma at the time of biopsy of unduly fragile and congested capillaries; no focus of old haemorrhage was found, no iron-containing brown pigment or macrophagic reaction was ever observed to suggest haemorrhage as part of the disease process, and in only one or two cases was the haemorrhagic artifact found in serial biopsy *after* treatment.

In 80% of cases deposition of an eosinophilic coagulum was found in the spaces of Disse (Figs. 3, 4, 5, and 6) and "cuffing" the centrilobular veins. This was associated in about one-third of these cases with oedema of the space of Disse mentioned above, as if the coagulum had been precipitated out of the serous fluid or perhaps the fluid, a sol, had become a gel.

At this stage the study of the chemical nature of the serous fluid has not been established, although we are of the opinion that it is probably initially exudative in character; accordingly the term "exudate" will be used in this context.

Sometimes the serous exudate alternated with the coagulum around the centrilobular veins, giving the lesions a laminated appearance; this was interpreted as indicating repeated attacks of liver disease. Although, however, in about two-thirds of the cases the eosinophilic coagulum was found alone, it was probably secondary to the serous exudation.

The eosinophilic coagulum gave the tinctorial reactions of collagen, and was not digested by trypsin. In appearance it varied from a granular amorphous coagulum to waxy-looking blobs of material; on occasion it had a fibrillary appearance although almost acellular—that is, there were no fibroblasts (Fig. 3). Tinctorially it was not amyloid, paramyloid, or atypical amyloid (Teilum, 1948), or fibrin or haemoglobin; it was not birefringent with Congo-red stain and not metachromatic with toluidine blue.

Reticulin stains (Figs. 7 and 11) revealed a perisinusoidal reticulinosis which showed swollen reticulin fibres in the perisinusoidal spaces (at the site of the coagulum), with condensation and possible proliferation, although this latter may be illusory. In places where the coagulum was abundant it could be seen as laminated yellow-coloured blobs adherent to black swollen reticulin fibres (Fig. 6).

In 50% of cases there was distension of the space of Mall in the portal triads by serous exudation (Fig. 8), and in some of these cases there was evidence of a recent deposition of eosinophilic coagulum within the exudate. Often there appeared to be a dilatation of the perivascular and periductal lymphatics.

The coagulum extended from the space of Mall, surrounding the intralobular and interlobular vessels arising from the vessels of the portal triads (Fig. 9).

In 75% of the cases fibrosis of the eosinophilic coagulum was seen. The youngest patient was aged 4 months. Fibroblasts could be seen invading the coagulum around the centrilobular vein and along the spaces of Disse (Fig. 10). In the former there were bands of perivascular fibrosis extending from lobule to lobule (reversed lobulation); in the latter there was perisinusoidal fibrosis distorting the lobule in all directions, and in some cases a vascular short-circuit was produced from portal triad to centrilobular vein. The fibrosis of the coagulum around the intralobular vessels contributed to the further intralobular distortion, whilst the fibrosis of the interlobular vessels produced the appearance of perilobular cirrhosis (Fig. 11).

Of the cases 30% showed extreme fibrosis with distortion, bile-duct proliferation, and nodular hyperplasia, an appearance generally associated with cirrhosis (Figs. 12 and 13).

In general, liver-cell damage was not observed except in cases with marked fibrosis, although at this stage of the investigation special histochemical stains have not been done. The liver cells were often slightly swollen or hydropic in appearance; generally, but not invariably, this was shown to be due to a high glycogen content. In five cases there was fatty metamorphosis, but in three cases this was associated with recent or old-standing serous exudation or deposition of eosinophilic coagulum. Cellular infiltration of portal triads was slight, and was associated with fibroblastic invasion of the eosinophilic coagulum; it was never observed to such an extent as to suggest infective hepatitis.

In summary, the histological picture appeared to show a train of events beginning with serous exudation followed by the deposition of an eosinophilic coagulum which was subsequently invaded by fibroblasts. Often the three processes were taking place concurrently in the same biopsy block of liver tissue but not necessarily at the same site. The end-result was extensive hepatic fibrosis.

A Pathogenesis of Hepatic Fibrosis: A Theory

The structure of the liver lobule is probably similar to that described by Elias (1949a, 1949b). Fig. A, I is a diagrammatic representation of part of a liver lobule (the centrilobular vein, sinusoid, liver cells, and the portal triad). The sinusoid lies in a lacuna which is lined by the liver cells making up the hepatic laminae (hepatic cell columns). The lacunar space between the hepatic laminae and the sinusoid is the perisinusoidal space of Disse. The hepatic laminae are continuous interconnecting sheets of cells and the lacunal spaces formed by them are also interconnecting to form a labyrinth. The capsule of the portal triad is circumscribed by a potential space—the space of Mall—which connects with the space of Disse. Branches of the portal vessels are the interlobular and intralobular vessels. These all pass through the space of Mall to enter the parenchyma, and in so doing carry with them an enveloping potential space which connects with the space of Mall. Structurally the spaces of Mall and Disse may well be a part of the "lymphatic" drainage of the liver.

The first stage of the pathogenesis of hepatic fibrosis is serous exudation into the space of Disse and around the centrilobular vein (Fig. A, II). Subsequently there is a deposition of eosinophilic coagulum in these areas (Fig. A, III).

Serous exudate and coagulum may be deposited in many areas as a result of repeated attacks; the lesions are focal and circumscribed. At the site of an initial lesion the serous exudation spreads out in all planes as the different lacunae interconnect to make up the hepatic labyrinth. The confinement of the exudation to focal areas may be due to the deposition of eosinophilic coagulum restricting the further spread of serous fluid. Thus any newly formed serous exudate will be prevented from flowing in the direction of the centrilobular vein or laterally into adjoining

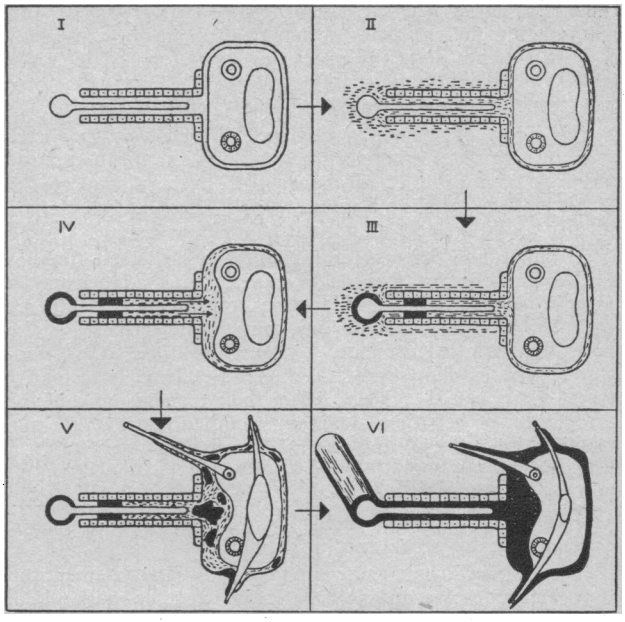

FIG. A.—Diagram showing the various stages of the pathogenesis of hepatic fibrosis. (I) Normal liver lobule with hepatic lacuna between the hepatic laminae; within the lacuna lies the centrilobular vein and sinusoid; the portal triad is shown with peripheral space of Mall which connects with the perisinusoidal space of Disse (lacuna). (II) Serous exudation in perisinusoidal space of Disse. (III) Deposition of coagulum around centrilobular vein and also within the space of Disse. (IV) Distension of space of Mall, following further serous exudation subsequent to the deposition of coagulum. (V) Deposition of coagulum from the serous exudate present in the space of Mall and in the sheaths of the intralobular and interlobular vessels. (VI) Late stage of deposition of coagulum which becomes fibrosed by the invasion of fibroblasts.

lacunae, but rather will be directed into what is probably the natural flow of the liver-tissue fluid, in the direction of the space of Mall in the portal triad. The space of Mall will thus become distended with serous exudate (Fig. A, IV). Subsequently, an eosinophilic coagulum will be deposited around the portal triad and also along the sheath-like spaces enveloping the intralobular and interlobular vessels (Fig. A, V). The sheaths are extensions of the space of Mall.

The next stage is the invasion of the coagulum by fibroblasts; thus there is established a fibrotic cuffing of the centrilobular vein and an intralobular extension of fibrous bands along the space of Disse. At the same time fibroblastic proliferation from the periphery of the portal triads spreads along the interlobular and intralobular vessels (Fig. A, VI).

Subsequent contraction of this fibrous tissue causes lobular distortion and disorganization, which, together with reactive nodular hyperplasia, produce the final picture of diffuse hepatic fibrosis.

Discussion

The series of cases under study illustrate a development of gross hepatic fibrosis beginning as a serous exudation (or oedema), followed by deposition of an eosinophilic coagulum, followed in turn by invasion by fibroblasts.

One outstanding feature of the study was the finding of a serous exudate or transudate and coagulum in the perisinusoidal spaces of Disse and around the centrilobular vein. The source of the serous fluid is, at this moment, undetermined; there are three possibilities: (1) from the sinusoid through the capillary wall; (2) from the liver cells; and (3) from blockage of the normal tissue-fluid drainage—that is, "hepatic lymph" in the spaces of Disse and Mall.

Increase of capillary permeability in the liver due to toxic causes, resulting in serous exudation, is not a new

concept. Roessle (1907, 1930, 1933, 1943) was of the opinion that the escape of serum from damaged capillaries is in the acute stage a serous inflammation. The acute serous inflammation may be followed by a sclerosing lesion; thus the initial stage of cirrhosis is a "serous hepatitis."

This point of view was further elaborated by Eppinger *et al.* (1935), who extended their studies on the escape of serum from capillaries in shock to the general concept of serous inflammation. Eppinger (1949) has lately referred to this condition as "albuminuria into the tissues."

Keschner and Klemperer (1936) have described findings similar to those of Roessle in the perisinusoidal space in 15% of a large series of necropsies; although not agreeing with all Roessle's conclusions, and while preferring the term "hepatic edema" to "serous hepatitis," they concluded that in many cases the hepatic oedema is primarily from toxic causes. They base their conclusion on the association of hepatic oedema with diabetic coma, uraemia, exophthalmic goitre, and thermal burns.

As far back as 1909, Helly had observed the focal flecking of the liver in sepsis, and Keschner and Klemperer (1936) were of the opinion that this was focal hepatic oedema due to generalized toxaemia.

It is interesting to note that Popper (1936b) mentions that Henschen regarded hepatic oedema as a kind of "glaucoma of the liver," and he relieved it in practice by an operation in which he injured the liver surface, thus facilitating the escape of oedematous fluid, with immediate decrease in the size of the liver. Biopsy specimens taken from such a liver with oedema visibly shrank within a few minutes of the operation.

Serous hepatitis has been produced experimentally in dogs by Popper (1936a, 1937), using allyl formate. The lesions produced were similar to those found in serous hepatitis in humans, although there was no certainty in production of the lesions. It would be interesting to note whether the lesions could be produced with 100% certainty if the animals were on low protein diet. Furthermore, the lesions of serous hepatitis have also been produced experimentally by Eppinger and Leuchtenberger (1932) by the intravenous injection of histamine.

Another cause of the escape of serous fluid from the capillaries may be congestion, which probably acts by a hydromechanical effect and/or by increasing capillary permeability due to anoxia. Popper (1948) has reported the agonal changes in human livers following acute heart failure, drowning, and suffocation, in which there is a dilatation of the perisinusoidal spaces usually associated with accumulation of "albuminoid" material. In a series of cases of instantaneous death no such dilatation of the perisinusoidal spaces was seen. Keschner and Klemperer (1936) record a similar finding in 36% of cases after cardiac failure and describe it as a "mechanical oedema." They were of the opinion that the term "serous hepatitis" for such conditions was inappropriate; after all, if the agonal changes are due only to congestion, the so-called exudate is in fact "transudate."

We have in our laboratory a section from a patient dying from acute right-sided heart failure which shows an eosinophilic coagulum around the centrilobular vein. The fact that these changes can occur agonally in acute right-sided heart failure, whether they be from exudates or transudates, none the less supports the theory that the material in the perisinusoidal spaces occurring in the series of biopsies under study may be derived from vascular sources.

Many of our sections show hepatic congestion—so much so that some of the sinusoids are grossly distended and filled with blood or, alternatively, probably owing to artifact, are wide open and empty. This latter condition was described by Roessle (1930). Further, in 15% of our cases there was fresh haemorrhage, interpreted as being due to capillary fragility, associated with trauma at the time of the biopsy. Our reason for this opinion was that we never at any time saw evidence of old haemorrhage such as iron-containing brown pigment or a macrophagic reaction; further, in only one or two cases, after treatment on a high-protein diet, did we obtain such an artifact, our assumption being that treatment had corrected the abnormal fragility of the capillary wall.

Cardiac failure was not the cause of liver (sinusoidal) congestion in our series of cases. Of the criteria for heart failure laid down by Sherlock (1951), such as crepitations of the lung bases, increased jugular pressure, peripheral oedema, and hepatic tenderness, only the last-mentioned was found clinically; histologically no centrilobular necrosis with graded histological change towards the periphery was found.

Maegraith *et al.* (1949, 1951) have shown that hepatic congestion can be produced in animals by hypersensitivity: this congestion is probably due to constriction *within* the hepatic venous tree. Essex and Thomas (1950) state that they have produced occlusive spasm of the hepatic veins in dogs and cats following intravenous injection of an extract of *Ascaris suis*, hydatid cyst fluid, and histamine.

Another source of the exudate may be from the liver cells themselves. This view has been put forward by Eger (1950), who suggests that there is a release of fluid from the liver cells into the space of Disse, with subsequent retraction of the liver cells. This gains a little support from the present study by the fact that in the foci of exudation the cells sometimes look flattened as though retracted; however, the cells are often swollen with glycogen or are hydropic, changes which are against the opening of the tissue spaces by the mechanical means of retraction.

Further, it is stated by Selye (1950) that the liver parenchymal cells in such conditions of serous inflammation imbibe serum from the tissue spaces with a rise in their sodium chloride, calcium, and water content, and a decrease in their phosphate and potassium content; this imbibition is a possible explanation of the hydropic appearance of liver cells in some of our cases.

The flattened appearance of the cells may be due to atrophy, but, in general, we have observed it only during the acute phase of serous exudation at the site of the exudation; further proof of this theory that the liver cell is the primary site of the liver lesion must await further investigation along the lines of histochemistry and cell and nuclear counts.

Dilatation of the space of Disse may be caused by blockage of the normal tissue-fluid drainage channels of the liver. Popper (1936b) describes the following morphological triad in serous hepatitis: (*a*) dilatation of the perisinusoidal space of Disse; (*b*) oedema of the portal canals; and (*c*) gall-bladder-bed oedema. In cases under study, dilatation of the perivascular and periductal (bile) lymphatics has been noted in association with the distension of the space of Mall. This, of course, as well as suggesting a block in the lymph drainage, may also indicate an increased production of the tissue fluid.

It is interesting to speculate at this stage whether or not the exudate in the perisinusoidal space flows into the perivascular lymphatics of the portal triads and then finally, as a back-pressure effect, into the peritoneal cavity to produce ascites. It is noteworthy that the ascitic fluid on first paracentesis has often a high protein content (2.1 to 2.8 g.%). Gray (1951) has indicated that the source of the ascitic fluid is an excess of hepatic lymph. The hepatic sinusoids are said to be unusually permeable to albumin both in experimental animals (McKee *et al.*, 1949) and in man (Patek *et al.*, 1948).

Experimentally, support for the theory of the drainage of tissue fluid from the perisinusoidal spaces into the lymphatics of the portal triad is given by the work of Koch-Weser (Popper, 1951), who ligated the common bile duct near the liver in rats and produced lesions resembling serous hepatitis. Several authors, including Bollman (1950), have stated that the bile ducts are surrounded by a plexus

of vessels in which the lymphatics are included. Hence ligation of the common duct will exert a block, producing back-pressure distension of the space of Disse.

In the cases under study no evidence of lymph-duct blockage, either inflammatory or mechanical, has been detected, and the evidence points to overproduction of tissue fluid to explain the dilatation of lymph and tissue spaces.

In summary, the evidence available in this preliminary report is that the serous exudation and the coagulum are produced from vascular sources. Whether this is due to an increase in capillary permeability *per se*, or to congestion producing its anoxic and hydromechanical effects, it is impossible to say at this stage of the investigation.

The possibility that toxic factors are a cause of the increase in capillary permeability *per se* has some support. It is significant that the left lobe appears to be enlarged as much as the right. This lobe may drain the blood of the large gut, and if the latter is a source of bacterial or other toxins then the involvement of the left lobe may be thus explained.

It is to be noted that McFarlane and Branday (1945) and Royes (1948), in their articles on liver disease of Jamaican children, suggest toxins in association with low-protein diet as the aetiological agents. The possible toxicity of the various Jamaican "bush teas" is now being investigated. Further, Watson (1951) has pointed out the efficacy of aureomycin and also of enemata on patients suffering from hepatic coma, and he suggests that the action may be to reduce the toxicity by altering the bacterial flora of the gut.

One constant feature is that the serous exudate and the coagulum are never associated with a cellular infiltrate, which is the usual accompaniment of inflammation. However, according to Selye (1950), the emigration of leucocytes can be inhibited by systemic intoxication with bacterial endotoxins and by anaphylactoid, traumatic, and "toxic" shock.

Increased capillary permeability producing hepatic oedema was found by Keschner and Klemperer (1936) in association with asthma; it has also been produced by Eppinger and Leuchtenberger (1932) by the intravenous injection of histamine. These examples would point to the circulation of a toxic histamine-like substance, and may well suggest further experimental work on the lines of hypersensitivity. It is to be noted that two of our cases with primary tuberculous lesions showed acute hepatic enlargement immediately after the tuberculin test, which, as was expected, was positive. Biopsy of the cases showed the histological picture which we have found associated with acute serous hepatosis.

Whatever the source of the exudate, the fact remains that an exudate and/or coagulum are constantly found, and the question may be asked, "What is the coagulum?" The coagulum gives all the tinctorial reactions of collagen and is not digested by trypsin. Is it in fact collagen, or a precursor of collagen? In many cases the coagulum has the waxy appearance of amyloid with H. and E. stain, and in some cases it has a fibrillary appearance although acellular. Reticulin staining shows the reticulin fibres black and swollen, and adherent to them are blobs of laminated material staining yellow. These blobs are in fact the coagulum. Are they blobs of protein from the serous exudate forming on the side of the swollen reticulin fibres or are they swollen reticulin fibres which are blowing up to bursting point at various places along their lengths owing to imbibition of serous fluid?

The fact that the coagulum is acellular does not preclude the possibility of its being collagen or pre-collagen protein material. Porter and Vanamee (1949) have shown in tissue culture, by studies using the electron microscope, that unit fibrils may combine to form protofibrils of collagen without the intermediary of fibroblasts. Further, Porter (1951), in an extension of these studies, has shown that after being shed from the fibroblasts the collagen fibrils increase in size by the accretion of a material from the ground substance. This method of accretion may explain the deposition of protein of serous origin on pre-existing connective-tissue fibres in the liver of the cases under study. The possibility of collagen-fibre formation by precipitation in a protein-rich exudate has also been advanced by Klemperer (1951), and Day and Armstrong (1940) have commented on the curious absence of fibroblastic activity in the genesis of cardiac cirrhosis.

Roessle (1930) explains the sclerosis following serous hepatitis due to the intermediation of endothelial proliferation. The endothelial cells (including the Kupffer cells) increase in number and become detached to form a connective-tissue reticulin—"the endothelialite." In the present study some endothelial swelling and proliferation have been noted, and the few cells seen in the perisinusoidal spaces are often endothelial or Kupffer-cell types.

The coagulum, whatever its derivation, is a precursor of fibrosis. Sections have been studied which show what is interpreted to be the fibroblastic invasion of the coagulum—that is, the coagulum is there first and at a later stage it is invaded by fibroblasts. It is tempting at this stage, therefore, to consider the coagulum as collagen protein or pre-collagen and the process of the laying down of the eosinophilic coagulum as a "collagenosis."

So far, the aetiology of the process of events occurring in the liver has not been determined. One salient fact elucidated has been the woefully deficient protein in the diets; this deficiency was not only in total protein but also in first-class protein of animal origin. It is not known whether the lack of single or multiple amino-acids, or the disproportion of protein to carbohydrates, or perhaps a combination of these factors, contributes to the development of liver disease. At this stage it is pertinent to mention that the cases of serous hepatosis differ both clinically and histologically from those cases of subnutrition with fatty liver disease in the Tropics described as kwashiorkor (Williams, 1933; Trowell, 1949; Davies, 1950; Waterlow, 1951).

It is true that about 7% of the cases conform to the classical description of kwashiorkor. It is of interest that these cases were on a low-calorie as well as a low-protein diet, in contradistinction to the main type of case, which had a low protein but normal calorie intake. Notwithstanding the clinical appearance of starvation and fatty metamorphosis of the liver, evidence of an underlying pathological condition similar to the main group of the cases was found. It is tempting, therefore, to assume that the fatty metamorphosis in these few cases was a side-effect to starvation—that is, deficient calories in the diet.

Mottram (1909) drew attention to the fact that fatty metamorphosis of the liver may be encountered in some cases of starvation, a feature now well recognized in severe deficiency states. Dible (1951) suggests that in such cases the liver cells receive more fat than they are capable of dealing with, and he strongly asserts that there is little evidence that fatty metamorphosis is a precursor of human cirrhosis, as, for example, accepted by Moschcowitz (1948), pointing out that the dietary evidence from experimental work cannot be directly applied to man. Hartz (1949) has described a fatty metamorphosis occurring in children in Curaçao which he claims never goes on to cirrhosis.

Liver-cell damage has been noted (using the usual routine staining methods) only in association with marked hepatic fibrosis. Further study is needed to decide whether or not liver-cell damage is an important feature of the disease under investigation. The results of liver-function tests are, except for a persistent lowered serum albumin and serum cholinesterase, equivocal, and do not conform to any set pattern. None the less, functionally the liver cells would be expected to be defective because the exudate and coagulum in the perisinusoidal spaces (haematoparenchymal barrier) must impair the diffusion of nutrients from the blood stream to the cells. Further, the removal of waste products from the cells to the capillaries will also be

impaired, and therefore local intoxication and malnutrition of the parenchymal elements must follow the initial stage of disturbed capillary permeability. This has been pointed out by Eppinger *et al.* (1935), as well as the fact that excessive amounts of serum proteins in the perisinusoidal spaces may well lead to the invasion of the parenchymal cells by serum proteins and by serum enzymes, resulting in damage to the cell (Böck and Popper, 1937).

The final picture of serous hepatosis is diffuse hepatic fibrosis. This has been arrived at by a slowly progressive fibrosis, intralobular and also perilobular in distribution, which occurs in the coagulum deposited in these positions. A theory has been postulated which attempts to explain the pathogenesis of this fibrosis.

Serous hepatosis, then, may well be one of the causes of polylobular cirrhosis, which Dible (1951) refers to as "cryptogenic."

Summary

A liver disease occurring in Jamaican children has been described; because of its clinico-pathological aspects it has been named "serous hepatosis." To date the only aetiological factor which has been ascertained is a low dietary protein intake. It is suggested that toxic factors may also play a part.

Clinically, the condition occurs in children, usually between the ages of 1 and 3 years, who have an enlarged firm liver and ascites; ultimately the appearance may be one of classical hepatic cirrhosis.

Histologically, the disease is a progressive one, passing from an initial exudation or oedema to the deposition of an eosinophilic coagulum which is finally invaded by fibroblasts.

The condition is similar to that described by Roessle (1930) as "serous hepatitis."

A theory of the pathogenesis of liver fibrosis has been postulated.

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TREATMENT AND PROGNOSIS OF ACUTE PERFORATED PEPTIC ULCER

BY

F. AVERY JONES, M.D., F.R.C.P.*

Physician in Charge of Gastro-enterological Department, Central Middlesex Hospital

AND

R. DOLL, M.D., M.R.C.P.

Associate Physician, Gastro-enterological Department, Central Middlesex Hospital; Member of the Statistical Research Unit, Medical Research Council

With the assistance of

KEENA JONES, M.A., and BARBARA WHITE, B.Sc.

During the last decade there has been a striking fall in the fatality of acute perforated peptic ulcer. Whereas before 1942 the operation mortality was commonly 20%, the figure to-day is not more than a quarter of that level. This fall can mainly be attributed to improvements in anaesthesia with the introduction of muscle relaxants and to the use of antibiotics. Deaths from peritonitis in the first week have almost ceased to occur, and fatal cases are now mainly due to concomitant bleeding, intestinal obstruction, and associated diseases. This was demonstrated in the series reported by Avery Jones, Parsons, and White (1950). With the reduction in fatality, interest has been aroused in new methods of management.

Three methods are currently recommended—medical management with gastric aspiration, simple surgical closure, and immediate partial gastrectomy. The choice, in the individual case, must depend on the facilities available, but it will be influenced by knowledge of the immediate and late prognosis in similar cases treated by each method, and it will not necessarily be the same for all patients. It is difficult, on the existing evidence, to assess the relative merits of the three methods, partly because the fatality associated with each method has been rapidly decreasing, and partly because insufficient attention has been paid to the end-results, after the patients have left hospital.

The series reported by Avery Jones, Parsons, and White included 490 patients treated at the Central Middlesex Hospital during 1938–48, the great majority of them by simple surgical closure of the perforation. Since 1948 patients at the hospital have, in the main, continued to be treated by the same method, and the results have been analysed for a further period of three years to see, first, whether the fatality has continued

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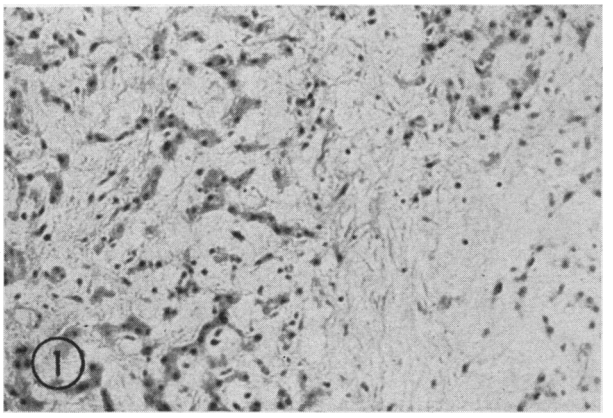
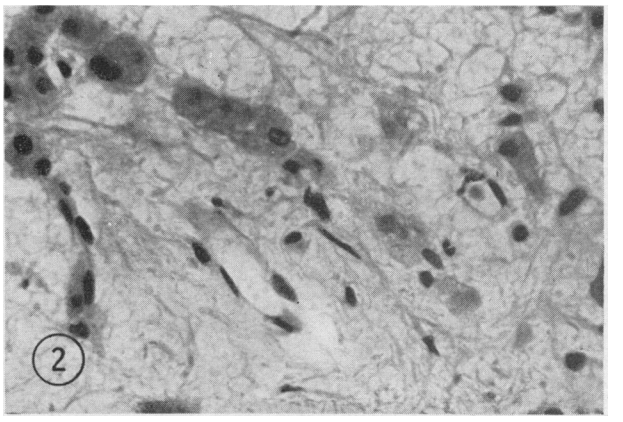
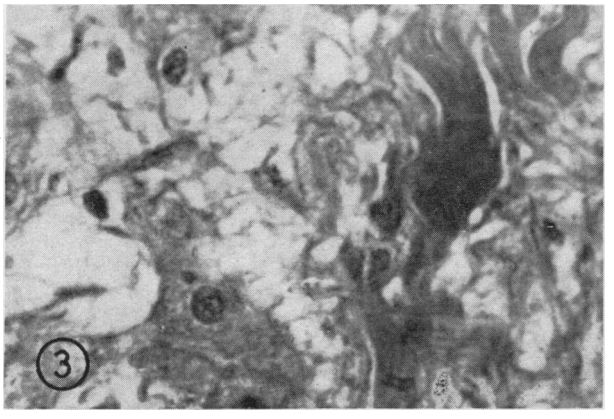
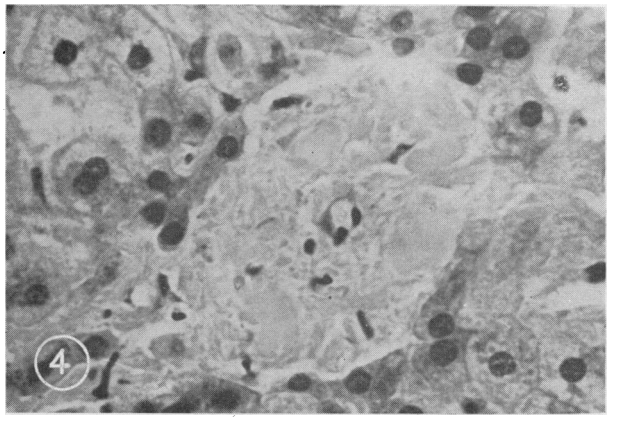
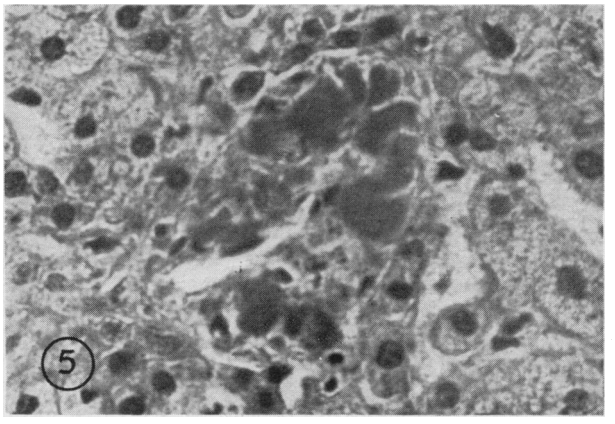
K. R. HILL, KATERINA RHODES, J. L. STAFFORD, AND R. AUB: SEROUS HEPATOSIS

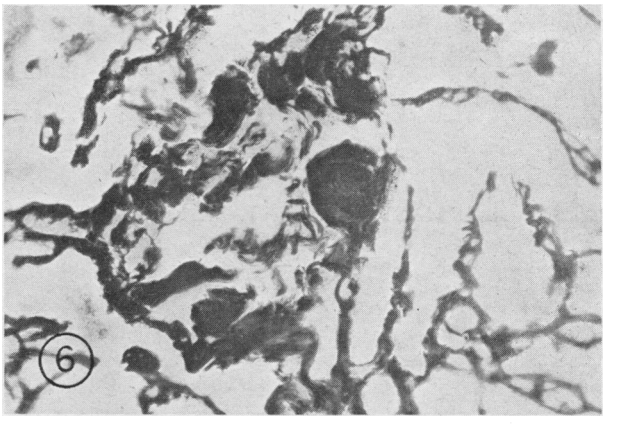


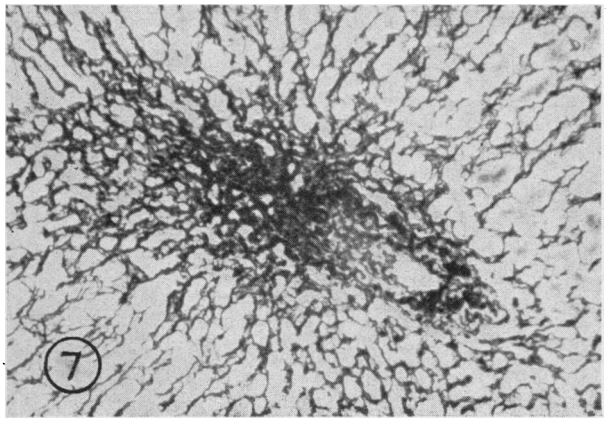


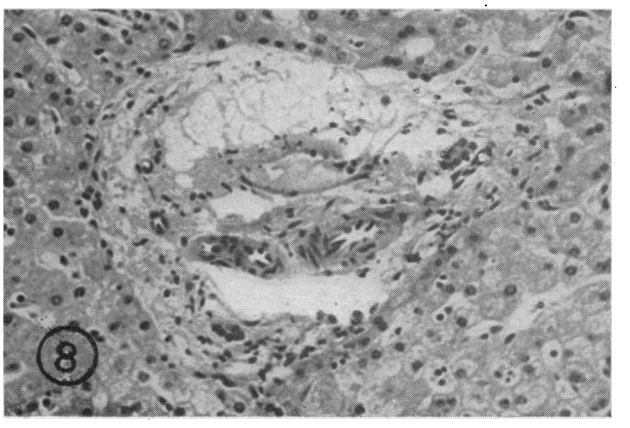




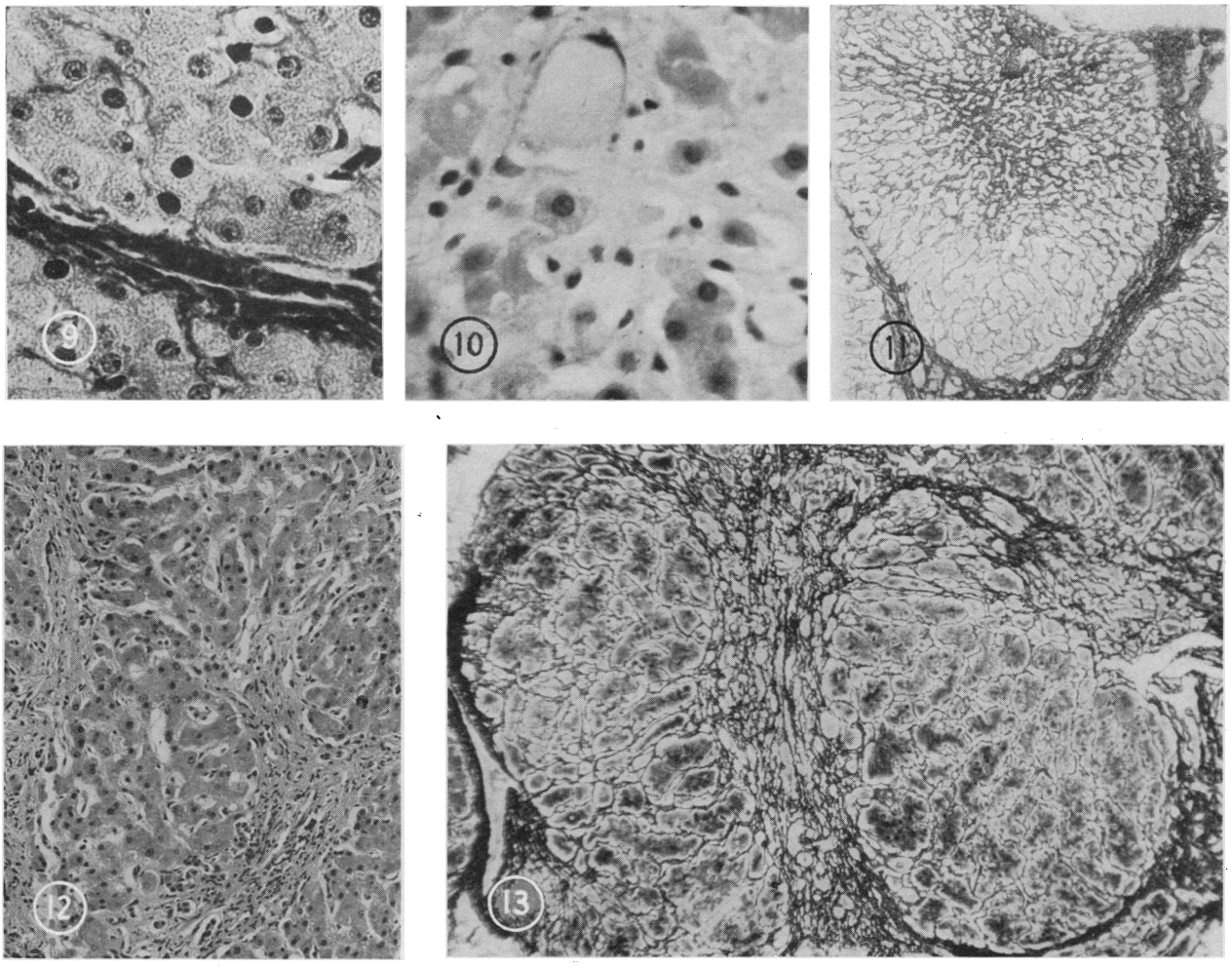








K. R. HILL, KATERINA RHODES, J. L. STAFFORD, AND R. AUB: SEROUS HEPATOSIS



H. J. M. STRATTON, T. M. L. PRICE, AND M. O. SKELTON: GRANULOMA OF NOSE AND PERIARTERITIS NODOSA

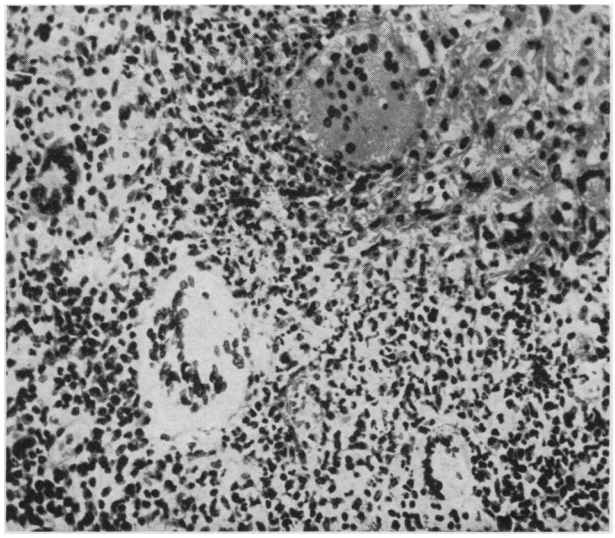


FIG. 1.—Nasal mucosa of Case 1, showing chronic inflammatory reaction and multinucleated giant cells. (H. and E. ×110.)

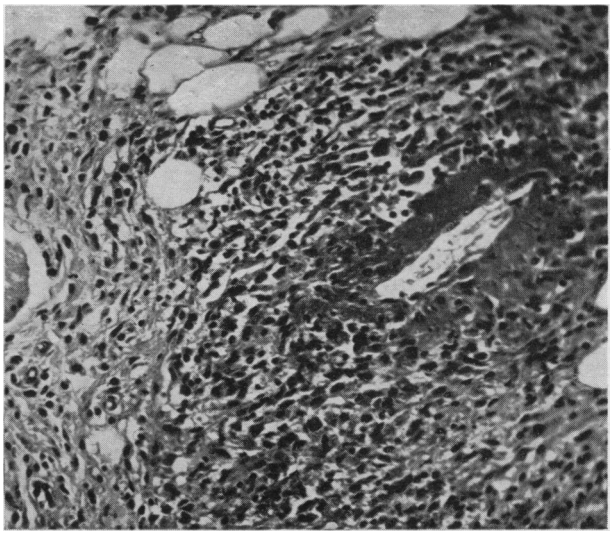


FIG. 2.—Muscle biopsy of Case 1, showing acute inflammatory reaction in wall of small artery. (H. and E. ×90.)