CHRONIC SPLENOMEGALY AND ITS RELATION TO HEPATIC PATHOLOGY*

BY

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The interrelationship between hepatic disease and chronic splenomegaly of apparently unknown aetiology has aroused the interest of numerous observers for well over half a century. Banti in 1894 drew attention to the syndrome of chronic splenomegaly initially associated with fever, anaemia, leucopenia, and occasionally with a history of haemorrhages. Subsequently these cases developed cirrhosis of liver and ascites. Banti postulated the idea of an unknown toxin which acted separately on the spleen as well as on the liver. In his account of the histology of the enlarged spleen he referred to fine widespread fibrosis in the pulp and proliferation of the endothelial cells of the sinuses. These changes gave rise later to macroscopic fibroid nodules—what he called "fibroadenae." This syndrome has also been discussed by Osler (1900) and Warthin (1910). The influence of vascular abnormalities in the portal bed in the pathogenesis of chronic splenomegaly was discussed by McNee (1931), Larrabee (1934), Rouselot (1936, 1949), Thompson *et al.* (1937), Ravenna (1940), and Learmonth (1951).

The role of chronic progressive splenomegaly as the responsible agent in inducing and accelerating fibrotic changes in the liver has been described by many observers. McMichael (1934), who has made the most extensive study of the pathology of the liver and spleen in this group of cases, came to the conclusion that there is no decisive proof that the liver is undamaged in any case of "hepato-lienal fibrosis"; that it is at present impossible to exonerate the liver from the initiation of the pathological process, and that the two organs, liver and spleen, probably suffer simultaneously, although in varying degrees.

Tidy (1952) was of the opinion that the hepatic fibrosis, the chronic splenomegaly, and the haematological changes were due to different and distinct aetiological agents, and made the interesting suggestion that abnormalities of the rhesus factor in the blood between the mother and the offspring, and consequent erythroblastosis foetalis of milder degrees, were probably responsible for development of the syndrome. He denied the benefits of splenectomy in the arrest or reversal of the process.

Sherlock (1955) believed that the hepatic changes were not the sequelae of chronic progressive splenomegaly but were from a different cause.

Milnes Walker (1952) described three types of histological changes in the liver—namely, periportal fibrosis alone, periportal fibrosis with diffuse ramifications between liver lobules, and fully developed fibrosis of the type of subacute hepatic necrosis with nodular hyperplasia, and discussed the different types of clinical manifestations which are associated with each of these types of histological changes.

Chronic splenomegaly is a common clinical entity in many parts of India, particularly in Bengal. Apart from known causes such as protozoal infections, there occurs a group of cases whose aetiology and pathogenesis are not clear even on careful investigation. Such cases have consequently been given the non-committal term of "tropical" or "Bengal" splenomegaly. These cases often give a history of previous malarial attacks. Many of them come from endemic malarious areas. Extensive antimalarial measures in recent times have reduced their frequency to some extent. It is therefore reasonable to think that the initial cause of splenomegaly in most of these cases is probably of malarial origin. However, the progressive enlargement of the spleen after the control and subsidence of the malarial infection is of great interest and remains as yet an unsolved problem.

Many of these cases are associated with clinical and haematological evidences of "hypersplenism." Others give a history of repeated haemorrhages. Still others come with ascites and other evidences of liver disorder.

The pathogenesis of this type of splenomegaly, and particularly the interrelationship of the splenomegaly with the pathological changes in the liver, have not yet been made clear. De (1932, 1937), Menon (1934, 1938), Hughes and Shrivastava (1931), Napier (1939), Sen Gupta (1943), and Chaudhuri (1957) have written on this interesting problem, but have not committed themselves entirely on the pathogenesis of the condition. De, however, postulated the question of a specific toxin elaborated by the spleen as being responsible for the hepatic damage.

From a study of this and other available literature a few significant questions arise. (1) What is the type and frequency of hepatic changes in chronic splenomegaly? (2) What role, if any, has splenomegaly in the initiation, persistence, and progressive increase of the hepatic changes? (3) Conversely, has hepatic fibrosis any role in the splenomegaly itself? (4) Is the hepatic damage an arrestable or reversible process, and can it be arrested or reversed by removal of the hypertrophied spleen?

Methods of Study

For several years we have been interested in this problem of chronic splenomegaly and related hepatic conditions, and have studied our cases according to the following schedule: (1) haematological—examination of the peripheral blood and bone-marrow study; (2) biochemical—examination of plasma proteins and liver function tests; (3) radiological—oesophagogram and splenoportal venogram (Basu and Das, 1956).

At the time of operation opportunity was taken to note the macroscopic appearances of the spleen, liver, and portal venous system, including the presence of collateral venous channels; to estimate the portal venous pressure; and to take a specimen of liver for biopsy. A detailed study of the histology of the spleen and the liver was made from the biopsy material.

After appropriate operative procedures these cases were carefully followed up, and the clinical, haematological, and structural and functional states of the liver were checked up at spaced intervals.

Material

Altogether we have dealt with 72 cases of this type, of which 39 have been studied in great detail from the point of view of liver pathology, and these form the basis of the

TABLE I.—*Categories of Cases*

1. Chronic splenomegaly without evidence of cirrhosis of liver or portal hypertension	1 case
2. Chronic splenomegaly associated with cirrhosis of liver and portal hypertension	22 cases
3. Chronic splenomegaly associated with extrahepatic obstruction	12 ,,
4. Chronic splenomegaly due to specific diseases (kala-azar, 2; haemolytic anaemia, 2)	4 ,,

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present communication. As the result of the overall study as outlined we were able to divide our 39 cases into four categories (Table I).

The cases in group 2 are of immediate interest for the purpose of this paper. The types of hepatic damage met with in this group of cases are given in Table II.

TABLE II.—*Types of Hepatic Damage in 22 Cases*

1. Post-necrotic cirrhosis with nodular hyperplasia	18 cases
2. Post-necrotic scarring	2 ,,
3. Diffuse hepatic fibrosis	2 ,,

In 12 cases in this group the splenomegaly was due to extrahepatic obstruction of the portal venous system, and these included tumours of the pancreas, pancreatic fibrosis, portal venous thrombosis, and congenital cavernomatous transformation of the portal vein. In these cases the histology of the liver biopsy taken at operation showed either a normal parenchymatous pattern or only reticulo-endothelial hyperplasia. Cases associated with kala-azar or haemolytic anaemias also showed reticulo-endothelial cell hyperplasia. In kala-azar cases L.D. bodies were seen in large numbers.

Discussion

A significant finding was the fact that in all the chronic splenomegaly cases where the histology of the spleen showed evidences of congestive changes—namely, dilatation of sinusoids, recent or old evidences of periarterial haemorrhages, and erythrophagocytosis—the liver parenchyma also revealed greater or lesser degrees of fibrosis. The significance of this association as regards the pathogenesis of the splenomegaly is commented upon below.

There was one exception to the usual type of "tropical" splenomegaly in our series. One case of chronic splenomegaly in the absence of any specific cause showed only reticulo-endothelial cell hyperplasia in the spleen. The portal venous pressure in this case was low. The liver did not reveal any evidence of fibrosis.

In conformity with the above findings were the cases of splenomegaly which were associated with extrahepatic obstruction of the portal venous system and also cases of chronic splenomegaly due to specific causes, such as kala-azar or blood dyscrasias—namely, haemolytic anaemias—where fibrosis was conspicuously absent in the liver. The various liver-function tests in this group also showed more or less normal results.

The large majority of cases of hepatic fibrosis were of the type of post-necrotic cirrhosis with large nodules of various sizes enclosed by fibrous reticula. On macroscopic examination at the time of operation, many of these cases showed large bossy nodules on the surface of the liver which were soft in consistency and congested in appearance. Some others showed diffuse granularity. It was not always possible to correlate the naked-eye appearance of the liver exactly with the histological appearance of the biopsy material, but, in general, the degree of fibrosis could be approximately guessed from the consistency and the irregularity of the surface of the liver. The portal venous pressure in these cases was invariably high, and varied between 230 and 480 mm. saline.

The typical Laennec type of cirrhosis, in which there is diffuse hepatic fibrosis enclosing smaller nodules of approximately uniform sizes, was present in only two of our cases. In another two cases there was only post-necrotic scarring, with fibrous septa sparsely distributed among large areas of healthy liver tissue. As is to be expected, the liver-function studies in the last type of cases gave relatively normal results.

From the study of our cases it appears that chronic splenomegaly *per se* has little effect on the histology of the liver and is certainly not responsible for the initiation of the fibrotic process. This is evidenced from the group of splenomegalies due to specific infections or to those due to blood dyscrasias. In one such case, for example, a woman of 30 had progressively increasing splenomegaly due to chronic drug-resistant kala-azar for over 10 years. Splenectomy ultimately helped cure her kala-azar and greatly improved her general health. The liver in this case did not show any evidence of cirrhosis. We also see in our country numerous cases of malarial splenomegaly, which are adequately treated and leave no residual disease either in the spleen or in the liver. Similarly, cases of infrahepatic obstruction of the portal venous system, although associated with chronic splenomegaly, do not show any evidence of functional or structural damage of the liver.

If the splenomegaly *per se* is not responsible for the initiation of the hepatic damage, where are we to look for the noxious agent? This question is difficult to answer, and is perhaps not entirely relevant for this particular discussion. However, as Dible (1951) has pointed out, in England the incriminating influence of viral hepatitis must be seriously considered. In India, too, the influence of virus infection in the morphogenesis of adult cirrhosis is being increasingly stressed (B. K. Aikat, 1957, personal communication), and it may be that the role of the nutritional factor in the pathogenesis of cirrhosis in the tropics has hitherto been unduly emphasized.

Whether the splenomegaly is in any way responsible for the persistence or increase of the fibrotic process in the liver is a moot question. On the evidence available from our cases as well as from the records of others, we are of the opinion that this hypothesis is probably correct. This belief is based mainly on the results of our follow-up studies after operations.

We have performed splenectomies on a large number of cases of fibrocongestive splenomegaly, and spleno-renal shunt operations with splenectomy in a smaller number of cases, and have followed these up very carefully with periodical haematological, liver-function, and liver biopsy studies. The data obtained have been analysed and compared with the pre-operative status. The results of the operations are shown in Table III.

TABLE III.—*Results of Operations*

	Cases
Death before operation	2
Operative mortality	3
Known deaths after operation	4
Lost in follow-up	9
Overall follow-up for periods varying from 6 months to 6 years	54
Clinical condition:	
Cases doing well	46
Cases with recurrence of haemorrhage	5
Cases developing ascites. (They did not have ascites prior to operation)	3
Repeated haematology study (done in 42 cases):	
Cases improved as compared with pre-operative status	36
Repeated liver-function study (done in 31 cases):	
Cases improved as compared with pre-operative status	26
Repeated liver biopsy study (done in 24 cases):	
Cases improved as compared with pre-operative status	16

Of these 72 cases, 41 belonged to the group of chronic splenomegaly which was associated with already existing cirrhosis of liver and evidences of portal hypertension, either manifest by haemorrhages or as actually measured at operation. Only 3 of the 54 cases followed up are known to have developed ascites after operation, and 5 have had recurrence of haemorrhage. 26 out of 31 repeated post-operative liver-function studies and 16 out of 24 repeated post-operative liver biopsy studies show improvement. We have several instances of a long-term follow-up of cases exceeding six years where patients with early cirrhosis of liver and fibrocongestive type of splenomegaly continue to do well after splenectomy and are free from any symptoms. Also there are records where in a short-term follow-up of six months to one year there have been significant changes in the liver-function studies, including reversal of the altered albumin and globulin ratio and also stunting of the pattern of the globulin peak in serum electrophoresis. The histology of the liver has shown satisfactory changes. All these, taken together, point to the fact that the large hypertrophied spleen, besides being inimical to the formed elements of the blood, does adversely affect hepatic function and structure in the pre-existing damaged liver.

How this is brought about is as yet problematical. The hypothetical toxin of the spleen that Banti postulated, and which was also supported by McNee (1931) and Pemberton and Kiernan (1945), can be discounted.

Hunt (1954) has suggested that the excessive splenic effluent in large splenomegalies may be responsible for "idiopathic" portal hypertension. It may, however, well be that this splenic venous hypervolaemia further injures the liver parenchyma by cutting down on the supply of the more important portal venous blood from the intestinal tract. The mean hepatic blood flow has been found in man to range between 1,300 and 1,800 ml. a minute (Ravdin, 1957). Only 25% of this blood normally comes from the spleen. In our large fibrocongestive splenomegalies the splenic effluent as measured in a few cases exceeded 600 ml. a minute. It is possible that, in cirrhosis of the liver, the hepatic parenchyma, already struggling for survival because of the many vascular abnormalities and shunts within the liver, further suffers because of this progressively increasing splenic effluent hypervolaemia, and the process becomes a vicious circle.

The part played by the cirrhotic liver in the pathogenesis of chronic splenomegaly is more easy to understand. There are at least two factors to be considered here. McMichael (1934) made the interesting suggestion that the spleen behaves as the particular drainage lymph node of the liver, and, like other lymph nodes, undergoes hypertrophy in consequence of the inflammatory and necrotic onslaughts affecting the hepatic parenchyma.

In addition, the part played by portal hypertension and the consequent venous stasis, and the effects of such chronic venous stasis resulting from the fibrotic process in the liver, must be considerable, and certainly accounts for the congestive type of splenomegaly that is a constant feature in these cases. The fibrotic process within the liver enhances the portal venous pressure in various ways.

As the result of distortion and disruption of the parenchymal integrity within the liver, abnormal communications develop between branches of the hepatic artery and the portal vein, producing arteriovenous shunts (Popper *et al.*, 1952; Mann *et al.*, 1953), and the high pressure of the systemic arterial circulation is reflected on the low-pressure portal veins, resulting in back pressure and stasis. On this concept is based the rationale of the hepatic artery ligation operation of Rienhoff (1951) and Berman *et al.* (1951). Secondly, the large nodules seen in the post-necrotic type of cirrhosis in our cases can conceivably be expected to obstruct the hepatic venous outflow mechanically and thus enhance portal venous pressure. Thirdly, the effect of the fibrosis itself may be significant, and is more serious when the outflow tract—that is, the central hepatic veins—are interfered with more than the inflow or the portal tracts. The part played by outflow obstruction in the pathogenesis of ascites in cirrhosis has been emphasized in recent years (Madden *et al.*, 1954). That this form of obstruction is also more important from the point of view of portal hypertension has been pointed out by Popper (1952).

In the post-necrotic type of cirrhosis many of the central veins are interfered with by large masses of fibrous tissue, and therefore portal hypertension is likely to be high.

The evidences of congestion in the splenic bed are quite obvious. Besides the enormous dilatation of the sinusoids, the periarterial haemorrhagic areas, etc., two other findings from our series may be mentioned. In many of our cases of large splenomegalies we could find a distinct thrill over the splenic artery at operation that at once stopped on compression of the artery near the hilum. This was therefore an evidence of turbulent flow through the artery, most probably due to intrasplenic arteriovenous communications brought about as the result of enormous sinus dilatation. This type of splenic artery thrill is uncommon in splenomegalies where pulp hyperplasia alone is the predominant element in the histology.

The other finding is the enormous mass of dense tortuous vascular adhesions which bind the spleen to surrounding structures in the fibrocongestive type of splenomegalies, rendering splenectomy in many cases a hazardous process. In contrast, other types of splenomegaly due to specific causes such as the haemolytic anaemias are usually free from adhesions, and splenectomy in such cases is an easy procedure. Obviously the vascular adhesions in the former type are an attempt of nature to compensate for the portal hypertension by creating new portosystemic anastomoses and bypassing the block, which may be either within or outside the liver.

Whether the cirrhotic process in the liver can be arrested to some extent or be reversed by splenectomy has already been partly answered from the experience gained from our series. It must, however, be emphasized that in late stages of cirrhosis of liver with severe functional damage splenectomy, instead of being beneficial, may in fact accelerate hepatic failure. Of this we have had few experiences. This is also to be expected, for, as Smetana (1956) has emphasized, the hepatic cells existing in a precarious balance due to intrahepatic vascular abnormalities in cirrhosis are unduly susceptible to anoxia, either from spontaneous or from operative haemorrhage.

However, it is our belief that splenectomy, with a shunt procedure where necessary, is an eminently suitable operation where the liver damage is not excessive and where hypersplenic manifestations are predominant. This opinion is in accord with the extensive experience of Learmonth (1951) and others. Judged from the clinical and haematological points of view, and from a study of the state of the liver function and of liver pathology of many of these cases before and after operation, there is no doubt that in the large majority the operation has been well worth while and has conferred estimable benefits on the patients.

Conclusion and Summary

I have attempted to review the interrelationship between chronic splenomegaly and the related hepatic pathology from the study of a group of cases which are common in our country and which in the absence of a specific terminology have been called "tropical" or sometimes "Bengal" splenomegaly. The histology of such splenomegalies shows usual fibrocongestive changes, and the liver histology in most cases reveals appearances of post-necrotic cirrhosis, although in a few cases the cirrhotic pattern is of the nature of diffuse hepatic fibrosis or of post-necrotic scarring. Initially such splenomegalies are likely to be of malarial origin and due either to inadequate treatment or to absence of treatment in the early stages; the splenomegaly persists in the long run, although the specific protozoal infection ceases to be manifest.

From a review of these cases and by comparison with other types of splenomegaly due to specific causes, it seems that enlargement of the spleen *per se* has little effect on the histology of the liver. However, once hepatic damage is established, as very commonly happens, the fibrotic and other consequences of such damage induce a state of portal hypertension, with resulting congestive changes in the splenic parenchyma. Along with further increase in the size of the spleen, the splenic effluent markedly increases and further damages the struggling hepatic cells by shunting off the more important effluent from the intestinal tract. A vicious circle is therefore established.

Our experience is that splenectomy at a stage where the cirrhotic process in the liver is not already irreversible cuts across the vicious circle and improves the clinical state of the patient. There is evidence to show that the functional and the structural state of the liver also improve *pari passu*, and the operation therefore can be confidently recommended in selected cases.

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ADDICTION TO UNRESTRICTED DRUGS

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The Pharmacy and Poisons Act, 1933, provides for the registration of sellers of poisons, places poisons in two lists for purpose of sale, and draws up the Poisons Rules under which various schedules of poisons have been arranged, either further restricting their sale or giving exemptions. The Dangerous Drugs Acts, 1920 to 1932, govern the sale of drugs of the morphine and cocaine series. One function of these Acts is to regulate the consumption of those drugs likely to lead to addiction, placing the onus of prescribing the drugs listed on registered medical and dental practitioners.

In the W.H.O. Technical Report Series No. 21 (1950) drug addiction is defined as a state of periodic or chronic intoxication detrimental to the individual, and to society, produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include : (1) an overpowering desire or need to continue taking the drug and to obtain it by any means ; (2) a tendency to increase the dose ; (3) a psychological and sometimes physical dependence on the effects of the drug.

Differentiation is made between addiction-producing and habit-forming drugs—the latter may be taken repeatedly without the production of all the characteristics outlined.

The sale of most drugs known to lead to addiction is governed by the Acts mentioned, but there are a few drugs, thought by many physicians to be "safe," which are not so included. In some cases this is because the drug is comparatively new, since a certain amount of time must elapse after clinical use of the drug has started, before evidence of its danger in this direction is available. Drugs which have been included in the list of scheduled poisons comparatively recently include those of the stimulant group such as benzedrine, and sedatives, such as methylpentynol, known to the lay public as relaxing drugs to allay apprehension. In other cases drugs which have been in use for many years are yet freely obtainable without prescription because they are thought not to be addiction-producing.

This small series of female patients, who have been under our care during the past two years, is described to draw attention to the possibility of addiction to drugs which can be obtained without prescription. That this possibility is not widely recognized is shown by the fact that in several articles in the *Practitioner* between 1951 and 1957 on sedatives and hypnotics (Ström-Olsen, 1951 ; Morgan, 1953 ; Shorvon, 1955 ; Sears, 1956 ; Dunlop, 1957), while the danger of addiction to barbiturates is mentioned, addiction to non-barbiturate hypnotics is not—and their safety is emphasized. Dunlop does point out that sedatives carry with them the danger of dependence and even addiction, but does not deal with the problem except in relation to barbiturates.

The following are the drugs taken by patients in this series, and may all be obtained from a chemist without prescription.

Carbromal is a white crystalline powder, almost odourless and tasteless. The tablets (*B.P.C.*) contain 5 gr. (0.32 g.). It is also made up in proprietary preparations such as "persomnia," containing carbromal 195 mg., and bromvaletone 65 mg. ; "dormiprin," containing carbromal 120 mg., bromvaletone 40 mg., and alkalized aspirin ; and "somnotil," containing chlorbutol 3 gr. (0.2 g.), carbromal 1 gr. (65 mg.), and bromvaletone 1 gr. (65 mg.). It is a mild hypnotic and sedative.

Chlorodyne (tinctura chloroformi et morphinae, *B.P.C.*) contains about 1/64 gr. (1 mg.) of anhydrous morphine in 10 m., as well as small quantities of chloroform, alcohol, and ether. It is used to control cough, vomiting, and diarrhoea.

"*Preludin*" (phenmetrazine hydrochloride) has been in use in this country only since 1955, when it was introduced from Germany for the treatment of obesity. It is a secondary amine, related pharmacologically to the amphetamine group of compounds.

Case 1

While working as a telephonist during the war this patient, unmarried, aged 44, had diarrhoea. She took chlorodyne in normal dosage for this, and found her fears and apprehenions relieved. She continued to take increasing amounts of chlorodyne during the rest of the war period, reaching 3 to 5 bottles a day. This amount produced intoxication and led to her admission to mental hospitals. At various times she attempted to give up the drug but succeeded for only a few months. She then would develop an overpowering urge to start again. The story continues with a four-year period in hospital from 1951 to 1955 and periods in hospital in 1956 and 1957. Even in hospital she would abscond, to be found in a drunken condition some hours later, having drunk two, three, or four bottles of chlorodyne. Her illness has led to her social downfall, to a situation of loneliness, to work much below her capabilities, and to family quarrels. This situation, together with her basic personality of cyclothymic type with periods of