**MEDICAL GRAND ROUNDS**

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# THE BLOODY LIVER

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## INTRODUCTION

The liver is a very vascular organ being composed of a syncytium of parenchymal cells each of which is almost completely surrounded by a blood-filled sinusoid. Blood reaches the liver from two different vascular beds; the hepatic artery and the portal vein. Afferent blood from these 2 sources is mixed in the hepatic sinusoid before leaving the liver via the hepatic veins. It is unusual to see much evidence of this blood when one examines liver biopsy specimens. The sinusoid like the larger vessels (arteries and veins) are empty. This phenomenon is fundamentally an artifact of the tissue preparation and fixation. Specimens are usually washed in saline and then immersed in a formalin solution. The liquid blood simply drains away during the process. When blood is visibly present in a biopsy specimen it usually indicates that the blood had solidified (i.e. clotted or agglutinated) before the biopsy was obtained. There are four disorders apart from hemorrhagic tumors that lead to the presence of large amounts of blood in hepatic tissue samples. These conditions, congestive heart failure, sickle cell disease, peliosis hepatis, and the Budd-Chiari syndrome have little else in common. Nonetheless, they form an interesting differential diagnosis one with the other and are therefore the focus of these grand rounds.

## SICKLE CELL DISEASE

Abnormalities of liver function are not only common in patients with sickle cell disease they are almost inevitable. The liver may be involved as a direct consequence of the disease or its treatment or it may suffer indirectly from the sickling process. The differential diagnosis of liver disease in patients with sickle cell disease may be difficult or even downright close to impossible. The major categories of liver disorders associated with this congenital hemolytic anemia are listed below:

**Unconjugated Hyperbilirubinemia**

**Cholelithiasis - Asymptomatic**
**- Symptomatic**
**- Choledocholithiasis**

**Hemochromatosis**

**Viral Hepatitis**

**"Hepatic" Crisis**

**Incidental and Unrelated**

### 1. UNCONJUGATED HYPERBILIRUBINEMIA

Sickle cell disease is a chronic hemolytic anemia in which red cell survival is markedly reduced and the production of bilirubin consequently increased. The hepatic reserve for the metabolism and disposition of bilirubin is very large so that in most patients with a stable (i.e. compensated) chronic hemolytic process it is unusual for the total serum

bilirubin to exceed 3.0 mg%. It is not uncommon, however, for patients with sickle cell disease who are asymptomatic and who have no other evidence of liver disease to maintain serum bilirubins from 5.0 to 10.0 mg% and occasionally even higher (e.g. 15 tO 20 mg%). It is not clear why this is so. It may simply represent the coexistence of two conditions; one being chronic hemolysis, the other Gilbert's syndrome. One would anticipate that as many as 10% of a young male population would manifest evidence of the mild glucuromyl transferase deficiency that characterizes Gilbert's syndrome. If a state of excess bilirubin production were superimposed one would expect to find greater degrees of unconjugated hyperbilirubinemia than is usual in patients with chronic hemolysis. On the other hand, there remains the possibility that these patients with unusually high levels of serum bilirubin are reflecting some consequence of the sickle state (? subtle liver cell injury) other than that of chronic hemolysis alone.

## 2. CHOLELITHIASIS

Gallstone formation is common in patients with sickle cell disease. As many as 40% of adult patients with SS disease have been reported to have gallstones. The stones that form are often radio-opaque as befits their composition of $Ca^{++}$ bilirubinate. The mechanism of production of these stones is linked to the increase in bilirubin load presented to the liver consequent to the chronic hemolytic process and is therefore not different from that operating in any chronic hemolytic anemia (e.g. hereditary spherocytosis) in which the risk of cholelithiasis is enhanced. Conventional wisdom argues that bilirubin is excreted into bile as a mono or diglucuronide conjugate that confers enhanced water solubility. Were this entirely true, increased excretion of bilirubin into bile occasioned by an increased load would not result in $Ca^{++}$ bilirubinate stone formation unless a mechanism for bilirubin deconjugation was present in the biliary system. Such a mechanism (in the form of the enzyme Beta glucuronidase) is operational in oriental cholangiohepatitis associated with infestation of the biliary system with chlonorcis sinensis and in some patients with biliary infection with E Coli. There is no reason to believe that deconjugation of bilirubin diglucuronide occurs in patients with chronic hemolysis. The only alternative is to suggest that a small but finite fraction of excreted bilirubin exists in the unconjugated form and that this fraction is increased absolutely when the load of bilirubin is enhanced by hemolysis. This moiety is highly hydrophobic, forms salts readily with $Ca^{++}$ and precipitates from solution to form the nidus of a bilirubinate stone. This hypothesis has been substantiated by studies of the composition of bile using high performance liquid chromatography.

It is said that the bilirubin stones that form in patients with sickle cell disease are less likely to cause symptoms and less likely to result in complications than are other gallstones. This may be true, but consequences of cholelithiasis remain a relative risk for affected patients with sickle cell disease. The stones may precipitate cholecystitis and provoke the usual gastrointestinal manifestations of this condition. The stones may also lodge in the common bile duct and result in acute pancreatitis or obstructive jaundice with or without acute ascending cholangitis.

The risks of surgery in patients with sickle cell disease used to be quite formidable. Improvements in the pre- and peri- operative care of these patients have rendered surgical procedures a much more reasonable proposition in these patients.

The identification of gallstones in a patient with sickle cell disease should prompt consideration of elective cholecystectomy unless the patient's clinical state renders the costs of the procedure untenable.

## 3. IRON STORAGE STATE

Patients with sickle cell disease are usually in a state of iron storage excess. This results from:

a) The need for multiple transfusions over time.

b) A state of hyperabsorption of iron occurs whenever the bone marrow is hyperactive. This is manifestly true in patients with sickle cell disease. The marrow is markedly expanded and proliferative and there is often evidence even of extra medullary hematopoiesis in these patients. The mechanism for this gastrointestinal hyperabsorption of iron is poorly understood, but it is sensible teleologically for an active marrow to be provided with extra essential hematinics.

It is very common, therefore, for there to be extra iron in the livers of patients with sickle cell disease and for the serum iron to be high and the iron binding capacity to be more saturated than is normal. Serum ferritin levels are often quite elevated especially in the presence of any form of liver injury, no matter what its cause.

It is unusual to rare for liver injury to be the consequence of this iron storage excess although the differential diagnosis of liver injury in patients with sickle cell disease is rendered difficult by the unquestioned excess of iron present in many of these patients. As survival of patients with sickle cell disease well into adulthood has become more commonplace the differential diagnosis of myocardial dysfunction has presented the same kind of dilemma. Once again it is fair to say that hemochromatosis is much more often considered to be a possible cause of the heart disease in these patients than it proves to be in the final event. This is just as well as there is very little useful therapy available to these patients even when the possibility of iron induced tissue injury (i.e. hemochromatosis) is considered likely. Iron depletion by repeated phlebotomy is not an option. The only therpay available is the use of desferrioxamine infusions. This is a slow and cumbersome way to reduce total body iron. It relies on the ability of DFO to bind iron and be cleared subsequently by urinary excretion. In occasional patients in whom transfusion requirements are very high such therapy might be justified.

## 4. VIRAL HEPATITIS

Patients with sickle cell disease are as likely as anyone else to acquire

hepatitis A or hepatitis B depending on their lifestyle and social habits. They are at increased risks to acquire non A/non B hepatitis (hepatitis C) because of their need for transfusions.

The clinical manifestations of viral hepatitis in patients with sickle cell disease are remarkable in two particular ways:

a) **The severity of jaundice** It is very common for the serum bilirubin in a patient with sickle cell disease and viral hepatitis to exceed 50 mg%. On occasion values greater than 100 mg% are recorded. The level of serum bilirubin is a useful gauge of the severity of an episode of viral hepatitis under normal circumstances. Values in excess of 20 mg% indicate severe parenchymal injury and serve as an alert to the likelihood of massive hepatic necrosis and hepatic coma. In patients with a marked increase in bilirubin production (as in chronic hemolysis) this prognostic indicator loses its significance. The serum bilirubin will be disproportionately high even in the face of mild hepatic injury if the bilirubin load presented to the damaged liver is markedly increased as it is in patients with sickle cell disease. The fractionation of the bilirubin in serum in patients with viral hepatitis is usually approximately 50:50 with respect to the conjugated and non-conjugated moieties. This same proportion is maintained in patients with sickle cell disease who have hepatitis. One sees occasional patients, therefore, with concentrations of unconjugated bilirubin as high as 50 mg% in their serum. This provokes no neurologic consequence and provides compelling testimony to the adequacy of an adult blood brain barrier in preventing kernicterus.

b) **A prolonged and fluctuating clinical course** Many patients with sickle cell disease who acquire viral hepatitis run a clinical course which is prolonged and which often is marked by fluctuations in severity over the time the acute process is present. These are not patients who subsequently progress to a form of chronic hepatitis although the presence of sickle cell disease is no amulet against this complication of viral infection. These are episodes which ultimately completely resolve but which are prolonged in their acute phase. Resolution of the acute icteric event may take three to four months. The hope engendered by the apparent amelioration of jaundice and the evidence of hepatic injury provided by declining activities of the aminotransferases (AST,ALT) is dashed recurrently by the sudden worsening of these parameters of severity. A number of such cycles of improvement followed by "relapse" may be seen before the liver function tests return completely to normal. Liver biopsies taken from patients whose disease runs this course demonstrate the usual features characteristic of viral hepatitis (i.e. generalized cell necrosis often more marked in the centrilobular regions accompanied by an infiltrate of mononuclear inflammatory cells in the portal triads and in the areas of cell fall out) but also demonstrate marked intrasinsuoidal sickling with intense erythrophagocytosis by Kupffer cells. This intrahepatic sickling is presumably initiated by local changes in oxygenation and pH resulting from the necrosis and inflammation caused by the viral infection. The consequences of the intrahepatic sickling are twofold:

   i) The sudden destruction of this mass of sickled red cells contributes

an extra burden of bilirubin to be presented to the injured liver and therefore contributes to the high levels of serum bilirubin seen in these patients and,

ii) The sludging of these cells coupled with the mechanical obstruction caused by markedly hypertrophied macrophages stuffed with red cells interferes with blood flow in the sinusoid and leads to an ischemic injury to parenchymal cells downstream. These episodes of ischemic necrosis explain the recrudescences of hepatic injury that one may see. Evidence that this phenomenon of intrahepatic sickling is indeed the cause of the prolonged and variable course sometimes seen in sickle cell patients with viral hepatitis is provided by the effect of hypertransfusion. The aim of such therapy is to raise the hematocrit of the patient to a point where the production of red cells by the marrow is inhibited and the proportion of sickle cells in the circulating blood is reduced below 50%. This approach has been shown to be very valuable in allowing pregnant women to carry their unborn babies to term. As a pre-operative measure it has markedly reduced the perioperative morbidity and mortality associated with elective surgery in patients with sickle cell disease. On occasion it has been a very successful ploy in abruptly leading to the resolution of these variable and prolonged episodes of liver injury initially provoked by an episode of viral hepatitis but sustained by intrahepatic sickling.

## 5. ACUTE "HEPATIC" SICKLE CRISIS

Although this phenomenon has been widely accepted and frequently described there is considerable doubt as to whether or not it ever arises de novo. The early descriptions of liver disease occurring in patients with sickle cell disease dwelt on the intense intrahepatic sickling seen in autopsy specimens from patients dying with liver disease. These authors assumed that the sickling was a primary phenomenon and was indeed the cause of the observed liver damage. The same autopsy reviews noted a high prevalence of cirrhosis in patients with sickle cell disease and considered this to represent the long term consequence of recurrent episodes of spontaneous intrahepatic sickling with subsequent hepatic infarction, hepatic fibrosis and nodular regeneration.

The acute illness as described by Diggs simulates acute cholecystitis and presents with right upper quadrant pain, fever, leukocytosis and variable elevations of serum bilirubin and aminotransferase activities. It is described as being self-limited (lasting two to three weeks) and is said to occur in approximately 10% of patients admitted with painful crises. There is very little histologic data available from such patients. Nor are serologic data presented to exclude specific hepatic disorders (e.g. hepatitis A or B) as the cause for these episodes of hepatic dysfunction. The description by Kaine and Udeozo of 38 Nigerian children with "hepatic" crises highlights the difficulties in determining whether or not this occurs as a spontaneous event. All of these children were brought to medical attention because of jaundice. There were common associations such as fever and abdominal pain, but other manifestations of sickle crisis were more unusual.

TABLE 2
*Presenting complaints*

| | Percentage of patients |
|---|---|
| Jaundice | 100 |
| Fever | 60 |
| Abdominal pain | 52 |
| Anorexia | 34 |
| Bone pain | 28 |
| Cough | 26 |
| Joint pain | 16 |
| Others | 32 |

from Kaine, et al.
J Trop Ped, 1988.

The severity of the liver disease varied from minor to fulminant. In some children the liver disease persisted for 6 to 7 weeks. Only seven children were screened for HBsAg. One was positive. Five children had an associated bacterial infection (pneumonia, osteomyelitis). Biopsies were obtained in eight children and showed dilated sinusoids with numerous sickled cells. The Kupffer cells were markedly hypertrophied and contained phagocytosed red cells. There were areas of liver cell necrosis and inflammation throughout the parenchyma with accentuation of this injury in the centrilobular areas and there was a cellular infiltrate in the portal tracts. The biopsy from the child with a positive HBsAg was not distinguishable from those taken from the other children.

It is clear that most episodes of sickle cell crisis are not associated with a change in the results of standard liver function tests except for an increase in serum bilirubin associated with enhanced hemolysis. Patients who have recurrent crises tend to present with similar patterns of crisis manifestations each time. Episodes of "hepatic" crisis, however, are random events which do not "breed true". It is very unusual for someone with an "hepatic" crisis to have a history of similar previous events. Hepatic crises, therefore, might not arise spontaneously but only develop in response to local intrahepatic pathology induced by some other agency. Once present, there is no doubt it has the potential to produce prolonged and severe liver injury and may cause the patient's death.

Our own experience tends to support but cannot prove this view. Dr. Eigenbrodt reviewed the liver tissue of all patients with sickle cell disease who underwent liver biopsy or came to autopsy from January 1970 through April 1982. Thirty such patients were identified, 20 of whom were known to have evidence of liver disease at the time tissue was obtained and 10 of whom were not known to have liver disease. These 10 patients were all women with SS disease who were carried through a pregnancy with a program of transfusion therapy designed to maintain the hematocrit above 25%, and the proportion of sickle cells in the circulating blood less than 50%. Liver biopsies were obtained in these otherwise well women at the time tubal ligation was carried out in the post partum state. The charts of all patients were reviewed and the cause of the liver disease present in these patients was determined based on clinical and laboratory data.

## CLINICAL ASSESSMENT

The categories of clinical liver disease thus identified were:

1) **Acute Liver Disease.** This was defined as an icteric illness present for less than one month when the patient first sought attention at PMH. Three potential causes were identified:

   a) **Hepatitis B.** Six patients were HBsAg positive and were presumed to have had acute hepatitis B.

   b) **Post Transfusion Hepatitis.** Three patients developed their acute episode of liver disease within 6 months of a blood transfusion and were thus considered to have had non A/non B hepatitis.

   c) **? Sickle Crisis.** Five patients had no serologic or epidemiologic evidence to incriminate viral hepatitis as the cause of their disease. They were not taking any drugs with known hepatotoxic potential. By exclusion it was considered possible that they represented examples of "hepatic crisis" although there was no way to positively exclude a viral cause for their disease.

2) **Chronic Liver Disease.** Abnormal liver function tests were documented in 6 patients for at least 6 months before the biopsy was taken.

3) **Pregnant Hyper-transfused Controls.** There were 10 patients in this category. One patient was found subsequently to have had a stone in her common bile duct which required surgical intervention in the post partum period. Liver disease was not clinically evident in any of these patients at term.

The liver tissue were examined without knowledge of the patients' clinical circumstances. A histologic assessment was conducted and a diagnosis determined. The following diagnostic categories were identified:

A. **Acute hepatitis consistent with viral cause** with some sickling. (n=6)

B. **Severe sickling** with cell necrosis and inflammation. (n=4)

C. **Chronic active hepatitis** with sickling. (n=2)

D. **Multiple non-specific abnormalities.** These varied from mild abnormalities (Kupffer cell hyperplasia, hemosiderosis, occasional focal necrosis with mild inflammation and a varying degree of sickling in the sinusoids) to more pronounced disturbances (e.g. fatty change, granulomata, reticular fibrosis or generalized regeneration with again varying degrees of sickling). The biopsies of 18 patients were assigned to this non-specific category.

The following table demonstrates the similarity of clinical presentation among patients in the acute liver disease group.

## CLINICAL MANIFESTATIONS IN SICKLE LIVER DISEASE

| | FEVER | RUQ PAIN | GI $S_x$ | MALAISE | BONE PAIN | HEPATOMEGALY |
|---|---|---|---|---|---|---|
| HEPATITIS B | + | + | + | + | + | - |
| PTH | + | + | + | + | - | - |
| ? CRISIS | + | + | + | + | + | + |
| CHRONIC DISEASE | + | + | + | - | - | - |
| CONTROLS | - | - | - | - | - | - |

(+ = present in > 50% of patients)

The majority of all patients in all diagnostic groups complained of malaise, GI symptoms, fever, and right upper quadrant discomfort. Of more interest was the commonness of typical symptoms of sickle cell crisis (e.g. bone pain) in patients with acute liver disease (but not those with chronic liver disease) whether or not this was caused by acute hepatitis B or was potentially due to an hepatic sickle crisis.

The results of the liver function tests are provided in the accompanying tables.

## SICKLE LIVER DISEASE

### Bilirubin Levels (mg/dl)

| | Maximum | | Chronic | |
|---|---|---|---|---|
| | Mean | Range | Mean | Range |
| Hepatitis B | 45 | 19-68 | 2.1 | 0.2-4.5 |
| PTH | 30 | 22-37 | 2.3 | 1.5-3.5 |
| ? Crisis | 48 | 18-79 | 3.0 | 0.8-5.0 |
| Chronic Disease | 9.1 | 1.1-18 | 3.6 | 0.5-8.0 |
| Control | 3.6 | 1.7-6.3 | 2.2 | 1.0-4.0 |

The degree of jaundice, as expected, was disproportionately high in all patients with acute disease but was not different from one etiologic group to the next. Occasional patients were profoundly icteric.

## SICKLE LIVER DISEASE

### Peak AST Level (u/ml)

| | Mean | Range |
|---|---|---|
| Hepatitis B | 3130 | 856 - 7224 |
| PTH | 907 | 380 - 1630 |
| ? Crisis | 1807 | 710 - 3000 |
| Chronic Disease | 348 | 78 - 1200 |
| Control | 75 | 16 - 235 |

All but one of the patients with acute liver disease had a peak AST liver in excess of 500 u/ml. The majority of these patients had AST activities that peaked well above the 1000 u/ml. Aminotransferase levels of this magnitude are seen for the most part only in patients with viral, drug, toxin, or ischemic induced liver disease.

Serum alkaline phosphatase levels and prothrombin times were similar in all 3 groups of patients with acute liver disease. The prothrombin time was normal in all but 2 patients both of whom ultimately died of liver failure.

### LFTs IN SICKLE LIVER DISEASE

| | HEPATITIS B (n=6) | PTH (n=3) | ? CRISIS (n=5) |
|---|---|---|---|
| MAX BIL mg/dl | 19-68 | 22-37 | 18-79 |
| MAX AST u/ml | 856-7224 | 380-1630 | 710->3000 |
| MAX SAP u/ml | 220-850 | 260-800 | 229-549 |
| MAX PROTIME seconds | 13-34 | 12 | 11->60 |

### HISTOLOGIC ASSESSMENT

Review of the histological sections showed some features common to most of the patients. There was sinusoidal congestion in all but an occasional biopsy. This varied from very mild (probably representing the artifact of fixation-induced sickling) to massive with extensive parenchymal cell atrophy. In most sections there was evidence of both Kupffer cell hyperplasia and of erythrophagocytosis.

An excess of stainable iron was found in parenchymal cells, the Kuffper cells, and the portal tract macrophages. Only an occasional slide was negative for the special iron stain. The amount of iron present varied enormously but was not defined by any clinical or histologic diagnostic grouping. In no instance was iron overload per se considered to be the cause of the liver disease present.

The correlation between the diagnosis made on clinical grounds and the diagnosis rendered histologically was quite poor. This is illustrated by the following table.

**SICKLE LIVER DISEASE**

| Clinical Category | Histologic Category | | | |
|---|---|---|---|---|
| | A | B | C | D |
| Hepatitis B | 3 | 1 | 1 | 1 |
| PTH | | 2 | | 1 |
| ? Crisis | 3 | 1 | | 1 |
| Chronic Disease | | | 1 | 5 |
| Control | | | | 10 |

Three of the patients who had acute viral hepatitis B by clinical criteria had liver biopsy findings which were classically those of acute viral hepatitis. One biopsy showed massive sickling, one demonstrated the histologic features of chronic active hepatitis and in one the findings were non-specific.

Only one of the 5 biopsies from patients who might have had an "hepatic" crisis by clinical criteria showed a compatible biopsy picture. Three others showed the findings of an acute viral hepatitis and in one the lesions were considered non-specific. Two of the three patients with putative non A/non B hepatitis from recent transfusions had histologic findings of massive intrahepatic sickling.

On the other hand, 3 of the 6 patients whose diagnosis on pathologic grounds was considered to be primarily acute viral hepatitis were considered clinically to be candidates for the diagnosis of "hepatic" crisis. The other 3 did indeed have acute hepatitis B. Massive sickling as the major histologic finding was seen in one patient who on clinical grounds had acute hepatitis B and two patients who were presumed to have post-transfusion hepatitis. Only one patient had both clinical and histologic evidence to suggest that intrahepatic sickling was the primary source of the liver disease.

As a result of this experience the following conclusions seem warranted.

## CONCLUSIONS

1. From any given histologic picture the patient's clinical status cannot be determined.

2. The biopsy findings cannot be predicted from the apparent clinical diagnoses.

3. The histologic findings in patients with undoubted acute viral hepatitis cannot be distinguished from those of patients who appear to have sickle crisis alone.

One might also ask the question: Are all episodes of "hepatic" crisis provoked initally by an acute local event such as viral hepatitis?

It is clear from this study that not all acute episodes of acute viral hepatitis provoke massive hepatic sickling. It does seem though that most (if not all) of the acute episodes of liver disease occurring in patients with sickle cell disease are initiated (at least) by another identifiable disease. Intrahepatic sickling usually accompanies the primary disorder and may become the dominant lesion but it is doubtful if spontaneous intrahepatic sickling ever occurs with sufficient severity to result in overt acute liver disease.

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## CONGESTIVE HEART FAILURE

It has been recognized for many years that clinical, chemical, and histological evidence of liver damage may accompany acute and/or chronic congestive heart failure. The abnormalities characteristic of this condition have been defined and categorized as to relative frequency. Hepatic dysfunction emanates from two distinct consequences of heart failure. Some manifestations results from the increase in hepatic venous pressure which is reflected back from the high right atrial pressure. Others are related to actual parenchymal cell necrosis which occurs zonally in the centrilobular regions of the liver.

Arterial hypoxemia unless it is extreme is considered to play only a minor aggravating role in the development of what is generally agreed to be hypoxic cellular necrosis. Some dispute persists as to the relative roles played in the genesis of this lesion by:

a) peripheral venous hypertension with sinusoidal congestion and pericellular edema creating a barrier to oxygen diffusion and,

b) a diminished cardiac output.

It is well established that hepatic blood flow diminishes parri passus with decreases in cardiac output such that the liver receives a rather fixed percentage (approx. 20%) of the cardiac output. The liver compensates for a decrease in blood flow (and hence a decrease in oxygen delivery) by increasing the amount of oxygen extracted from the blood as it flows across the sinusoidal bed. If the hepatic blood flow drops below a certain critical level, however, this compensatory mechanism becomes inadequate. There is no sense of rationing by the hepatic cells. The cells first perfused by blood (the periportal cells) take what they need. The cells last to be perfused (i.e. the centrilobular cells) are the ones likely to receive blood with insufficient oxygen to meet their metabolic needs. The end result then is a zonal area of cell necrosis whose extent is determined principally by the degree to which cardiac output is impaired and is aggravated by the degree to which hypoxemia is present.

The increase in intrasinusoidal pressure influences the movement of fluid between the vascular compartment and the extravascular extracellular space. Sinusoids have discontinuous lining membranes which are marked histologically by the presence of large pores. These pores do not permit the passage of circulating cells, but pose no barrier to the movement of proteins. This makes sense teleologically in so far as the liver is involved in:

a) the synthesis of export proteins (e.g. albumin, coagulation factors) which must reach the blood and

b) the detoxification and disposition of numerous molecules which are protein bound and which must have access to the parenchymal cells from the blood.

Free movement of protein molecules across the sinusoidal membrane leads to the absence of any osmotic forces of note being generated across the sinusoids. The only Starling force operating in the liver lobules is hydrostatic pressure. The intrasinusoidal pressure is governed by the pressure in the hepatic veins which

is governed by the pressure in the right atrium. When the sinusoidal pressure rises in patients with congestive heart failure fluid leaves the sinusoid and moves into the interstitium of the liver. This fluid (in effect plasma) is rich in protein because there is no barrier posed by the sinusoidal membrane to restrict protein movement. This increase in interstitial fluid results in a marked increase in hepatic lymph flow. If the capacity of the hepatic lymph channels to remove interstitial fluid is exceeded by the rate of fluid formation fluid accumulates in the hepatic interstitium and causes hepatomegaly. Some of this fluid seeps directly across the capsule of the liver and collects in the peritoneal cavity as ascites. The process is one of transudation, but the protein content of the fluid is high because the fluid is derived principally from the discontinuous membranes of the sinusoidal bed. Fluid (e.g. peripheral edema) generated across capillaries which (by design) are very effective in restricting protein movement is fluid that is very low in protein concentration.

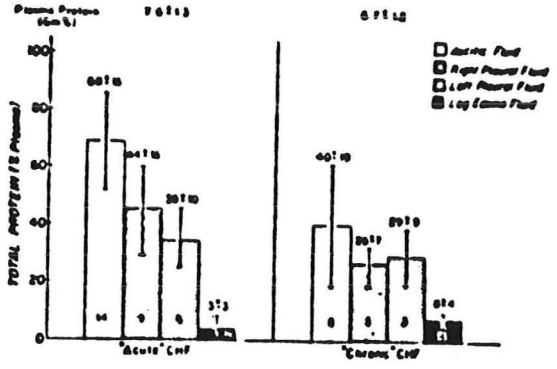

**Figure 3**

*Total protein in ascitic, pleural, and peripheral edema fluid in acute and chronic congestive heart failure (CHF). Numbers on the bottom of each bar represent number of patients studied.*

Witte figure
Circ. 40:623, 1969

These studies by Witte, et al. in patients with <u>acute</u> congestive heart failure demonstrate the wide difference between protein concentrations of ascitic fluid (mean approx. 5g/dl) and peripheral edema fluid (mean approx. 0.2g/dl). Patients who were considered to be in chronic congestive heart failure had a lower (but still high) protein concentration in their ascitic fluid (mean approx. 2.7g/dl). Two phenomena contribute to this change in ascitic protein concentration as heart failure becomes chronic. If the hepatic sinusoids are subjected to an increased hydrostatic pressure for a period of time an anatomical change occurs in their structure. This modification is called "capillarisation" and results in the sinusoid assuming some of the structural and therefore some of the functional attributes of capillaries. The large pores disappear and a more continuous membrane is effected. Some restriction of protein movement is then possible so that the protein concentration of the interstitial fluid,

hepatic lymph, and ultimately the ascites generated from the liver itself becomes somewhat lower.

The second factor contributing to the more dilute ascitic fluid in chronic CHF is the presence of portal hypertension which develops secondarily to the high sinusoidal pressure. Portal hypertension contributes to the generation of ascitic fluid by influencing hydrostatic pressure in the splanchnic bed. This fluid is formed by transudation across capillaries and has therefore a very low protein concentration. The fluid derived from the splanchnic bed accumulates as ascites and dilutes the higher protein fluid derived from the hepatic compartment. The final protein concentration measured in the peritoneal fluid is a function of the relative contributions made by each of the two pools of fluid.

When there are areas of hemorrhagic ischemic necrosis near the capsule of the liver it is not unusual for the ascitic fluid to contain a number of red blood cells. This blood may evoke a leukocyte response by its irritative effect on the peritoneum. One may see, therefore, a "hemorrhagic" fluid with an increased number of white cells and a high protein concentration in a patient with heart failure. These are the characteristics of an exudative ascites. It is very important that the compatibility of such findings with the diagnosis of heart failure be recognized so that high risk procedures are not initiated to exclude other diagnostic possibilities in these sick and vulnerable patients.

## CLINICAL MANIFESTATIONS

### SYMPTOMS:

The majority of patients in congestive heart failure have no hepatic symptoms. Some patients complain of right upper quadrant discomfort due to stretching of the liver capsule. This is more likely to occur during the acute stage of heart failure or when an acute exacerbation of chronic congestion occurs. This discomfort is sometimes accompanied by gastrointestinal symptoms such as anorexia, nausea, and even vomiting. Any change in cerebral function noted in such patients is most likely to be the result of hypoxia. It would be very rare for hepatic encephalopathy to be the cause of confusion in this setting although blood ammonia levels may rise. Alterations in mental status in patients with severe heart failure may at times be the result of hypoglycemia resulting from the associated liver injury coupled with lack of oral intake of glucose.

### SIGNS:

Hepatomegaly is demonstrable in most patients with right heart failure. Diffuse tenderness in the right upper quadrant to palpation or to punch percussion is also common. Palpable splenomegaly is a surprisingly frequent finding in these patients with and even without the superimposition of cardiac cirrhosis. The frequency with which ascites is reported in patients with CHF is very variable. Most series describe an incidence of approximately 25% but this figure probably reflects only those patients with very evident abdominal distension. Lesser degrees of ascites may be much more common.

## LABORATORY FINDINGS

Increased levels of serum bilirubin occur quite frequently in patients with CHF but the levels are usually less than 3.0 mg/dl and most of the increase is in the unconjugated fraction. In occasional patients the serum bilirubin level will be much higher, increases in both conjugated and unconjugated moieties are present and the patient will be noticeably jaundiced. This is most likely to occur in instances of sudden severe failure or if there is an increase in the production of bilirubin (hemolysis, transfusion) or interference with its other means of excretion (e.g. renal insufficiency).

The activities of the aminotransferases (AST, ALT) in serum are elevated in perhaps a third of patients with heart failure. Usually these increases are quite trivial. When the onset of heart failure is abrupt the resultant hepatic hypoxia may cause the destruction of a large number of parenchymal cells all at the same time. The resultant rise in the aminotransferase activities may be dramatic and levels in excess of 1000 u/ml may be recorded. These levels don't persist, however, because the injury to the parenchymal cells is an "all or nothing" event and cells are either destroyed or they are not. The enzyme circulating in the blood stream has a half life of 8 to 12 hours and the serum level consequently falls rapidly towards normal when no continuing cell injury occurs to sustain the activity in the circulation. This particular hemodynamic situation is also likely to evoke frank jaundice because of the extent of the associated hepatic cell destruction and the clinical picture may easily be mistaken for an episode of acute viral or drug-induced hepatitis.

The serum alkaline phosphatase may be normal, somewhat elevated, or on rare occasion quite markedly elevated in patients with CHF. No particular significance should be attached to the level of this enzyme in these patients.

The prothrombin tissue is perhaps the liver test most often found to be abnormal in patients with CHF. The cells in different zones of the hepatic lobule are preferentially engaged in different hepatic functions. The centrilobular cells are particularly concerned with oxidative metabolism via the P450 system and with the synthesis of coagulation proteins. Injury to these cells then is likely to produce a prolongation of the prothrombin tissue (not correctable with Vit. K) that seems to be disproportionate to the other evidences of hepatic cell injury. This seldom proves to be of any clinical significance but such patients are often particularly sensitive to the effects of vitamin K inhibiting anticoagulants.

Plasma proteins are usually normal in these patients unless the condition is chronic and inanition contributes to a decrease in serum levels of albumin.

## PATHOLOGY

Macroscopically the liver is enlarged, dark, and mottled in appearance. The cut surface shows alternating areas that are light and dark. This has been dubbed the "nutmeg" liver. Areas of frank hemorrhage may also be noted where extensive infarction has occurred.

The histological lesions are confined to the centrilobular zones of the liver. Sinusoidal dilatation and congestion are accompanied by progressive atrophy of

the cells in the parenchymal cords as they approach the central veins. The cells around the central veins may be lost and replaced by areas of hemorrhage and collapse. The extent of this hemorrhagic necrosis varies from patient to patient and may be extensive enough for linkage to occur between these central zones of necrosis. Even when these central-central "bridges" are established, however, there is remarkably little inflammatory response to the cell death. With time fibrous tissue is deposited in these areas of necrotic collapse and the picture of cardiac cirrhosis ensues. the parenchymal cells in the zones around the portal triads remain quite normal although surrounded by fibrous bands. This pattern of reverse lobulation is not strictly a cirrhosis (defined as bands of fibrosis and nodules of regenerating liver cells) but the term cardiac cirrhosis is well entrenched and serves the purpose of communication quite well.

## PROGNOSIS AND TREATMENT

The treatment and prognosis of the liver abnormalities in patients with CHF is aimed at and determined by the underlying heart disease. The importance of recognizing that there are hepatic sequelae of heart failure lies in the avoidance of unnecessary tests and procedures that might otherwise be performed to elucidate the nature of these manifestations.

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## BUDD-CHIARI SYNDROME

Thrombosis of the hepatic venous outflow tract may occur anywhere from the central veins in the hepatic lobules to the right atrium. Irrespective of the site of the occlusion, when the venous drainage of the liver is compromised sufficiently there ensues a series of hepatic sequelae, the clinical manifestations of which depend on the degree of the obstruction and the rapidity of its development. Thus, if the process is a gradual one, a collateral circulation may evolve sufficiently to maintain the patient in apparent normal health for years. On the other hand, sudden and complete cessation of hepatic venous flow will result almost immediately in rather dramatic clinical manifestations and usually causes the patient's death within a matter of weeks.

Lesions which are restricted to the hepatic veins or their tributaries give rise to symptoms and signs referable to hepatic congestion (viz. abdominal pain, hepatomegaly, ascites, icterus and encephalopathy), and to portal hypertension (prominent abdominal veins, splenomegaly, varices and hematemesis). If the lesion also involves the inferior vena cava, or is confined to the cava above the ostia of the hepatic veins, signs of inferior vena caval obstruction (pedal and trunal edema, upward draining abdominal veins, proteinuria) will be superimposed on the hepatic manifestations.

### ETIOLOGY

No apparent cause for the hepatic vein thrombosis is evident in approximately 30% of the reported cases of the Budd-Chiari syndrome. Whether the thrombosis is a primary event or one secondary to a preexisting endophlebitis has been a point of dispute for many years. The available evidence supports the former concept although in most instances the factor precipitating thrombus formation remains undetermined. The vena caval ostia of the hepatic veins are the sites most commonly occluded in this idiopathic group of patients. The thrombosis extends to a variable extent along the hepatic vein branches and, in about half of the patients, there is coexistent involvement of the inferior vena cava.

Multiple thrombosis confined to the central and sublobular veins with sparing of the larger vessels are much less common. The initial description of this phenomenon was in patients who had ingested pyrolizidine alkaloids derived from plants such as Senecio (ragwort). The resultant syndrome which has been termed veno-occlusive disease of the liver was reported mainly from the West Indies and South Africa where there is widespread consumption of bush teas (on the one hand) and flour (on the other) which have been contaminated by these alkaloids. More recently, reports have been published describing the occurrence of veno-occlusive disease in renal transplant recipients. The suggestion of a drug-induced etiology (i.e. azathioprine) has been put forward. It is not clear that the lesions so described are indeed different from the lesions described by others as representing peliosis hepatis in transplant recipients. It is probable that the toxins and drugs initiate an endophlebitis of the small hepatic veins leading to secondary thrombosis.

Obstructing lesions restricted to the suprahepatic part of the inferior vena cava have been reported principally from Japan. A congenital origin has been ascribed

to the thin membranous webs which have been found in the vena cava of some of these patients.

When hepatic vein thrombosis is associated with an underlying disease the disorder most frequently found is polycythemia rubra vera. Hypernephroma with extension of the tumor and associated thrombus formation from the renal veins into the inferior vena cava is the next most common underlying disease. Primary or metastatic tumors of the liver as well as other local intrahepatic lesions such as hydatid cysts or abscesses may also be complicated by hepatic vein thrombosis. Blunt abdominal trauma, congestive heart failure, ulcerative colitis, and other hypercoagulable states such as paroxysmal nocturnal hemoglobinuria, sickle cell disease, and chronic myeloid leukemia have all been implicated occasionally as precipitating events for this syndrome. In recent years a large number of cases have been associated with pregnancy or ascribed to the use of oral contraceptive agents. Indeed, this association accounts for the majority of cases of Budd-Chiari syndrome described in the past 20 years.

## CLINICAL MANIFESTATIONS

The idiopathic process is found equally in both sexes. It has been described in children and in the very old, but more than half of the patients are between 20 and 40 years of age. Partial thrombosis of the hepatic venous bed is not an infrequent finding at autopsy in patients who, during life, showed none of the manifestations of the Budd-Chiari syndrome. More complete interference with hepatic venous drainage does, however, result in a reasonably distinct clinical syndrome the most constant feature of which is gross ascites.

Abdominal pain, the consequence of the sudden distension of Glisson's capsule by the rapid enlargement of the congested liver is often the first symptom noted in acute and complete cases. Anorexia, nausea, vomiting, and even diarrhea may be present initially and are provoked by acute gastric and intestinal congestion. The ascites is rapidly progressive and soon becomes tense. Symptoms associated with marked ascites may then be manifest and the patient may complain of early satiety, dyspepsia and heartburn from reflux esophagitis, back ache, and generalized abdominal discomfort. As time passes, the patient may become quite cachectic and manifestations of markedly deranged hepatic function may appear (coagulopathy, jaundice, encephalopathy).

In other patients the thrombotic process is less complete and the clinical manifestations are more gradual and less dramatic. In these instances the patient will usually complain of the onset of abdominal distension which slowly increases until ultimately the patient begins to suffer from the mechanical consequences of a large volume of ascites. The clinical picture is not very different in these patients from that seen in many patients with cirrhosis who first come to attention because of the new onset of ascites. Patients with Budd-Chiari syndrome do not usually have evidence of peripheral edema, however, unless there is involvement of the inferior vena cava.

On physical exam hepatomegaly is almost always present although it is often masked by the presence of tense ascites. Splenomegaly is detected clinically in only a third of patients, but prominent collateral veins in the abdominal wall are seen more frequently. If inferior vena caval obstruction coexists pedal and

truncal edema will be present and the blood in all the abdominal wall collateral veins will drain upwards toward the superior vena cava. Proteinuria and evidence of renal dysfunction may be present if renal congestion is marked.

## LABORATORY FINDINGS

The results of liver function tests show a pattern which reflects non-specific hepatocellular dysfunction. Deep jaundice is found rarely and then only in the terminal stages of the disease. The serum bilirubin in some patients may remain entirely normal throughout the illness. Serum alkaline phosphatase activity is raised sometimes to very high levels, but the aminotransferase activities are usually less than 200 units. The prothrombin time is often quite prolonged and resistant to therapy with vitamin K. This often disproportionate effect on the prothrombin time reflects the predominantly centrilobular injury seen in these patients. The serum albumin may be slightly depressed but early on, at least, is generally well above 3.0 gm/dl.

The ascitic fluid is characteristically a high protein fluid even though it is formed by transudation. It is generated in basically the same manner that the high protein transudative ascites forms in congestive heart failure. The presence of red cells (from areas of hemorrhagic necrosis) and "reactive" white cells once again may render the differential diagnosis difficult.

Confirmation of the diagnosis of Budd-Chiari syndrome, in vivo, has best been achieved by a combination of liver biopsy (unless precluded by coagulopathy or marked ascites) and hepatic venous angiography. Recent dramatic improvements in the capacity to define intravascular detail by non-invasive radiographic techniques have provided powerful means to evaluate patients for this disorder and may ultimately render the previously definitive studies unnecessary.

The caudate lobe has its own particular venous communication with the vena cava. It is not unusual for these veins to remain uninvolved when the other hepatic veins become obstructed. This leads to hypertrophy of the caudate lobe as the other lobes of the liver become congested and atrophic. This may be visualized on a radionuclide liver spleen scan as a central "hot" spot. The hypertrophied caudate lobe also may interfere substantially with access to the vena cava during attempts to create a side to side portacaval shunt. When there is obstruction to the suprahepatic vena cava the caudate lobe is equally involved in the disease process and the "hot" spot is not found.

Histologically, the liver shows dilatation and congestion of the central veins and sinusoids with atrophy and necrosis of the centrilobular parenchymal cells. In severe acute cases this necrosis may be hemorrhagic and so extensive that only a rim of cells in the periportal zones remain viable. If the patient survives and the process becomes subacute, fibrous tissue forms and replaces the central necrotic areas and the surviving peripheral cells regenerate. Eventually, in chronic cases, a picture akin to cardiac cirrhosis is found. The central fibrous bands link up with each other isolating rounded masses of regenerating cells in the centers of which one sees portal tracts. Actual thrombi in varying stages of organization may be visualized in the larger tributaries of the hepatic vein.

## COMPLICATIONS AND PROGNOSIS

Untreated, the Budd-Chiari syndrome carries with it an extremely poor prognosis. Few patients survive more than 6 months beyond the onset of the acute lesion. The majority of patients die in hepatic coma after a short and severe illness in which electrolyte disturbances, peripheral circulatory failure, gastrointestinal hemorrhage and intercurrent infections may all be prominent features. Should the patient survive the acute episode, death from the complications of portal hypertension frequently ensues within a few months. An associated thrombosis of the portal vein is found in 20% of patients with Budd-Chiari syndrome, presumably because of stagnant flow in the portal system. The extension of this process to the mesenteric veins may result in intestinal infarction. Variceal hemorrhage is a constant threat and is poorly tolerated by these debilitated patients. Nonetheless, an occasional patient will survive for years after the onset of the condition. Presumably such patients have developed a collateral circulation extensive enough to partially decompress the portal bed. Some recanalization of the hepatic veins may also have occurred. Acute rethrombosis of these veins may precipitate the return of the complete syndrome in these people and variceal hemorrhage remains an ever-present threat to their lives.

## TREATMENT

If the disorder is recognized when the thrombosis is very acute (i.e. within one week) thrombolytic therapy with streptokinase or plasminogen activator is worthwhile. Use of anticoagulants to prevent progression of the thrombus is indicated in the acute setting despite the potential for hemorrhagic consequences. Other conservative measures are aimed at dealing with the consequences of the syndrome (e.g. the use of salt restriction and diuretics) and their success is determined principally by the completeness of the obstruction to hepatic venous outflow. It is not unusual for the ascites to be refractory to such measures.

The prognosis of this condition is so poor that an aggressive surgical approach to its management increasingly has been urged. The surgical options include:

1) side to side portacaval shunt
2) meso-atrial shunt
3) percutaneous transluminal angioplasty ($\pm$ laser assist)
4) hepatic transplantation
5) LeVeen or Denver shunt

The option chosen depends on the particular circumstances present in a given patient.

If there is obstruction of the inferior vena cava the current approach would be to attempt to cut through the obstruction transluminally and then to dilate the area of obstruction with a balloon device. The advent of laser technology has facilitated our capacity to do this although the risk of vena caval perforation remains real. Failing this, a surgical attempt to bypass the obstruction with a shunt connecting the portal system to the right atrium might be tried.

If the lesion is confined to the hepatic veins a side-to-side portacaval shunt is the procedure of choice. This shunt promotes reversal of flow in the portal vein in the liver and relieves sinusoidal pressure. Thus it prevents further cell injury and ascitic fluid formation. At the same time it allows decompression of the portal veins and deals with potential problems associated with varices. When possible, this proves to be a very effective form of therapy and is associated with prolonged life and good health in the majority of patients who survive the acute problems associated with such surgery. When technical problems prevent its accomplishment a similar hemodynamic effect can be achieved by an interposition meso-caval shunt using an autologous vein.

In patients with severe acute liver dysfunction or in a patient whose clinical condition is worsening progressively hepatic transplantation offers an alternative to otherwise certain death. Some success has been described using this approach. Post-operative anticoagulation therapy appears to be necessary to avoid recurrence of the venous thrombosis post-operatively.

When these surgical options are precluded by an associated obliteration of the portal venous system, control of otherwise intractable ascites can be achieved by the placement of a peritoneovenous shunt. To the extent that massive ascites is directly responsible for the deaths of patients with Budd-Chiari syndrome this measure is useful in improving the morbidity and mortality of the condition.

Complications such as hemorrhage, infection and hepatic coma require their own specific therapeutic responses and when the thrombosis is secondary to an underlying process appropriate therapy must be directed to the primary condition.

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# PELIOSIS HEPATIS

**Definition:** **This is a rare disorder which is characterized histologically by the presence of multiple blood filled lacunar spaces throughout the liver.**

## PATHOLOGY

The earliest manifestation one sees is a non-zonal dilatation and congestion of sinusoids with an associated atrophy of the parenchymal cell cords. The hepatic cells undergo necrosis and disappear leaving microscopic unlined cystic spaces filled with clotted blood. These lesions increase in size (as more cells are lost) and become visible to the naked eye. They are usually quite small (2 to 3 mm in diameter) but on occasion they may attain a diameter of as much as 6 cm. If this process is interrupted the lesions usually are not reversible. Indeed fibrous tissue is deposited throughout the congested areas resulting in a chronic obliterative process involving the sinusoids. In areas where parenchymal cells survive this fibrous tissue is distributed in a reticular pattern. Similar peliotic lesions have been noted in the spleen, lymph nodes, and even the bone marrow on occasion.

## ASSOCIATED CONDITIONS

Peliosis was described initially in patients suffering from chronic wasting disorders (particularly tuberculosis and malignancies). More recently the lesion has been more commonly associated with drug therapy. Any one of a number of $C^{17}$ substituted steroids; methyltestosterone, oxymetholone, fluoxymesterone, norethandrolone, testosterone propionate as well as oral contraceptive agents have been incriminated as causes of peliosis hepatis with or without an associated hepatoma or hepatic adenoma.

Azathioprine (Imuran) has been proposed as the agent responsible for this lesion in patients who have received a renal transplant. The occurrence of peliosis in the post-transplant setting does seem to correlate in a dose related manner with the use of this drug. Most commonly it is seen accompanying another predictable dose-related hepatic complication of azathioprine namely cholestasis.

The most recently described association is that between peliosis and patients dying with AIDS. Whether or not this is a specific association with the HIV virus or whether it represents another example of the occurrence of peliosis in chronic wasting disorders has not yet been clarified.

## PATHOGENESIS

There is little information that addresses the means by which peliosis hepatis arises. Nor is it clear what chronic wasting disorders, $C^{17}$ substituted steroids, azathioprine and the HIV virus have in common that would favor their creating these remarkable lesions. Three hypotheses are current:

1. Hepatocellular necrosis with disruption of the reticulin framework of the sinusoid leads to cystic dilatation of the sinusoids, coalescence of which results in the larger lesions. This hypothesis is almost certainly invalid. The cell necrosis one sees is much more likely to be the consequence of the peliosis than its cause. Surrounding cell plates usually show marked atrophy, the consequence of the dilated, congested sinusoids. On the other hand, none of the usual causes of hepatic cell necrosis are associated with these peliotic lesions even when the necrosis is confluent and extensive.

2. Obstruction of outflow of blood. The lesions seen in patients with Budd-Chiari syndrome or veno-occlusive disease of the liver can look the same as the early lesions present in patients with peliosis. The distinction may rest on the pattern of distribution of the lesions. Thus in Budd-Chiari and VOD the lesions are zonal and occur around the central veins. In peliosis they are randomly distributed through the lobule and have no zonal pattern. There is no questions that there are areas of the liver in peliosis where obstruction to blood flow exists. The sinusoids are dilated and filled with coagulated blood. This interference with flow accounts for the progressive atrophy and ultimate loss of the associated parenchymal cells. The question is whether this obstruction is caused by a primary intrasinusoidal thrombosis or whether there is an underlying precipitant for the coagulation of blood. Intuition argues strongly in favor of a local precipitant. Peliosis is not a feature of diseases in which there is a primary hypercoaguable state.

3. There is a direct injury to the sinusoidal living cells. In patients with peliosis the endothelial cells lining the sinusoid show ultrastructural evidence of degeneration with edema, cytoplasmic fragmentation and fatty change. Leakage of red blood cells through this damaged sinusoidal barrier into the space of Disse provokes ultrastructural changes in the exposed hepatocytes (flattening of microvilli and extensive blebbing). The presence of blood in the space of Disse also seems to be the trigger initiating the deposition of collagen (produced presumably by the ITO cells) throughout the sinusoidal network. Similar injury to the endothelial lining of the terminal branches of the hepatic veins (central veins) appears to account for the co-occurrence of veno-occlusive disease and peliosis in the same patients. The site of major endothelial injury determines the pathologic pattern of vascular occlusion and determine whether a given patient develops VOD, peliosis hepatis or both. This hypothesis of endothelial injury induced by a variety of different agents is the most satisfactory explanation for the occurrence of peliosis in such otherwise unrelated clinical states.

## CLINICAL MANIFESTATIONS

**ACUTE** - Many episodes of peliosis are silent clinically and are identified only at autopsy. In others the clinical manifestations that draw attention to the presence of liver disease are not caused directly by peliosis, but by other hepatotoxic consequences of the inciting agent (e.g. cholestasis in patients receiving azathioprine). In patients with chronic wasting disorders the finding of hepatomegaly with non-specific abnormalities in the results of the liver function tests is usually interpreted as evidence of hepatic involvement with the underlying process. At times, however, these findings represent the deveopment of widespread peliotic changes. In certain clinical situations (e.g.

recipients of renal transplantation, patients receiving androgen therapy, and patients being followed with AIDS) an aggressive biopsy approach to the investigation of abnormal LFTs in asymptomatic patients leads to the identification of this lesion in its early form. In its later, more developed form, this is a serious liver disease. Some patients present with spontaneous rupture of the liver and hemoperitoneum. At other times the lesions are so extensive that the patient develops signs of liver failure with jaundice, coagulopathy, ascites, and encephalopathy.

Even when the cause can be identified and interdicted peliosis is likely to progress to a chronic liver injury with widespread sinusoidal fibrosis leading to portal hypertension, varices and all the long-term clinical consequences of this state.

## PROGNOSIS AND TREATMENT

Only a rare case report has identified resolution of established peliosis. The early manifestations of sinusoidal dilatation seem to be completely reversible if the specific cause can be identified and dealt with specifically. More extensive lesions progress commonly to a chronic state with substantial intrahepatic fibrosis. Some patients die directly from this lesion but it is difficult to measure this in a proportional way because of the vagaries of diagnosis and cause. It is a sufficiently serious disorder to warrant the future avoidance of any drug known to provoke it. Otherwise the management is focused on treating any underlying cause and dealing with the hepatic consequences of the lesion as they occur.

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