

Cirrhosis: What Is It?*

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"For the King of Babylon stood at the parting of the way, at the head of the two ways, to use divination: he made his arrows bright, he consulted with images, he looked in the liver." Ezekiel 21. The liver has been looked upon by primitive man as the probable source of health, disease and even of evil spirits, and in 304 B.C. Erasistratus recognized that there was an association between ascites and liver disease. In 1689 John Browne described it as hardening of the liver, and Bailly noted its relation to alcohol in 1793. Then, in 1819, Laennec called it cirrhosis after the Greek word *kiros*, meaning orange or yellow. Of interest, I believe, is a picture found in *Life* magazine about ten years ago. It is of a tombstone dated 1790 in a New Hampshire graveyard, the tombstone of a man from whose peritoneal cavity was drawn 2,385 pounds of water. Unquestionably he had cirrhosis.

Definition of Cirrhosis

A proper definition of cirrhosis is difficult, but for this discussion I think the following probably serves our purpose: It is a chronic liver disease characterized by destruction of cells, by the formation of new tissue—particularly connective—and by diffuse regeneration. No effort will be made to offer a classification, because one cannot be found which satisfies the criteria we would like to discuss.

* Presented at the Thirty-Ninth Annual McGuire Lecture Series, November 9-10, 1967, Medical College of Virginia, Richmond.

Distribution of Cirrhosis

I would now like to talk about the extent and the implications of the disease itself. The first thing I think we ought to note is that cirrhosis is global—very widespread. About a third of a million people die every year from cirrhosis of the liver; it is the eighth cause of death, and in the age group from 45 to 64, it is surpassed only by cardiovascular and neoplastic disease. It has a very interesting distribution. For instance, in France there are 26 deaths per hundred thousand population; but in England, just across the Channel, there are only two per hundred thousand. In Virginia there are 7.7 deaths per hundred thousand; in New York there are 19. We reviewed the vital statistics of Virginia for five years, 1960-1964, and there were 1,545 deaths, about equally divided between whites and non-whites, with males predominating, and with the average age being from 48 to 50. The records at MCV from 1960-1963 showed 94 cases diagnosed as cirrhosis, but could confirm only 44.

In reviewing the problem of cirrhosis in any area, one is impressed with its probable association with alcohol. By extrapolation, it is accurate to state that more than 50% of cases of cirrhosis are associated with excessive consumption of alcohol. In the Virginia Vital Statistics 33% of the death certificates indicated that alcohol was a probable factor. The Mayo Clinic report of 1950 on a five-year study indicated there was an alcoholic history in 64% of their patients. In Los Angeles in 1953, of 16,000

autopsies there were 782 cases of cirrhosis, and 78% of these were reported as heavy drinkers. A report from Minneapolis over 20 years ago reported that only 25% of their cirrhotics were associated with alcohol, but I call your attention to the fact that there were only 100 cases studied. It is important to consider that only one alcoholic in 12 develops cirrhosis. What happens to the other 11? Why do they not develop cirrhosis? At this time the answer is not available.

Etiology of Cirrhosis

Actually this chronic liver disease probably starts as an acute insult to the liver, to the hepatocyte itself, and to the mesenchymal cells; and then a reaction develops, probably associated with ischemia. The pathological states that are most responsible for this injury are steatosis, necrosis, cholestasis, and hypoxia. In chronic liver disease these processes are perpetuated by persistence of an original offender such as piecemeal necrosis, which is probably the most important factor in the production of cirrhosis. In the proximity of these dead cells, there are immunoglobulin-containing cells—mesenchymal cells—which may assist in the perpetuation of this reaction. A hypersensitivity reaction may be an important factor in the continuance of the inflammatory reaction, but no circulating antibodies to the hepatocyte have been demonstrated, although antibodies to nuclear DNA, as well as to proliferating bile ducts, have been demonstrated. Disturbances in the hepatic circulation must be an important factor in the perpetuation of cirrhosis. These may be most profound. The most striking change, which can be demonstrated clearly by utilizing injection techniques, consists of marked distortion of the hepatic vasculature with pronounced dis-

turbance of the venous outflow tract and post-sinusoidal obstruction.

Hepatitis

There are certain clinical disorders that may be etiological factors in liver disease. Let us consider some of these. How big a factor is hepatitis? It is very difficult to document that a patient with primary viral hepatitis develops cirrhosis. He probably does, but actually one has to have biopsy studies over a period of time to prove this. The same thing may be said about ethanol, malnutrition, and others. Schaefer et al., in March of 1967, reported on five individuals with viral hepatitis on whom they performed punch biopsies; these individuals presented a characteristic picture of acute hepatitis with necrosis, inflammation, distortion, and many different types of cells. In biopsies taken some months after the onset, they found fairly normal liver cells without radial pattern and widened scarring with many lymphoid cells, which is a characteristic picture of post-necrotic cirrhosis. In this series, quiescent cirrhosis was found

in three of these individuals at the end of 18 months, and all five probably had viral hepatitis. There are now other histological reports available showing progression from viral hepatitis to definite cirrhosis. However, Franken et al. (1967) reexamined 154 patients some years after they had had clinical hepatitis. Thirty-three showed some abnormal biochemical changes, but only three were found to have cirrhosis, and they were alcoholics.

Malnutrition

What is the role of malnutrition? Malnutrition's role is not clearly understood. It is thought now that it plays a much smaller role than formerly believed (Jolliffe and Jellinek, 1941). There are few nutritional states in which cirrhosis is common; one of these is chronic ulcerative colitis, in which liver pathology occurs and cirrhosis may develop (Palmer et al., 1964). There are other nutritional disorders in which people do not develop cirrhosis. For instance, in the patient with kwashiorkor, a disease caused by protein deficiency, why is it that the patient does not

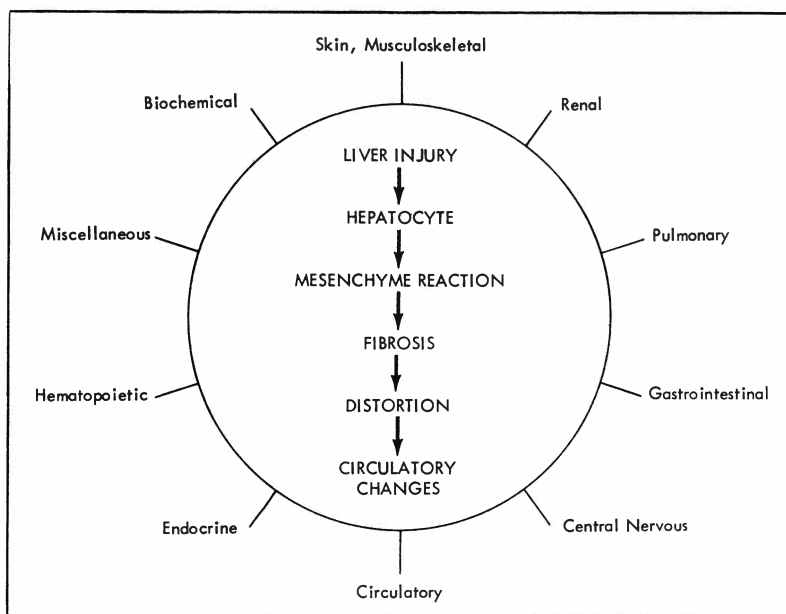


Fig. 1—Liver pathology and organ systems affected by cirrhosis.

develop cirrhosis (Scrimshaw et al., 1959)? A marked fatty liver is very common in this disorder, but it never develops cirrhosis. It is not known why, but it is clear that some fatty livers may be followed by typical "nutritional" cirrhosis, whereas others may not.

Stasis

Stasis, especially that caused by extrahepatic obstruction resulting from benign disorders such as common duct stones, causes cholangitis. This, in turn, may result in cirrhosis of the biliary type, but biliary cirrhosis may be found in the absence of extrabiliary obstruction.

Alcohol

Now what about alcohol? What does alcohol do to the liver? Does it produce a toxic or a metabolic effect? Alcohol can produce a definite direct effect on the hepatic parenchyma. It is not necessary, also, to have malnutrition or the lack of any substance, for alcohol per se is toxic to liver cells. Alcohol may cause a type of hepatitis with necrosis, inflammation, cholestasis, deposition of hyalin; and all these pathological abnormalities

may be factors that result in cirrhosis. The steatosis associated with alcoholism may predispose the liver to cirrhosis; at least fatty changes often precede the deposition of fibrous tissue. Does steatosis really cause cirrhosis, and, if so, how does it do it? The work of Leevy (1962) suggests that the fatty liver seen in alcoholics often progresses to cirrhosis, and fat per se may be an important etiologic factor in the production of cirrhosis. Hartroft and Ridout (1954) are in agreement with this view. However, some authors, such as Popper, Szanto, and Elias (1955), doubt the role of steatosis as an etiologic agent in cirrhosis but feel strongly that the necrosis of cells produced by alcohol initiates the changes which lead to cirrhosis.

Drugs

While drugs and chemical agents frequently cause liver injury and even death, their use seldom ends in cirrhosis. This is difficult to explain, because the original injury may be indistinguishable from viral hepatitis.

Pathophysiological Disturbances

When cirrhosis occurs, there are multi-system pathophysiological disturbances, which at times are very pronounced. We will discuss a few of the important extrahepatic changes occurring in individuals with cirrhosis. In Figure 1 the chief hepatic alterations are listed within the circle; the organ systems which may be functionally and structurally affected by the liver pathology are indicated outside the circle.

Changes in skin and musculoskeletal system

First, let us consider the skin and musculoskeletal system (Table 1). Beginning with the fingers, there is often clubbing of the nails, the so-called Terry nails or the blue nails of Wilson's disease (Kleeberg, 1954; Terry, 1954; Morey,

1955). There is often marked muscle wasting and the characteristic alopecia, as well as Dupuytren's contracture, which Wolfe, Summerhill, and Davidson (1956) state occurs in two-thirds of the people with cirrhosis but, in our experience, is not seen as frequently. Even though Hijams van den Bergh in 1901 described pulmonary osteoarthropathy in a patient with cirrhosis and cyanosis, little emphasis has been placed on it. Recently, however, we have seen several such patients, and each showed low arterial oxygen saturation, which was first reported by Snell (1935). Hansoti and Shah in 1966 reported that one out of seven cases of cirrhosis seen by them in India showed osteoarthropathy. Figure 2 shows a clear x-ray picture of subperiosteal thickening of the tibia characteristic of osteoarthropathy in an individual who has severe cirrhosis. Such osteal changes may be seen quite frequently, if radiological examination of the bones is performed on cirrhotics.

The spider nevus, which is like a coiled end artery raised on the skin with a central pulsating hub from which many divisions of the vessels divide, is actually a vein-like vessel but contains arterial blood. There may be a pressure ranging from 60 to 100 mm Hg in these "spiders." According to Bean (1945), "spiders" can be seen in about 60% of cirrhotics. Why do these angiomas occur in portions of the body supplied by the superior caval vessels? Occasionally they occur in other areas such as the legs, but very rarely, and almost as rarely on the forearms or hands.

Changes in circulatory system

The cardiovascular changes are among the most striking seen in cirrhosis. Some of the more common are listed below.

1. Gross distortion of hepatic vasculature.
2. Portal hypertension.

TABLE 1

Changes in Skin and Musculoskeletal System

Icterus
Pellagra-Like Changes
Palmar Erythema
Nails: Flat. Terry. Bluish.
Muscle Wasting
Alopecia
Xanthomata
Pruritis
Dupuytren's Contracture
Osteoarthropathy
Dilated Veins
Spider Nevi

3. Venous anastomoses.
4. Multiple A-V fistulae.
5. Tachycardia.
6. Increased aortic blood flow.
7. Low arterial oxygen saturation.
8. Increased cardiac output.
9. Short circulation time.
10. Low peripheral vascular resistance.
11. Reduced arterial hypertension with varices.

A hyperdynamic cardiovascular system is manifested by many changes. Many of these are due to multiple A-V shunts that occur in the lungs and pleurae, as well as in the liver, with venous admixture and arterial unsaturation (Hecker and Sherlock, 1956). Heart failure may occur, particularly after surgical shunts.

Schwartz (1967) has recently shown that arterial hypertension is rare in cirrhotics, unless it is associated with renal disease. But if those patients who have renal disease and also have arterial hypertension and cirrhosis develop varices, then the arterial blood pressure becomes normal. If one does an end-to-side shunt on those individuals, the blood pressure goes

back again. What does this mean? Is there some substance inhibitory to the hepatic angiotensinase that is diverted from the liver in patients with varices?

Changes in hematopoietic system

The hematological changes occurring in the cirrhotic are many (Table 2). There is frequently a quantitative diminution in platelets, as well as changes in platelet aggregation (Thomas, Ream, and Stuart, 1967), and, at times, thrombasthenia (Mandel and Lazerson, 1961). Further, there may be significant abnormalities in the red and white cell in the presence of anemia and leukopenia or even leukocytosis. There may be folic acid deficiency due to faulty storage (Herbert, Zalusky, and Davidson, 1963), as well as production defects such as a deficit in fibrinogen and prothrombin (Ratnoff, 1963). Production of abnormal complexes, such as the macroglobulins—notably the 7-S macroglobulin—is not infrequent, and recently deficiency in immunoglobulin A has been reported (Wilson et al., 1968). Hemolysis is not uncommon and may be related to the

presence of acanthocytes (Douglass, McCall, and Frenkel, 1968). There is quite frequently an excess of fibrinolysins, according to Ratnoff (1963).

Changes in renal system

One of the most important functional derangements is the renal change, the so-called hepato-renal syndrome. Many patients who have advanced cirrhosis die in hepatic failure without any significant disease of the kidney. While specific renal abnormalities which cause renal failure are occasionally demonstrated (Laube, Norris, and Robbins, 1967), they are quite rare. A study in Boston by Garceau and Chalmers (1962) of 253 cases of patients with varices who had died revealed that renal shutdown preceded death in 11% of the cases. The pathophysiology of the hepato-renal syndrome is still unclear, though reduced glomerular filtration may be one of the mechanisms responsible for the renal failure. There is significant reduction in maximum urine concentration and the rate of solute-free water reabsorption in cirrhosis. This is reversible if hepatic compensation improves (Vaamonde et al., 1967).

Changes in endocrine system

The endocrine features shown below are but a few encountered.

1. Gynecomastia.
2. Hyperestrogenism.
3. Hyperaldosteronism.
4. Amenorrhea.
5. Gonadal atrophy.

Gynecomastia may be marked, and such breast changes, as well as testicular atrophy, are thought to be due to the inability of the liver to conjugate estrogen (Pincus et al., 1951; Morrione, 1944). The most important feature in the management of patients is the increase in serum aldosterone. If one gives 500 mg of aldosterone to a patient with ascites, he will excrete about 15% of this mass. If the same load is given to a normal



Fig. 2—Radiological appearance of the periosteum showing marked thickening seen frequently in cirrhosis.

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individual, he will excrete about 5% of aldosterone. This indicates that the liver is not degrading the aldosterone delivered to it, and, therefore, more of it is going to the kidney. As a consequence, there is more sodium retention. Amenorrhea was reported by Armas-Cruz (1951) in 39 of 66 females, and testicular atrophy was found by Morrione in 90% of males under the age of 50 (1944).

Changes in nervous system

Below are some of the central nervous abnormalities that may be seen in advanced cirrhosis.

1. Encephalopathy.
2. Asterixis.
3. Variable reflexes.
4. Coma.
5. Convulsions.
6. Hemiplegia.
7. EEG.
8. Polyneuritis.

Drowsiness and asterixis are common, as are stupor and coma. Convulsions also are not unusual. In fact, one may find any type of encephalopathy associated with hepatic failure. Reflexes may change frequently. For instance, one may get a positive Babinski in the morning, and in the afternoon the Babinski may disappear. The electroencephalogram may be helpful in differentiating hepatic decompensation from other types of encephalopathy, but the patterns are often non-specific. While at autopsy the brain sometimes shows an increase of astrocytes, there is really no known specific brain lesion that causes the encephalopathy. Peripheral neuritis with hyperesthesia, including pain, is often seen and is thought to be caused by the direct effect of ethanol and/or malnutrition.

Changes in pulmonary system

Hydrothorax is one of the more frequent chest findings in chronic liver disease. It occurs in 5% to 10% of people who have ascites. It is caused by the ascitic fluid

filtering directly through the diaphragm into the right hemothorax. Occasionally one will see hemothorax, probably as a result of the bleeding tendencies such patients develop (Christian, 1927; Meigs, 1954). There are often arteriovenous fistulae in the lungs and pleurae.

Changes in gastrointestinal system

Abnormalities in the gastrointestinal tract are many, as noted in Table 3. Varices of the esophagus and stomach with portal hypertension may be considered almost a part of the disease. Splenomegaly is evident in about 50% of cases (Ratnoff and Patek, 1942). Peptic ulcer is more common than in normal individuals, and its incidence is increased even more after shunt surgery (Lipp and Lipsitz, 1952; Patek, 1963). Feter hepatitis, which in the past was frequently encountered and which indicates liver decompensation, is now quite rare (Challenger and Walshe, 1955). This clinical finding may be less because of the frequent administration of such antibiotics as neomycin in the management of the disorder.

Ascites, a peritoneal transudate, is a hallmark of cirrhosis with which we are all familiar. We will not go into the mechanisms involved. Recently two types of peritonitis in cirrhotics have been reported, one caused by pneumococci (Epstein, Calia, and Gabuzda, 1968) and the other by enteric organisms (Conn, 1964), the diagnosis being made by culture of ascitic fluid. Pancreatitis is found clinically in about 5% of cirrhotics, according to Lipp and Lipsitz (1952).

Hepatoma is a rather common complication of cirrhosis, especially of the post-necrotic type. Recent studies by Alpert, Wogan and Davidson (unpublished data) in Uganda have demonstrated that certain fungal toxins, particularly aflatoxins from the aspergillae, may cause cirrhosis and hepatoma in animals. These aflatoxins are

TABLE 2

Changes in Hematopoietic System

Faulty Storage
Destruction
Production Defect—(Prothrombin-Fibrinogen)
Blood Loss
Production of Abnormal Complexes (Macroglobulins)
Poor Absorption
Anemia
Leukopenia. Leukocytosis
Thrombocytopenia—Platelet Aggregation
Clotting Defects
Folic Acid Deficiency
Acanthocytes
L. E. Cells
Fibrinolysis
Immunoglobulin A Deficiency

TABLE 3

Changes in Gastrointestinal System

Feter Hepaticus
Varices
Ascites
Pancreatitis
Splenomegaly
Abdominal Hernia
Peritonitis: Spontaneous.
Pneumococcic.
Peptic Ulcer
Hepatoma

found in the soil and in certain foods such as ground nuts. This brings up the important questions: Are there other toxins that may produce cirrhosis and hepatoma? Is fungal toxin, for instance, present in alcohol itself, and is this the factor that causes its toxic effect on the liver? Some recent work suggests this. One of the most interesting studies on hepatoma is by Lee in England (1966). In this study he reviewed a large group of alcoholic patients, all of whom had a finely granular type of cirrhosis. When these patients stopped drinking, within five or six months, according to his study, they developed very large nodules in the liver, a nodular type of cirrhosis; 16 (55%) of the 29 individuals who gave up drinking developed hepatoma, but only 9 (16%) of the 56 who continued to drink developed hepatoma. It was of interest that fewer females had hepatomas, but at the same time a much smaller percentage of women discontinued alcohol. We have recently seen advanced post-necrotic cirrhosis with very large nodules in which a transition from benign to malignant cells is clearly evident. Why neoplasia develops in this type of environment is still unclear (Parker, 1957; Kay, 1964; Miyai and Reubner, 1963).

Changes in blood chemistry

Abnormal blood chemical findings are frequently seen, and hyperlipemia is one of the more common, especially in biliary cirrhosis. Hyponatremia is almost the rule in the decompensated ascitic, in spite of the fact that the individual has increased body sodium; when the sodium level is 125 mM or below, it may be a poor prognostic sign (Hecker and Sherlock, 1956; Eisenmenger et al., 1950; Pecikyan, Kanzaki, and Berger, 1967; Galambos and Wilkinson, 1962). Hypomagnesemia may be found in the advanced cirrhotic and may be responsible for some of the encephalopathies that occur. A marked increase in globulins, espe-

cially in the gamma fractions, is frequently seen in chronic liver disease, and probably more often in post-necrotic cirrhosis. Hypoglycemia may occur in severe liver disease, as the liver is depleted of glycogen. It may also occur in hepatoma, but the cause of it is still unclear. Hypoalbuminemia with values below 2 mg/100 ml is not unusual in advanced chronic liver disease. This plays an important role in the fluid retention so often observed.

Changes in temperature regulation

Continued low-grade fever is not too rare, and, while cirrhosis predisposes to many types of infection, it is now known that the hepatic pathology itself may produce a febrile response (Tisdale and Klatzkin, 1960). In animals an hepatic pyrogen has been isolated, and it is likely that in some instances in humans the damaged liver releases a pyrogen capable of inciting fever in the host. In animals this hepatic pyrogen is easily extractable and may be suppressed by glucocorticoids.

Of 80 patients studied by Klatzkin and Tisdale, 58 had unexplained fever. It was concluded that this was probably a reflection of the diseased liver and not a result of any other complications.

Miscellaneous changes

One rather commonly observed finding is parotitis. There is no specificity to the pathological changes found in the parotid glands. The glands are usually bilaterally enlarged, firm and rubbery, and are probably more commonly seen in cirrhotics associated with alcoholism (Ratnoff and Patek, 1942; Patek, 1963).

Unexplained abdominal pain may be present in patients with uncomplicated cirrhosis. At times it may be quite severe. Several authorities have observed that it is more commonly found in patients who have concomitant ascites.

It should be emphasized that advanced cirrhosis may be present

with concomitant portal hypertension, although the patient may have no subjective symptoms. Rolleston and McNee (1929), in a study of 167 postmortem examinations of cirrhotics, noted that 87 of these had had minimal or no symptoms. McCartney (1933) found no evidence that the patient had symptoms in 35% of individuals who died with cirrhosis.

Summary

An effort has been made to present a panoramic view of cirrhosis. It has been indicated that many agents may initiate an intrahepatic process which may progress to advanced cirrhosis, that the characteristic abnormalities may cause both functional and pathologic multi-system changes, and that these encompass almost every body structure. As the altered structural and physiological changes progress, hepatic decompensation develops, and this often is terminal.

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