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Portal cirrhosis

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PORTAL CIRRHOSIS

by

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Introduction

Throughout this paper the author has chosen to use the term portal cirrhosis in the same sense as that used by Chaikin and Schwimmer (1945). According to their definition, portal cirrhosis is a progressive destructive process characterized by atrophy, fatty degeneration and necrosis of the individual liver cells, with proliferation of new connective tissue and regeneration of new lobules.

Such terms as atropic, hypertropic, hob-nailed, Laennec's, alcoholic, gin-drinker's, monolobular, multilobular, etc. well be entirely abandoned, because they are entirely descriptive or historical terms, and are of no value to the pathologist or clinician what-soever.

Likewise the author has used the same classification as that used by Boyd (1944) who divided all the cirrhotic processes into two main groups, viz., biliary and portal. Biliary cirrhosis is used to describe that condition where the primary pathology begins in the bile ducts and the symptoms resulting therefrom are some manifestation of biliary obstruction. Portal cirr osis is any other cirrhotic condition within the liver that conforms to the above definition.

This thesis will deal entirely with the subject of portal cirrhosis. Special emphasis will be placed upon the diagnosis and treatment of the disease; however, a relatively minor discussion will be devoted to the etiology of the disease and also to its pathology and pathogenesis.

At this time I wish to express my sincere appreciation to Doctor E. J. Kirk for his gracious enthusiasm and loyal cooperation in helping me with the organization and presentation of this thesis.

Anatomy of the Liver

Before presenting a comprehensive review of cirrhosis of the liver, it is imperative that both the author and the reader be familiar with the normal deveolpmental, gross and microscopic anatomy of the liver. It is imperative, for without this it is impossible to appreciate the pathological changes that take place in the liver, and how these pathological changes manifest themselves in every organ and system in the body. It is not within the scope of this article to delve into the minute details of the subject from this standpoint, but a brief review of these fundamental relationships will be presented.

Developmental Anatomy- Arey (1941) described the liver as developing from a ventral outgrowth from the floor of the future duodenum in the region of the anterior intestinal portal at about the fourth week of intrauterine life. This hepatic diverticulum consists of a cranial portion that later on develops into the glandular tissue and its bile ducts, and a caudal portion that becomes the gall bladder and cystic duct. This hepatic diverticulum then forces its way ventrally into a mass of mesoderm that in the future furnishes most of the body of the diaphragm.

A little later the region of the septum occup-

ied by the liver becomes drawn out as the ventral mesentery or falciform ligament.

After the appearance of the falciform ligament, the cranial portion of the hepatic diverticulum buds off epithelial cords which invade the diaphragm (actually septum transversum at this stage) and continues to proliferate there into a rapidly expanding spongework. The vitelline veins lying close-by send branches into this region of proliferation and as a result there is a mutual and intimate ingrowth of tortuous liver cords and sinusoidal channels. Because of this rich blood supply the hepatic mass enlarges very rapidly and by the eighth week of intraute ine life the liver is a large crecentric mass. While these changes have progressed, the original diverticulum is enlongating and differentiating into the duct system and by the twelfth week of intrauterine life the duct system is well established and gall bladder is secreting bile.

Adult Anatomy- Gray (1943) described the liver as being the largest gland in the body. It is located in the upper and right parts of the abdominal cavity, occupying almost the whole right hypochondrium, the greater part of the epigastrium, and not uncommonly extending into the left hypochondrium as far as the

mamillary line.

In the male it weighs from 1.4 to 1.6 kilograms, in the female from 1.2 to 1.4 kilograms. The superior surface fits under the vault of the diaphragm and the under concave surface of the organ fits over the right kidney. The upper portion of the ascending colon and th pyloric end of the stomach.

It is divided into four lobes: (1) The right lobe, the largest of all and occupies the right hypochondrium; (2) The caudate lobe lying on the posterior surface of the right lobe; (3) The quadrate lobe situated on the inferior surface of the right lobe; (4) The left lobe situated in the epigastric and left hypochondriac regions.

Several factors contribute to maintain the liver in place. The attachments of the liver to the diaphragm by the coronary and triangular ligaments and the intervening connective tissue of the uncovered area, together with the intimate connections of the inferior vena cava by the connective tissue and hepatic veins would hold the posterior part of the liver. Some support is derived from the pressure of the abdominal viscera which completely fill the abdomen whose muscular walls are always in a state of tonic contraction.

The superior surface of the liver is so perfectly fitted to the under surface of the diaphragm that atmospheric pressure alone would be enough to hold it against the diaphragm. The latter in turn is held up by the negative pressure in the thorax. The lax falciform ligament gives it no support though it probably limits lateral displacement.

Histology- Maximow and Bloom (1942) give an excellent description of the liver lobule and the following discussion is a condensation of the material presented in their latest textbook.

They describe the liver as being made up of small polygonal areas, each of which represents an architectural unit or lobule, 0.7 to 2.0 mm. in diameter. Each of these lobules are separated by very thin strands of connective tissue called the interlobular connective tissue. In man, the outlines of the lobules are very indestinct and the interlobular connective tissue barely suffices to from a framework for the interlobular artery., portal vein, bile ducts and lymphatics. Running through the center of the lobule, in its long axis, is the central vein.

The principal afferent blood vessel of the liver is the portal vein. It collects the blood from the viscera of the digestive tract and from the spleen

and enters the liver at the porta together with the hepatic artery. The liver also recieves a smaller part of its blood supply from the hepatic artery. This relatively small vessel supplies the interlobular connective tissue and its contained structures and helps to nourish the parenchyma of the gland. The blood is drained from the inferior vena cava as it passes through the fossa for this vessel.

Throughout the liver the terminal branches of the portal vein and the radicles of the hepatic vein are at about equal distances apart. Each radicle of the hepatic vein is surrounded by a layer of liver tissue of uniform thickness and this mass constitutes the hepatic lobule. Several central veins join to form an intercalated vein, several of these veins unit to form the collecting veins and these in turn join to form hepatic veins which pursue a course through the liver independent of the portal venous system.

The liver cell cords are separated from one another by the irregular tortuous blood spaces called sinusoids which pursue a radial course in the lobule and connect the ends of the interlobular portal veins with the intralobular central veins. Likewise the fine branches of the hepatic artery empty into these sinusoids. The lining of these sinusoids is composed of

an irregular alternation of two kinds of cells the undifferentiated lining cells and the phagocytic cells of Kupffer.

The hepatic cells are arranged more or less regularly in cords which form columns extending radially from the central vein to the periphery of the lobule. Between them lie the broad, irregular, thin-walled sinusoids. The liver cells are polygonal in shape and contain one laege round nucleus, although binucleated cells are not uncommon. The nucleus is quite vesicular; it has a smooth membrane and one or more very prominent nucleoli and a few small chromatin dots.

The cytoplasm of the liver cell presents and extremely variable appearance which reflects to some extent the functional state of the cell. Both glycogen and fat are dissolved in the preparation of the usual sections but by appropriate methods glycogen and fat inclusions are readily demonstrable in them. Their actual content of these constituents shows great variations under normal conditions and depends primarily on the amounts of carbohydrates, fat and protein in the diet and on the stage of digestion.

In adult man the liver cell cords in cross section consist of but two adjacent cells, between which

runs a thin bile canalicule. These bile canalicules run through the length of the liver cell cord and recieve short lateral branches which extend between the sides of adjoining liver cells. The canalicules are always intercellular and communicate with the interlobular bile ducts from a richly anastomosing network which closely surrounds the branches of the portal vein. In progressing toward the porta the lumen of the ducts becomes gradually larger and larger and at the transvers fossa of the liver the main ducts from the different lobes of the liver fuse to form the common bile duct.

The Etiology of Portal Cirrhosis

Age- Rolleston and McNee in 1929 found that in 165 adults whose livers were cirrhotic the average age was 48.7 years. The average for the males in this group was 49.7 years and that for the females was 47 years. Henrikson in 1936, found that the average age of 124 males with cirrhosis of the liver was 50 years, and of the 38 females in the same group, the average age was 45 years. Evans and Gray in 1938 in their study of the autopsy records of 217 patients with cirrhosis of the liver, found the peak of incidence in the sixth decade but stated that the peak for women is about a decade earlier than for men. Ratnoff and Patek (1942) reported that in their series of 386 cases the first symptoms appeared between 40 and 59 years of age. Kirshbaum and Shure in 1942, in their study of 356 fatal cases noted that the highest incidence was between the ages of 51 and 60, with 31.2 percent occurring in this decade. They further stated that 64 percent of the male fall into the 41 to 60 age group. Spain (1945) in reviewing the necropsy records of 250 cases of portal cirrhosis found that the average age at the time of death was 56.3 years for the males and 48.6 for females. He further emphasized the fact that these figures are more

Evans and Gray (1938) in their study of the autopsy records of 217 patients who died of cirrhosis of the liver, observed that males were inflicted 2.5 times mor frequently than the females. Ratnoff and Patek (1942) in their study of 386 cases of cirrhosis of the liver found a ratio of 2.2 males to 1 female. Kirshbaum and Shure (1942) in their analysis of 356 cases found that males were inflicted 2.2 times as frequently as the female. Wade (1945) noted a sex incidence of three males to one female out of their series of 175 cases studied at autopsy. Spain (1945) in reviewing the necropsy records of 250 cases of cirrhosis of the liver found 190 were in males and 60 in females, a ratio of three males to one female. He further commented on the fact that these figures reflect the ratio of male necropsies to female necropsies in that particular hospital which is also about three to one.

A total of 2,363 cases of portal cirrhosis have been reviewed above, and it can be seen that of this entire group males were found to be inflicted with the disease 2.73 times more frequently than females.

Toxic Agents and Cirrhosis of the Liver

Chlorinated Hydrocarbons- Many of the chlorinated hydrocarbons have been found to produce marked hepatic damage following their administration, many which apparently result in cirrhosis of the liver. Lambert (1923) produced hepatic injury in animals experimentally by the use of carbon tetrachloride in the treatment of hookworm disease. Poindexter and Greene (1934) reported an instance of hepatic cirrhosis in man, verified at autopsy, following exposure to a cleaning mixture containing 55 percent carbon tetrachloride. Cameron and Karunaratue (1936) administered chemically pure carbon tetrachloride to fifty adult albino rats and found that after a small toxic dose there is but little change in the liver cells; however, with larger doses, one could see by the end of the third day, hydropic and fatty degenerative changes about the central zone of the liver lobules and inflammatory cells soon appear. If the anim survives the attack evidence of repair is seen by the third day following exposure, as indicated by the presence of mitocic division of the hepatic cells. Repeated doses over longer periods of time resulted in marked fibrosis. These authors concluded that in order to produce cirrhosis in the rat by means of carbon

tetrachloride, a certain dose greater than the minimal toxic dose for the liver must be used. It must be administered either continously or at short intervals over a prolonged period of time. The intervals between repeated doses must be sufficiently short to avoid complete repair of the damage produced by the preceeding dose. They also emphasized that the first changes seen following exposure were fatty degeneration and necrosis of the hepatic cells, and if exposure were continued cirrhotic changes developed. Similar observations and conclusions were reached by Mann in 1937.

Cinchophen- Since the time cinchophen was introduced for the treatment of rheumatoid arthritis, there have been several reports in the literature with reguard to its toxicity. Weiss (1932) reported 89 cases of hepato-toxic reactions due to cinchophen poisoning, and of this group 52 recovered and 37 were seen at autopsy. The hepatic changes consisted of marked fatty degeneration and considerable necrosis of the hepatic cells. This author further pointed out that the toxicity of the drug seemed to be entirely independent of the amount of drug administered. Block and Rosenberg (1934) described the hepatic changes seen in seven cases of cinchophen poisoning as consisting of extensive destruction and necrosis of the liver parenchyna, simu-

lating the pathology seen in subacute yellow atrophy. Regeneration of the hepatic cells and of the bile ducts and proliferation of the connective tissue stroma supervened. The resulting picture being one of a "nodular" cirrhosis. Conklin (1934) believes that the toxic effect of cinchophen is derived from a splitting of the guinoline nucleus which gives rise to a free benzene ring, and states it is this free benzene ring that causes the liver damage. This author is also of the opinion that pre-existing gall bladder or liver disease with jaundice, malnutrition, pregnancy, and chronic alcoholism are predisposing factors. He likewise agrees with Weis, and stated that the toxicity of the drug is independent of the period of time over which the drug is administered and also of the size of the dose used.

Other substances including lead, copper, arsenic silicates, phosphorous, coal tars, butter yellow (p-dimethylaminoazobenzene) and manganese have been used to produce cirrhosis of the liver in experimental cirrhosis, but according to the studies of Ratnoff and Patek (1942) all of these substances are remote as far as being considered as etiological agents in man.

Bacterial and Paracitic Infections in Cirrhosis

Several authors are of the opinion that bacterial infections are important in the production of cirrhosis of the liver. Rolleston (1912) states that micro-organisms passing into the mesenteric veins are carried into the portal vein where they undergo bacteriolysis and there toxins are carried to the liver and set up the cirrhotic process. They further stated that the colon bacillus are almost constantly present in the human liver. When the livers are healthy, the bacilli appear to have been killed by the liver cells. The lymphatics may become obstructed from lymphangitis and perilymphangitis producing an acute hepatitis and cirrhosis of the liver may result.

Lambert (1923) suggested that cirrhosis may be set up by the specific fever, typhoid fever, measles, smallpox and pneumonia. Theoretically, the toxins of the diseases may, when absorbed into the general circulation, set up focal necrosis of the liver cells and under certain conditions fibrosis might develop around these areas of necrosis. Menne and Johnston (1933) concluded that it is logical to assume that the greater source of substances injurious to the liver is from the gastro-intestinal tract, drained by the portal vein.

Here are found the end products of digestion as well as bacteria. These toxins are soluble and are absorbed.

MacMahon (1931) reported five cases of streptococci hepatitis, in four of which he demonstrated streptocci in the liver. Two were acute and showed degeneration and necrosis of the hepatic cells with an associated inflammatory reaction. One was subacute and of six weeks duration and showed marked zonal necrosis affecting all the lobules. There was proliferation of the hepatic cells and of fibrous tissue such as is characteristicly seen in early cirrhosis. In another case, the liver, seen during cholecystotomy, appeared normal and an excised section had normal histologic features. Subsequently, chills and fever developed, accompanied by jaundice. The liver became enlarged, ascites developed and was removed by tapping on two occasions. The condition progressed to a fatal termination eitht and one-half months following the operation. Pronounced cirrhosis was found post mortem, and numerous streptococci were demonstrated in the liver. It was regarded as a chronic hepatitis due to the streptococci of moderate virulence, causing a diffuse progressive destruction of hepatic cells resulting in cirrhosis.

patients lived during the time when typhoid fever was endemic, and thought it probable that this number is no larger than would be expected from any similar age group.

Tuberculosis seems to be only occasionally associated with cirrhosis of the liver. McCartney (1933) reported three cases of active tuberculosis among his 158 cases of portal cirrhosis seen at autopsy. Evans and Gray (1938) found six cases of active tuberculosis among 217 patients found to have cirrhosis at postmortem. Ratnoff and Patek (1942) noted that four patients in their series of 386 cases gave a past history of tuberculosis, and four others had active tuberculosis during the course of the disease. These same authors cited several references in the foreign literature at earlier dates and pointed out the fact that their figures were remarkably higher. They attributed this to the higher natural incidence of tuberculosis in some of these countries and also to the fact that of relatively recent years the incidence of tuberculosis has been on the decline.

Syphilis is apparently a frequent concomitant of cirrhosis of the liver. Boles and Clark (1936) reported an incidence of 9.3 percent of their cases studied at necropsy with portal cirrhosis. Evans and Gray (1938)

noted that 12 percent of their 217 cases of cirrhosis seen at autopsy likewise had syphilis. Ratnoff and Pate (1942) found syphilis present in 62, or 16 percent of their 386 cases of cirrhosis. They also pointed out that as far as they could ascertain none of these patients had syphilis of the liver.

The explanation for this rather frequent association is obscure. Arsenic derived from the arsenicals used in treating the disease has been suggested, but Ratnoff and Patek do not think this has much of a role. It is known that the alcoholic is inclined to be promiscuous in his sexual relationships and I thought this to be an adequate explanation; however Ratnoff and Patek (1942) found that syphilis is found as a precursor of cirrhosis in countries where alcoholism is unimportant as a predisposing factor, and he mentioned Syria where it was found that 12 percent of 70 patients with cirrhosis had syphilis and in Southern India the series of 41 of 55 patients with portal cirrhosis and ascites gave a positive Wassermann reaction.

The relationship of malaria to cirrhosis is very obscure. Chapman, Snell and Rowntree (1931) found that 11 percent of their 112 patients with cirrhosis and ascites have a past history of malaria. Ratnoff and Patek (1942) obtained a past history of malaria in 33

of their 386 patients with cirrhosis of the liver. These same authors pointed out that the proportion is much higher in those countries where malaria is commonplace, reaching as high as 84 percent in one large Indian Series. They concluded their discussion by saying, "Malaria is thus a frequent factor in the background of patients with cirrhosis of the liver, but there is no evidence that it plays a direct role in its etiology."

The Role of Alcohol in Portal Cirrhosis

Boles- (1943) states that cirrhosis of the liver was known to the ancients some two thousand years ago, but up to the present time its role is still obscure. As long ago as the sixteenth century it was associated with inebriety; in the eighteenth century Mathew Baille commented on its frequency in hard drinkers, and while he said he could see no connection between hard drinking and the disease, it has generally been assumed since his time that such was the case. Laennec (1826) first described the atropic nodular liver to which he gave the name cirrhosis and at the present time Laennec's atrophic or portal type of cirrhosis is commonly alluded to as "alcoholic cirrhosis".

Budd (1846) thought that cirrhosis of the liver in chronic alcoholics was brought about through obstructed circulation through the lungs and heart. Foxwell (1896) stated that cirrhosis of the liver is due to the direct action of alcohol on the supporting structure of the liver rather than the parenchyma causing the portal spaces to suffer most. In contrast to this Eccles (1902) believes it is due to the direct action of the alcohol itself upon the liver cells and it is the direct toxicity that produces the symptoms and

signs of cirrhosis and not pressure caused by contracting interlobular connective tissue. He further believes that there is no real inflammation and hyperplasia of the connective tissue, and the assumed inflammatory cell formation is nothing more or less than the remains of atrophied liver cells, the result of the primary action of alcohol upon them. White in 1903 suggested that it was the "alcoholic drink" and not the alcohol itself that caused the cirrhosis. This was based upon his finding arsenic in the beer during an epidemic of cirrhosis of the liver in Manchester. He further stated that cirrhosis of the liver caused by the "alcoholic drink" is a distinct entity of its own and should not be lumped together with all the diseased of the liver characterized by an increase in fibrous connective tissue. Futhermore cirrhosis of the liver caused by the "alcoholic drink " can by recognized by the naked eye on the post-mortem table.

Mallory (1933) supports this theory by stating that ethyl alcohol alone will not cuase cirrhosis, but he does think that certain liquors are contaminated by some injurious agent and it is these impurities that produce the cirrhosis. He suggested that the contaminents may be phosphorous because this given in small amounts over prolonged periods of time will pro-

duce a microscopic picture identical to that seen in "alcoholic" cirrhosis. He suggested that these contaminants may enter the liquors through "acid erosion" of the metal cans in which the liquor is made and stored. It is also interesting to note that this same author in 1932 laid stress on the presence of hyaline droplets within the cytoplasm of the hepatic cells and said they were diagnostic of any cirrhotic process induced by alcohol. These will be discussed more fully later.

Rolleston and McNee- (1929) conclude that while alcohol is frequently an antecedent condition, alcohol itself has no specific action of the liver except fatty degeneration; it produces cirrhosis indirectly either by leading to the formation of "sclerogenic poisons" or by enabling such poisons to exert their effect on the liver. They also emphasized that it has not been sufficiently recognized that other factors may be of equal importance and that an inherited or acquired lack of resistance on the part of the liver probably plays a prominent part.

To further substantiate the evidence that alcohol is a contributing factor in the production of cirrhosis of the liver, some interesting facts have been pointed out by several investigators.

Boles and Clark- (1936) found that the relative

incidence of cirrhosis of the liver in inebriates is approximately 6.7 times as great as in temperate or abstinent persons. This figure agrees quite closely with the data of Jolliffe and Jellinec who found that the cirrhosis rate of inebriate patients is 7.1 times as great as that for temperate and abstinent ones.

Further evidence of this relationship is also supplied by Kirshbaum and Shure (1942) who published the results of their autopsies between the years of 1929 and 1937. The following table summarized their results.

Year	Autopsies	Cirrhosis	Percent
1929	955	28	2.93
1930	986	21	2.13
1931	1,114	25	2.24
1932	1,207	21	1.74
1933	1,192	31	2.60
1934	1,300	35	2.69
1935	1,176	40	3.40
1936	1,242	38	3.06
1937	1,167	52	4.45
1938	1,327	45	3.39
1939	601	20	3.33
Totals	12,267	356	2.83 Ave.

From this table it can be seen that since the repeal of the National Prohibition Law in 1932, there has been a progressive increase in the percentage of

the number of patients who died yearly with cirrhosis of the liver.

Further evidence of this relationship is also supplied by Boles (1943) who obtained some interesting figures from the Metropolitan Life Insurance Company. In 1911 this company cited a death rate for cirrhosis of the liver in the United States as 58.6 per 100,000 in individuals 35 to 74 years of age. For this same decade the death rate in 1933 was 22.9 per 100,000 which is a decline of nearly 36 percent in the 24 year period. Statistical analysis of the detailed data covering this period, which included the years of partial and complete prohibition, indicates that this conspicuous decline in the death rate accompanied a corresponding decline in the consumption of alcoholic beverages.

From the theories and facts cited above one must conclude that alcohol is a common precursor to cirrhosis of the liver, but this does not mean that it is the only or the most important predisposing cause. It is a well established fact that portal cirrhosis occurs in children who have never indulged in intoxicating beverages and also in adults who likewise have lived a life of complete abstinance. (Connor, 1939)

Within the past few years there has been a tremen-

dous amount of material published pertaining to the role of alcohol, inadequate nutrition and vitamin deficiencies as etiological factors in the production of cirrhosis of the liver. Repetition can well be avoided by presenting these relationships under the section devoted to the treatment of cirrhosis of the liver, or more specifically that portion dealing with animal experimentations.

Pathogenesis and Pathology of Cirrhosis of the Liver

With but a few exceptions, the pathological changes seen in the liver in portal cirrhosis are fairly well established; however, some brilliant experiments have been performed in the past and a search for newer concepts, and confirmation of older ideas, is continually being carried out. In the following discussion, the author has attempted to present a brief but thorough concept of the pathological changes seen in portal cirrhosis of the liver, and at the same time correlate the clinical and experimental findings that have bought about the present day opinions.

Gross Pathology- According to Boyd (1944) the name cirrhosis, meaning yellow or tawny, was first used by Laennec to describe that form of liver disease which is now known by his name, and in spite of the fact that many cirrhotic livers are not yellow but green, the name has persisted and is now synomomous with sclerosis or fibrosis. Even so, this same author is of the opinion that the original description of the gross appearance of the cirrhotic liver presented by Laennec in 1826, can still not be bettered. "The liver reduced to a third of its ordinary size was, so to say, hidden in the region it occupied; its external surface, lightly mammillated

and wrinkled, showed a grayish yellow tint; indented, it seemed entirely composed of a multitude of small grains, round to ovoid in form, the size of which varied from that of a millet seed to that of a hemp seed. These grains, easy to separate one from the other, showed between them no place in which one could still distinguish any amount of liver tissue itself: their color was fawn or a yellowish russet, bordering on greenish; their tissue, rather moist, opaque, was flabby to the touch rather than soft, and on pressing the grains between the fingers one could not mash but a small portion; the rest gave to the touch the sensation of a piece of soft leather."

In analyzing some of the statements made in the above quotation some interesting findings have been revealed. Mallory (1932) in his study of the protocols of 550 cases of cirrhosis found that 175 livers weigh over 1500 grams, the largest weighing 5,335 grams and 375 weighed less than 1500 grams. Of the 343 cases reported by Kirshbaum and Shure (1942), 214 weighed over 1500 grams and the remaining 129 weighed less than 1500 grams. In a small series reported by Karsner (1943) 30 of the 58 livers examined weighed more than 1500 grams and the remaining 28 were found to weigh less than 1500 grams. In a series of 78 cirrhotic livers seen at autop-

sy by Ratnoff and Patek (1942) 35 were found to weigh more than 1800 grams and the remaining 43 weighed less than 1800 grams. From this it seems safe to say that about half of the cirrhotic livers seen at autopsy are reduced in size.

Kirschbaum and Shure (1942) are of the opinion tha the large liver does not progress to the small liver of "Laennec's" cirrhosis. This is contrary to most other opinions. Karsner (1943) states that the periodic observation of patients with cirrhosis of liver strongly favors the view that, "the cirrhotic liver, large at the time of first observation, may become markedly shrunken by the time of death."

This same author is of the opinion that the size of the nodules is variable and states they may be less than a millimeter or more than a centimeter in diameter and the uniformity in size of the nodules is not constant, because occassionally large irregular nodules are interspersed. He further stated that the distinction between monolobular and multilobular cirrhosis is not justifiable because the small nodules often contain several shrunken nodules and the large nodules are more often "masses of proliferated cells than collections of lobules."

Karsner (1943) again takes issue with Laennec and

states that the color of the cirrhotic liver depends upon the hyperemia, hemosiderosis, necrosis, fat content and icterus, and the nodules of regeneration are generally pale faun or brownish yellow and the connective tissue bands are pale gray. Boyd (1944) support this description given by Karsner.

Mallory (1933) believes the color of the cirrhotic liver is not characteristic and depends entirely upon the pathological changes that are present. Fat in the cells turns it yellow. The connective tissue of stoma is grayish. Congestion makes it red and bile stasis yellow and brown to green. The result then, is often a marked combination of colors.

In considering the consistency of the cirrhotic Karsner (1943) agrees with the description given by Laennec as far as the small liver is concerned, but he believes there is a marked difference in the larger liver. The large livers are not nearly as firm, even though there is a good deal of fibrosis, passive hyperemia degeneration and necrosis.

In cross section Karsner (1943) described the cut surface as corresponding in appearance to the outer surface except that the bulging of the parenchyma and the retardiation of the connective tissue are not so great.

Pathogenesis and Pathogenic Physiology:

Menne and Johnson (1933) presented a very comprehensive description of the sequence of events that take place in portal cirrhosis. They described the first damage to the liver cells as occuring about the periphery of the lobules. Such changes as hydrops rarefaction, vaccuole formation, parenchymatous and fatty death occur. Simultaneously invasion of histiocytes and leucocytes, which together with the Kupffer cell prolifer tion congregate in the "hepatic trinities", is noted. The liver cells adjoining the injured area soon exhibit signs of regeneration by increasing in size and multiplying. At the same time there occurs an increasing number of invading phagocytes in the interstitial tissue of the "hepatic trinities." As the progress continues, newly formed fibrous connective tissue, origination from the Kupffer cells, the histocyte or the preexisting fi rous tissue, makes its appearance. As the inflammatory supportive stroma encroaches more and more upon the parenchyma, tending to produce false lobulations of various sizes. Eventually a vicious relationship is established, to the end that the elements of parenchyma and supportive stroma become antagonistic to each other. Gradual diminulation of the less resistant parenchyma and progressive accumulation of the more

durable supportive stroma eventually lead to a small, hard, nodular liver. The necessity for continued hyperplasia often leads to the formation of adinomatous nodules.

Mallory (1932) stated that the perilobular connective tissue contracts with age and as a result of this the flow of blood through the organ is impeded and the outflow of bile is blocked more or less completely. The obstruction of the circulation, especially in the portal system, causes chronic passive congestion of the gastro-intestinal tract with increase of mucous secretions from the glands; mechanical enlargement of the spleen owing to distension of the venous sinuses; escape of fluid into the peritoneal cavity; and dilatation of various veins in attempt at establishing collateral circulation. Of the distended veins those in the abdominal wall forming the "caput medusae" are the most conspicuous but those in the esophagus and gastric cardia are the most to be feared owing to the danger of erosion followed by hematemesis.

Connor (1938) is of the opinion that the first stage in the development of cirrhosis of the liver is fatty infiltration. This fat, as it accumulates in the hepatic cells, exerts a pressure upon the sinusoids. This causes the sinusoids to collapse and a thickening

of the wall of the sinusoids is an early feature. This thickening of the walls with the formation of a collagenous material promotes a reticulum production about the liver cells which have degenerated as a result of anoxemia. Fibroblastic proliferation follows. The interlobular stroma likewise is often stimulated to proliferate by mechanical pressure of the distended liver lobules.

Spellberg, Keeton and Ginsberg (1942) are of the opinion that certain fats which are metabolizing with difficulty are improtant factors in the production of cirrhosis. These fats, once anchored there; would by their presence set up irritation, which would eventually result in cirrhosis.

Microscopic Pathology:

According to Karsner (1943) the principal microscopic feature of advanced cirrhosis is the growth of the perilobular connective tissue so that the lobules, variable in size, are completely surrounded by connective tissue. There is likewise a picture of cloudy swelling, fatty degeneration, focal necrosis, alterati in regularity of the cords and infiltration of inflammation cells such as lymphocytis, plasma cells and polymorphonuclear leucocytes into the perilobular connective tissue. As was mentioned previously, Mallor

(1932) in describing alcoholic" cirrhosis stated that the lesion seen is diagnostic of this particular type of cirrhosis. The cytoplasm very slowly undergoes a degenerative change in consequence of which minute hyaline droplets appear in it and gradually enlarge and fuse to form an irregular fine to coarse hyaline meshwork which tends to surround the nuclei. These degenerative changes may attack single cells or large groups of them. Of the first evidence of these changes are usually seen in the central portion of the lobule. Moon (1934) reported that hyaline droplets are present in all varieties of active "Laennec's" cirrhosis, even in young persons without any history of alcoholism. Karsner (1943) is of the opinion that hyaline droplets have no significance other than an indication of parenchymal cellular degeneration, and he pointed out that the same findings are seen in the renal epithelium in a variety of diseases.

There appears to be a multiplication of the ductal epithelium in cirrhosis of the liver, but the exact nature of these changes is still questionable. Moon (1934) counted the bile ducts in measured sections of a normal and cirrhotic liver and estimated that the cirrhotic liver contains about 14 times as many ducts per gram as the normal liver. He believes that in pre-

cess of repair all hepatic structures are stimulated to proliferation. Not only do the cells of the liver regenerate but there is also proliferation of bile ducts, young fibrous connective tissue, Kupffer cells and vascular structures. -MacMahon, Lawrence and Maddock (1929) studied the changes of the liver, principally of the guniea pig, following experimental ligation of the common duct. They demonstrated mitotic figures shortly after the ducts became enlongated and tortuous and they thought this due to multiplication of the epithelial cells. The tortuosity, they believed, accounts for the appearance of proliferation of the ducts in the single section. Karsner (1943) stated that what appears to be proliferated small bile ducts may represent a peripheral collection of hepatic cells reduced in size and arranged in parallel rows, this may be true multiplication of biliary passages, or may be a tortuous elongation of the ducts. Regardless of what they may be, he does not think that they are of any importance in producing new parenchymal cells.

Moon (1934) described the cirrhotic process as consisting of degeneration and destruction of hepatic cells, followed by regeneration and fibrous porliferation. "It is essentially nothing else than chronic, progressive, diffuse hepatitis." He further pointed

out that if such destruction is limited in extent, involving only portions of the lobules, no marked structural or functional disturbance results. Biliary obstruction may occur, but there is no obstruction to the portal circulation or obliteration of hepatic architecture. Karsner (1943) pointed out that acute hepatitis may be superimposed on cirrhosis, but to recognize this he emphasized that there is little or no proliferation of fibroblasts and furthermore other organs such as the heart and kidney show similar acute interstitial inflammation in acute hepatitis.

Moon (1934) states that the latent or healed stages of cirrhosis is more difficult to identify microscopically. In this stage he describes complete absence of parenchymal degeneration, of hyaline droplets, or infiltration of polymorphonuclear leukocytes and pictures the portal spaces as being made up of dense mature connective tissue with little or no evidence of fibroblastic proliferation.

McIndoe's (1928) injection studies of cirrhotic liver showed a marked diminulation if the total vascular bed. The main trunks were attenuated and irregularly stenosed. The larger branches were given off at unusually abrupt angles and showed irregular deviation to one side as if it were displaced by some invisible

force and he suggested that the expansive force of a growing mass of hepatic cells would produce such an effect. He found it difficult to find any normal central veins whatever and the terminal branches of portal and hepatic veins were markdely deranged. These terminls were found in distorted positions in the stroma surrounding the regenerated hepatic nodules and he noted that these nodules had no channels into which an injection could penetrate form the portal vein; however, he did note that these nodules recieved their blood supply principally through branches of the hepatic artery. He assumed this was because the terminal of the hepatic artery are less easily obstructed than the portal vein. As a result of these changes he concluded that a portohepatic venous obstruction develops and the portal blood supply to the remaining parenchyma of the liver is reduced to a minimum.

Symptomatology of Portal Cirrhosis

Gastrointestinal Symptoms- Loss in weight is a common complaint of the patient with cirrhosis of the liver. Snell (1931) observed that it was present in 62 out of 112 patients with cirrhosis of the liver. Chapman, Snell and Rowntree (1933) noted its presence in 21 of his 58 cases. Henrikson (1936) observed weight loss in 56 of his 162 cases. Ratnoff and Patek (1942) in their series of 386 patients with cirrhosis found 206 had a history of weight loss and 158 showed this in spite of the presence of ascites. Fagin and Thompson (1944) found that weight loss was found in the history of 34 percent of his cases. He noted that this was the earliest manifestation in three patients and constituted the presenting complaint of one. Maluntrition was evident on physical examination in 24 patients.

A total of 789 cases has been reviewed above and it can be seen that of this number, 369 or 47 percent, gave a history of loss in weight during the course of the disease. From this we can conclude that a history of a loss in weight is a valuable adjuvant in establishing a diagnosis of cirrhosis of the liver.

Anorexia is likewise a common early symptom of cirrhosis of the liver. Ratnoff and Patek (1942) noted its

presence in 35 percent of their series of 386 patients. Snell (1931) found that "flatulent indigestion" was the most common early symptom present in his 112 cases with portal cirrhosis. Of their 58 cases of compensated cirrhosis of the liver, Chapman,,Snell and Rowntree (1933) described flatulence in 33 cases. Wade (1945) states that the earliest manifestations of the disease are insidious in onset. Of his 175 cases studied he reported that periodic bouts of digestive disturbances characterized by anorexia, morning nausea and vomiting, gaseous distention and irregularity of the bowel were present in 73 percent of this series. He further stated that if these above symptoms are accompanied by a history of an inadequate diet, chronic alcoholism and an enlarged liver, the diagnosis of cirrhosis should be strongly suspected and therapy instituted unless these symptoms can be adequately explained on the basis of other demonstrable disease processes.

The cause of anorexia in cirrhosis was ascribed to "alcoholic gastritis" by Saundby in 1905. This view is upheld by Chaikin and Schwimmer (1945) who subjected five of their patients to gastroscopic examination and all of them showed evidence of "chronic superficial gastritis". Ratnoff and Patek (1942) believe that abdominal distension resulting from flatulence or the accumu-

lation of ascitic fluid is a large factor in the production of anorexia. Lichtman (1942) suggested that venous congestion in the veins of the stomach, due largely to the increased tension in the portal vein, may be responsible for the anorexia.

From the data presented it would be impossible to state exactly the exact percentage of patients giving a history of anorexia or flatulent indigestion, but one could safely say that flatulent indigestion or anorexia are present, usually as an early complaint, in over 60 percent of patients with cirrhosis of the liver. The cause of these digestive disturbances are probably due to: (1) The accumulation of ascitic fluid in the peritoneal cavity, (2) The presence of a chronic gastritis, especially in those who have given a history of the long continued use of alcohol, (3) Gaseous distension of the stomach and (4) Increased tension in the portal vein.

Nausea and vomiting has briefly been referred to above by Wade (1945). Rolleston and McNee (1929) stated that "dyspepsia" is an almost constant finding and nausea and vomiting were "frequent" in their experiences. Ratnoff and Patek (1942) noted its presence in 30 percent of their 386 cases. Fagin and Thompson (1944) noted its presence in 44 percent of their 71 cases. Of this 71, it was included in the earliest complaint of five

patients, but was the presenting complaint of only one.

Changes in bowel habits have frequently been described in the patient with cirrhosis of the liver. Rolleston and McNee (1929) stated that in their experience patients with cirrhosis may have alternate bouts of diarrhea and constipation. Diarrhea was present in 32 of 112 patients who had cirrhosis with ascites studied at Mayo Clinic by Snell in 1931. Fourty-one of the patients of this same group had constipation. Ratnoff and Patek (1942) described changes in bowel habits in about 25 percent of their 386 cases. Diarrhea which lasted for varying periods of time, occurred in 78 of the patients and constipation in 33. Fagin and Thompson (1944) found that in their 71 cases eight of them complained of constipation while an equal number were distressed by diarrhea.

Hematemesis is another very common symptom of portal cirrhosis. Chapman, Snell and Rowntree (1933) observed gastrointestinal hemorrhage in 16 of their 58 cases of cirrhosis. Henrikson (1936) observed that 39 of his 162 cases gave a history of having vomited blood. Evans and Gray (1938) noted that 20 percent of their 217 cases had hemorrhage from the gastrointestinal tract and 13.9 percent had ruptured esophageal varices with fatal hemorrhage. Fifteen of this last group did not have ascites. Ratnoff and Patek found that 27 percent of their 386

cases gave a history of hematemesis. Fifty-five of these patients died following the episode. Of these 55, 22 had survived a previous hematemesis, while 33 succumbed to the initial attack. There were therefore 73 patients who survived an episode of hematemesis. Fagin and Thompson (1944) found hematemesis to occur in 21 percent of their 71 cases and was the presenting complaint of four, in three of whom it was the earliest manifestation of the cirrhotic process. They further state that seven of the 15 patients with hematemesis were among the group that improved and were discharged from the hospital. Chaikin and Schwimmer (1945) noted that hematemesis occurred in 63 of 246 cases studied by them. In 12 of this group it was the first sign indicating cirrhosis, and in eight of these the first hemorrhage proved fatal. In the non-fata cases the amount of blood lost varied from a few ounces to a quart. Spain (1945) observed at necropsy the presence of ruptured esophageal varices in 26 of their 250 subjects examined.

A total of 1,390 cases of cirrhosis of the liver has been sited above and of this group 310, or 22.3 percent, gave a history of hematemesis. In many of the cases, approximately one-third, the initial hemorrhage proved to be fatal. Occasionally this was the only symptom of any cirrhosis process whatsoever.

Most observers are of the opinion that hematemesis in a patient with cirrhosis of the liver is usually the result of ruptured esophageal varices. Others, including Ratnoff and Patek (1942), question this assumption because of the frequent inability to locate a bleeding point at autopsy. Preble in 1900 reviewed 60 cases of fatal hematemesis which had been recorded up to that time. Esophageal varices were noted in 35 of 42 cases in which the esophagus was examined. Preble believed that fatal hematemesis might occur in the absence of esophageal varicies as the result of the simultaneous rupture of many gastrointestinal capillaries. According to Rolleston and McNee (1929) hematemesis may rarely be the result of rupture of a gastric varix. Ratnoff and Patek (1942) state that the failure to establish a locus of hemorrhage is not surprising when the vast size of esophageal varicies seen by the X-ray is compared with their collapse state post-mortem; furthermore, the sudden, large amount of blood lost by hematemesis seems best explained by the rupture of a large marix. Occasionally, such hemorrhage has proved to be the result of co-existing peptic ulcer in patients with cirrhosis.

Lichtman (1942) pointed out two anatomical and mechanical factors which favor the formation of esophageal varicies. They are so close to the seat of obstruction

and their course is so direct that they encounter the increased pressure sooner and to a greater degree than the more remote and indirect paths for collateral circulation. Secondly, they are but slightly supported by the submucous tissue of the esophagous, and the support becomes progressively less as the dialating veins lead to pressure atrophy of the tissue about them. Preble (1900) also called attention to another important factor which favors the early formation of esophageal varicies. He emphasized the fact that the esophageal veins are intrathoracic and with each inspiration there is a negative intrathoracic pressure. At the same time the descent of the diaphragm indirectly, by forcing the viscera downward ahead of it, produces an increase in tension in the portal vein of 14 mm. to 18mm. of mercury. As a result of this the blood is thrown from the coronary into the esophageal veins with a great force and this leads to permanent dilatation of the esophageal veins.

Ratnoff and Patek made studies of the blood in 15 patients following a gastrointestinal hemorrhage, and found a rise to abnormal levels of the plasma urea-nitrogen or non-protein nitrogen. The cause of this azotemia associated with gastrointestinal bleeding has been recently studied by Gregory, Ewing and Levine (1945). They attributed this to decreased renal function caused by low

blood pressure and dehydration or to absorption of digested blood proteins. They further stated that anemia is not a factor, and absorption of digested blood from the gastrointestinal tract does not impair renal function.

Abdominal pain is another gastrointestinal symptom that is frequently encountered in patients with cirrhosis of the liver. Nissen (1920) described abdominal pain in 34 of his 77 cases. The duration of the pain varied from a few days to a few years and was constant or intermittent. Right hypochondrial pain was mentioned 13 times, epigastric pain three times, small of the back, twice, umbilical pain, once, and pain in the right shoulder once. In two cases, right upper quadrant pain appeared as the first symptom. Henrikson (1936) found that 82 of his 162 cases of cirrhosis complained of abdominal pain or distress. Katnoff and Patek (1942) found that abdominal pain was present at some time during the course of the disease in 121 of their 386 cases. In 32 instances it was generalized, in 37 the pain was localized in the upper right quadrant, and in 29 it was located in the epigastrium. Pain was usually described as being sharp, or less frequently as cramp-like. Only occasionally was tendernous associated with the abdominal pain. Fagin and Thompson (1944), in their series of 71

cases, noted that abdominal pain occurred in 38 patients during the course of their illness; in 12 patients it was the presenting complaint. The pain was usually a dull persistent aching sensation in the abdomen, particularly in the epigastrum, aggravated by the ingestion of food and not relieved by the usual antacid medications and carminatives.

Henrikson (1936) attributes the pain to three possible causes: (1) Occlusion of the mesenteric vessels, (2) Intermittent vascular spasm and (3) Perisplenitis. Fagin and Thompson (1944) attribute the pain to displacement and compression of the hollow viscera by hepatomegaly and ascites, or to "functional" gastrointestinal disturbances resulting from the impairment of the portal circulation. They also brought out some other interesting findings. In nine patients abdominal pain was present without ascites; in three of these patients there was roentgenographic evidence of a duodenal ulcer; and a fourth patient had evidence of impaired cholecystic function as gauged by the dye excretion test. The remaining five patients without ascites were chronic alcoholics, and the pain may have been due, partially at least, to digestive disturbances secondary to the alcoholism. Ratnoff and Patek (1942) found that 3.6 percent of their 386 patients had a history of peptic ulcer

concurrent with, or preceding their present illness and 3 percent had cholecystitis.

In summarizing the above material, it has been shown that 270, or 39 percent of the total 696 patients had a history of abdominal pain at some time during the course of the disease. It has also been shown that the pain is most frequently located in the upper right quadrant of the abdomen; however, it may be located anywhere. Occasionally, abdominal pain is the presenting complaint of the patient, and there may be no other symptoms of the disease present.

The pain may be due to a number of factors, among which are included the following: (1) Displacement and compression of the hollow viscera by hepatomegaly or ascites, (2) Functional gastrointestinal disturbances, (3) Chronic gastritis associated with alcoholism, (4) Associated gastrointestinal diseases such as ulcers or cholecystitis, (5) Perisplenitis and splenomegally and (6) Spasm or occlusion of the mesenteric vessels.

Hemorrhagic Phenomena- Another not uncommon symptom of portal cirrhosis, are the various hemorrhagic phenomena. Nissen (1920) observed epistaxis in four of 77 cases with cirhosis of the liver. Patek and Post (1941) obtained a history of epistaxis in 46 percent of their cases studied. Ratnoff and Patek (1942) in their analysis

of 386 cases noted that 70 patients had given a history of epistaxis, and 33 of purpura; of these, 12 patients had both symptoms. Fagin and Thompson (1944) noted epistaxis, purpura, ecchymosis, or bleeding from the gums in 10 percent of their 71 cases, generally in association with clinically severe stages of the disease. These hemorrhagic tendencies were noticed only in jaundiced patients and they considered it due to the hypoprothrombinemia which results from the inability of the damaged liver to manufacture prothrombin, even in the presence of vitamin K..

It was demonstrated by Smith, Warner and Brinkhous (1937) that the prothrombin concentration in the blood depends upon the integrity of the liver and that the liver damage is followed by corresponding impairment of prothrombin production. Since prothrombin is essential to the clotting mechanism of the blood, this could account in part at least for the hemorrhagic phenomena. Patek, Post and Victor (1940) suggested that it is very likely that the "vascular spider", especially when present in the mucous membranes, provide a bleeding site in certain cases. Chaikin and Schwimmer (1945) add to the above two factors, the presence of thrombocytopenia.

In summary, bleeding phenomena occur in approximately 25 percent of patients with cirrhosis of the liver.

The hemorrhagic diathesis may be explained in part by: (1) Low prothrombin level, (2) Thrombocytopenia and (3) The presence of abnormal blood vessels in the mucous membranes.

Cardio-respiratory Signs- Katzin, Waller and Blumgart (1939) reviewed cardiac cirrhosis and concluded that it is clinically a relatively rare condition. They did say though that chronic hepatic congestion secondary to congestive heart failure causes an increase in hepatic fibrous tissue. This resulting fibrosis may be central or portal or both, and is directly proportional to the duration of the heart failure. Cyanosis was described in 23 of the 162 patients reported by Henrikson in 1936. Ratnoff and Patek (1942) observed cyanosis in 19 patients, or five percent of the series studied. Of these, 3 had clubbed fingers and 8 were dyspneic. None of the patients had hydrothorax. Fifteen patients were noted to be cyanosed either at the same time or after the appearance of ascites. In 2 of the patients who were cyanosed, ascites was not described. In 2 others, the cyanosis was said to precede the onset of ascites. Fagin and Thompson (1944) found organic heart disease present in 15 percent of their 71 cases of cirrhosis of the liver. One case of rheumatic heart disease, two of hypertensive heart disease, and seven of arteriosclerotic heart

disease. However, in only four of these was there evidence of congestive failure. They further pointed out that the detection congestive failure in association with cirrhosis of the liver is a difficult clinical problem, since dependent edema is common in cirrhosis and dyspnea and orthopnea may result from ascites or hydrothorax.

Keys and Snell (1938) observed that the oxygen saturation of the arterial blood was subnormal in 8 to 14 patients with cirrhosis of the liver. They suggested that in cirrhosis there might be an alteration in the affinity between oxygen and hemoglobin. Darling (1940) found the mean oxygen saturation of the arterial blood of 34 patients with cirrhosis was 95.0 per cent, only 0.5 percent below normal. Ratnoff and Patek (1942) observed abnormal oxygen saturation in the arterial blood in 9 of their 386 cases. In three of these there was a co-existing pulmonary disease.

A survey of 619 cases of portal cirrhosis has been given and ofthis group it was found that 53, or 8.5 percent, were found to have organic heart disease. From this it seems reasonable to conclude that the cardiovascular status of patients with cirrhosis of the liver does not differ materially from that of patients of a comparable age group. The oxygen tension of the arterial

blood may be lowered slightly in cirrhosis of the liver but its effect is practically negligible.

Urinary Symptoms- Nocturia was noted in 48 of 163 cases of cirrhosis of the liver by Henrikson in 1936. Ratnoff and Patek noticed increased frequency of urination or nocturia in 130, or 34 percent of their 386 cases. Twenty-three of these patients were said not to have ascites at the time these symptoms were noted. Fagin and Thompson (1944) noted one case of hematura in their series of 71 cases studied in 1944. They attributed this to the rupture of a urethral varix.

I was unable to find any explanation, in the literature that I covered, for these urinary symptoms. It is my opinion that they amy be due to any one of three different causes: (1) Pressure of ascitic fluid upon a distended bladder, (2) Hepatomegaly and splenomegaly, forcing the viscera downward and thus referring the resulting pressure upon the underlying bladder and (3) These patients are in the proper age group for benign prostatic hypertrophy, and the obstruction to the urinary tract offered by the enlarged prostate may play a role. This evidence seems more plausable when you consider the fact that cirrhosis of the liver, as has been shown, occurs from two to three times more frequently in the male than it does in the female.

Symptoms Referable to Endocrine Disturbances- In the female these symptoms seem to be unimportant and relatively rare. Rolleston and McNee (1929) are of the opinion that metrorrhagia is frequent early in the disease, to be followed later by amenorrhea. Hartwell and Johnson (1937) described a young girl found to have cirrhosis at operation, in whom remission of ascites occured coincident with the onset of emnsis in her twenty-first year. Tenney and King (1933) reported the case of a woman known to have cirrhosis who delivered a child by Caesarian section under spinal anesthesia. They discovered two cases in the literature in which cirrhosis was first noticed during the course of pregnaney.

Edmondson, Glass and Soll (1939) observed that testicular atrophy was present in each of 14 patients with liver disease, and gyncomastia in eight instances. Endocrine assay showed that the urine androgens was below normal. Estrogen, normally excreted in the combined form was excreded in the free state in patients with cirrhosis. Fagin and Thompson (1944) noted that "unilateral" gynecomastica was present in one of their 71 cases. Spain (1945) has given an excellent review of the subject. He stated, "It is well known that in males with portal cirrhosis there is very often either sparce hair or complete absence of it over the pectoral regions;

that not infrequently, there is atrophy of the seminiferous tubules of the testes, while the interstitial cells of Leydig increase in number, and that occasionally breast changes are present similar in appearance to gynecomastia. Some observers have stated that the pectoral alopecia in the cases antedated the portal cirrhosis but at present, it is generally believed that all these changes are attributable to the inability of the patient's damaged liver to neutralize the estrogenic hormones is present that results in the above-mentioned changes. Thus, these changes are secondary to the cirrhosis and there is as yet no evidence pointing to primary underlying endocrine difference to account for the different behavior of males and females with portal cirrhosis."

Physical Signs of Portal Cirrhosis

Ascites- Ascites, or the accumulation of fluid in the peritoneal cavity is one of the most common physical signs of advanced portal cirrhosis. Snell (1931) reported the presence of ascites in all of his 112 cases of cirrhosis. Henrikson (1936) noted its presence in 121 of his 162 cases. Rolleston and McNee (1929) reported that of the 80 patients they examined post-mortem, whose death was due to cirrhosis, 85 percent had ascites. Ratnoff and Patek (1942) state that ascites is the most frequent and most characteristic sign of cirrhosis of the liver and its presence was noted in 78 percent of their series of 386 patients. In 220 of this group, the ascites was associated with edema of the lower extremities and usually preceeded the latter in appearance. Fagin and Thompson (1944) found, in their series of 71 cases, abdominal enlargement due to the accumulation of ascitic fluid in 55 percent of their subjects. It was the chief complaint at the time of admission in 31 cases and an incidental complaint in eight others. Chaikin and Schwimmer (1945) stated that ascites is one of the most outstanding "obstructive" signs in cirrhosis and noted its presence in 93 of their 246 cases. Spain (1945) observed the presence of fluid within the peri-

toneal cavity at the time of autopsy in 99 of their 250 subjects examined. They further emphasized that 37 percent of this group were males and 46.9 percent were in females.

A total of 1,307 combined necropsy and clinical cases of portal cirrhosis have been sited above, and it was found that of this group 833, or 63.7, had a history of ascites.

The exact mechanism whereby this ascitic fluid accumulates in the peritoneal cavity is rather complex, and a number of factors are involved. In the section devoted to the pathogenesis of portal cirrhosis, it was mentioned that the perilobular connective tissue contracts with age, thus compressing the terminals of the portal vein. This would lead one to believe that there is an increased tension within the portal vein as a result of this increased resistence to the flow of blood. This assumption was confirmed by the work of Thompson, Caughey, Whipple and Rousselot (1937) and Thompson (1940) when they demonstrated hypertension in the portal system in 7 patients with cirrhosis of the liver and splenomegaly. Direct readings of the splenic vein pressure was made and found to range from 225 to 470 mm. of saline; in five instances the pressure was 325 mm. or higher. In 19 of 20 control patients the splenic vein pressure was

less than 300 mm. of saline. Further evidence for increased tension within the portal vein is offered by McIndo (1928). In his injection studies of the cirrhotic liver, he not only noticed a marked diminution of the total vascular bed, but that it required much more pressure to inject the cirrhotic liver than it did the normal liver.

This increased tension within the portal system cannot alone account for the presence of ascites, because it was shown above that all cases of cirrhosis seen at autopsy do not show evidence of ascites. According to Lichtman (1942) qualitative and quantitative changes in everyone of 16 patients, (15 of them having ascites) the serum albumin was 2.63 grams per 100 cc. Foley, Keetan, Kendrick and Darling (1937) state that hypoproteinemia primarily due to lowered serum albumin content, with decrease or inversion of the albumin to globulin ratio, is a common finding in patients with cirrhosis of the liver. Butt, Snell and Keys (1939) measured the colloid osmotic pressure of the serum in cirrhosis and found it reduced to half the normal value. The colloid osmotic pressure averaged between 200 and 250 mm. of water (normal, 375 mm. water). Ratnoff and Patek (1942) observed that in addition to the decline in serum albumin, there is a fall in the level of serum albumin and a rise

in the serum globulin, the total serum protein is only moderately affected. Post and Patek (1943) showed that there is a "critical level" (3.1 plus or minus 0.2 grams per 100 cc.) of serum albumin at which diuresis and loss of ascites takes place. Chaikin and Schwimmer (1945) are of the opinion that the occurrence of ascites is directly related to the serum proteins. When the value for the total proteins falls below five grams per 100 cc., or that for albumin below 2.2 grams per 100 cc., with a consequent reversal of the albumin to globulin ratio, ascites invariably accumulated in the peritoneal cavity because of a decrease in the intravascular osmotic tension. Wade (1945) found a decrease in the serum albumin in 95 percent of the subjects that he studied. He further noted that compensatory increase in the globulin fraction usually occurs and this results in a fairly normal total protein and a reversal of the albumin to globulin ratio.

Other possible causes for the accumulation of ascitic fluid, including increased vascular permeability and cardiac decompensation have already been discussed, and will not be repeated at this time.

In summarizing the above material it can be shown that ascites occurs in approximately 63.7 percent of the cases with cirrhosis of the liver. The most common

cause of the ascites is reduction of the osmotic pressure of the blood serum as a result of loss of serum protein and a reversal of the albumin to globulin ratio; however, there is usually a compensatory increase in the serum globulin so that the total serum protein is not altered to a great extent. The second most common cause is increased tension within the portal vein as a result of the progressive contraction of the perilobular connective tissue constricting the terminal radicles of the portal vein causing an increase in the peripheral resistance. Other causitive factors are of less importance among which may be included increased capillary permeability and associated cardio-respiratory diseases.

Edema- This is another very common finding in patients with cirrhosis of the liver. Chapman, Snell and Rowntree (1931) found that edema was present in 20 of 58 of their patients who had cirrhosis of the liver without ascites and in 85 of 112 patients with cirrhosis and ascites. Henrikson in 1936 found that 44 percent of 163 patients with cirrhosis had edema. Patek and Post (1941), in a study of 54 cases of cirrhosis of the liver, found edema present in 85 percent of this group. Ratnoff and Patek (1942) observed the presence of edema in 61 percent of their 386 cases. They further stated that the edema was usually noticed in the lower

extremities and in 32 cases it preceded the appearance of the ascites. Edema was also noted in 16 patients in whom ascites was not described. Fagin and Thompson (1944) noted that edema was present in 59 percent of their 71 cases of cirrhosis of the liver. It was the earliest symptom in 13 patients and the presenting complaint of nine patients. They also stated that the edema in these cases "usually" involved the lower extremities.

The mechanism producing the edema is, in part at least, the same as that producing ascites. Patek and Post (1941) noted that in all instances where edema was present it was associated with low serum albumin; furthermore, edema was not present in those whose serum albumin was normal. As another causative factor, these authors state that the accumulation of ascitic fluid in the abdominal cavity causes a pressure to be exerted on the inferior vena cava and lymphatic trunk, thus impairing both venous and lymphatic drainage from the lower extremities. This theory is supported by Fagin and Thompson (1944).

In summary, a total of 844 patients with cirrhosis of the liver has been described, and of this group a history of edema was found in 498 cases, or 59 percent. The edema is usually of the dependent type. Occasionally it is the presenting complaint of the patient with cir-

of cirrhosis in 10 patients, and the presenting complaint of eight. Physical examination of the patients revealed icterus in an additional 10 patients, bringing the total of jaundiced patients to 52 percent. Of 44 patients in whom the icteric index was determined, 28 had values of 10 units or higher, and 15 had values of 30 units or higher. Chaikin and Schwimmer (1945) noted the presence of jaundice in 44 percent of their 246 cases, and it varied intensely from a mild fleeting attack of a few days duration to one with deep icterus lasting for weeks. Nine patients in this group were admitted in a state of "hepatic insufficiency" characterized by confusion, disorientation, and deep coma from which the patient could not be aroused. Spain (1945) by the use of simple gross observation of the sclera and skin found 75 of his 250 subjects had jaundice at the time of autopsy. They also stated that jaundice occurred twice as frequently in the female at the time of death as in the male.

Other symptoms and signs frequently seen in the presence of jaundice have been described by these authors, but there are marked discrepancies among their findings. Henrikson (1936) observed this finding in 13 of their 386 cases. Fagin and Thompson (1944) state, "Pruritus was a frequent accompaniment of the higher degrees of

jaundice, but clay colored stools were rarely noted."

Ratnoff and Patek (1942) stated that the pathogenesis of jaundice is not well understood. In an attempt to correlate the presence of jaundice with the presence of the parenchymal cells of the liver, these authors analyzed the protocols of 77 patients with cirrhosis and found that only half of those patients with jaundice had necrosis of the liver cells on histologic examination. Patek and Post (1941) made autopsy studies of the liver in 21 cases of cirrhosis of the liver and they reported they could see no correlation between the presence of jaundice and necrosis of liver cells and from this they concluded that the absence of necrosis does not exclude functional derangement of the liver. Mallory (1932) is of the opinion that obstruction of the bile ducts in cirrhosis is usually focal, but he stated that it may be widespread and involve large parts of the liver so that much bile passes into the circulation and gives rise to intense jaundice.

In summary, a total of 1,735 cases of cirrhosis of the liver, seen both clinically and at necropsy, have been presented and of this group 767, or 44.3 percent, were found to have a history of jaundice. The jaundice is usually mild, but occasionally severe. The icteric index was usually somewhere between 10 and 25 units.

Jaundice was occasionally described as being the presenting complaint. The pathogenesis of jaundice is not well understood, but it may be due to diffuse fibrotic changes throughout the parenchyma of the liver blocking the bile capillaries forcing the bile into the circulation. It does not appear to be due to necrosis of hepatic cells.

Palpable Liver- Nissen (1920) found that the liver was palpable below the costal margin in 43 of 77 patients with cirrhosis of the liver. Chapman, Snell and Rowntree (1931) observed that the liver was palpable in 48 of 58 patients who had cirrhosis of the liver without ascites and in 69 of 112 patients with ascites. Henrikson (1936) found that the liver was palpable in 101 of 162 cases with cirrhosis. Ratnoff and Patek (1942) found that 75 percent of the patients in their series of 386 cases of cirrhosis had palpable liver. They also attempted to correlate the weight of the liver as found at autopsy, with its palpability. The average weight of 78 palpable livers which showed cirrhosis was 1820 grams, the weights ranging from 695 to 5100 grams. On the other hand, they found that 30 nonpalpable livers with cirrhosis weighed an average of 1370 grams, ranging from 570 grams to 2920 grams. Fagin and Thomson (1944) noted that a palpable liver was their most

common physical finding in their series of 71 patients with cirrhosis of the liver, and noted its presence in 70 percent of the group. The average weight of the liver in the patients examined post-mortem was 2207 grams, the weight varying from 915 grams to 4420 grams.

Lichtman (1942) is of the opinion that palpation of the liver below the costal margin may be due to ptosis, fatty changes, venous congestion or mere hypertrophy without pathological changes.

A total of 704 cirrhotic livers have been described, and of this group it was found that 499, or 70.8 percent of these were palpable. It was noted that if the liver was palpated it was usually found to be enlarged, but this is not always true.

Palpable Spleen- Nissen (1920) described a palpable spleen in 6 of 77 patients with cirrhosis of the liver. Chapman, Snell and Rowntree (1931) reported the spleen was palpable in 27 of 58 patients who had cirrhosis without ascites, and in 49 of 112 patients with ascites. Henrikson (1936) reported 75 of his series of 162 cases had palpable spleens. Ratnoff and Patek (1942) noted the presence of a palpable spleen in 170 of their 386 cases of cirrhosis. They found the average weight of 43 palpable spleens was 580 grams, ranging from 180 to 1700 grams. Sixty-eight non-palpable spleens weighed an average of

320 grams, ranging from 30 to 940 grams. These same authors compared this with the figures on the liver with regard to its palpability and size, and concluded that a palapble spleen is much more likely to represent an enlarged spleen than a palpable liver is to represent an enlargedliver. Fagin and Thompson (1944) noted the presence of a palpable spleen in 24 percent of their 71 cases. They found that the weight of the spleen in the patients examined post-mortem averaged 395 grams and varied from 150 to 800 grams.

The causes of splenomegaly in cirrhosis of the liver is still a debated question. Why it should be enlarged in one patient and not in the other is difficult to explain. Johnston (1931) emphasized that age was an important factor in the causation of splenomegaly, the young being more prone to the development of splenic enlargement. Mallory (1932) found the largest spleen in his 550 cases to weigh 3990 grams, and he attributed this to congestion and multiple infarcts. Thompson, Caughey, and Whipple (1937) measured the splenic vein pressure at laporatomy and reported that an obstructing factor was the cause of portal hypertension in 52 percent of cases of congestive splenomegaly. In a second group of 24 cases, these same authors noticed that 70 percent had a demonstrable obstructive factor. Lichtman (1942) feels

that the primary result of portal hypertension is congestive splenomegaly. The venous radical in the rich venous collaterals often enveloping the spleen are visible phenomena in congestive splenomegaly. This same author also suggested that splenic enlargement may be due to general infections or intoxication, and portal stasis enhances the affect of these toxic substances upon the spleen. He also believes that the absence of splenomegaly may be due to either extreme fibrosis or calcification of the capsule of the spleen which offers great resistance to distension of the organ or to the presence of collateral channels draining in the portal system. Both of these factors may be acting simultaneously. It is commonly agreed that the presence of ascitic fluid in the peritoneal cavity makes palpation of the spleen more difficult.

A total of 866 enlarged spleens found in association with cirrhosis of the liver have been described above and of this group 345, or 39.6 percent, were found to be palpable. Contributing factors to the production of an enlarged spleen include: (1) Increased tension within the portal vein, (2) Generalized intoxication, especially in the presence of venous stasis and (3) Youth. Factors which may prevent splenic enlargement include: (1) Extreme fibrosis or calcification of the splenic

stance, the pleural fluid was grossly bloody. Chaikin and Schwimmer (1945) in their report on 246 cases of cirrhosis of the liver found right-sided pleural effusion in 7 cases and left-sided in four. The effusions were non-hemorrhagic, and no evidence of tuberculosis was found.

The mechanism underlying the development of hydrothorax in cirrhosis of the liver is not clear. Mallory (1940) believes that in many cases there is a fairly free pallage of fluid through the diaphragm, and in one of the patients studied by Fagin and Thompson (1944) thoracentesis usually resulted in an obvious decrease in the degree of ascites; however, the autopsy examination of this case disclosed no gross evidence of abnormality of the diaphragm. Ratnoff and Patek (1942) believe it is due to decreased osmotic pressure and mechanical interference with pulmonary circulation due to ascites. Chaikin and Schwimmer (1945) are of the opinion that it is due to a high diaphragm due to ascites with subsequent stasis of the pulmonary vascular bed, hyprotenemia with reduction of the serum albumin or possibly as a result of portopulmonary venous anastomosis.

A total of 697 cases of cirrhosis of the liver with ascites has been reviewed, and of this group 42,

or 6.0 percent were found to have either unilateral or bilateral hydrothorax. The mechanism whereby this is produced is probably due to combination of any of the following factors: (1) Free communication between the plueral and peritoneal cavity allowing flow of ascitic fluid into the pleural space, (2) Reduction in the serum albumin, thus decreasing the osmotic tension of the latter, (3) Elevation of the diaphragm due to the presence of ascitic fluid, which results in pulmonary stasis and (4) Portopulmonary anastomosis.

Collateral Circulatory Changes- Chapman, Snell and Rowntree (1931) reported that of 58 patients who had cirrhosis without ascites, 7 had evidence of collateral circulation whereas this was present in 57 of 112 who had cirrhosis with ascites. Jankelson and Baker (1938) demonstrated that dilated subcutaneous veins in cirrhosis not visible to the naked eye may be made visible by means of infra-red photography of the abdominal wall. Ratnoff and Patek (1942) in their analysis of 386 patients with cirrhosis of the liver, noted evidence of collateral circulation between the portal and systemic circulations in 23.6 percent of their patients. In four patients a large group of dialated veins, the "caput madusae" appeared around the umbilicus. Fagin and Thompson (1944) noted the prominence of the veins of the ab-

dominal wall in 41 percent of their 71 cases of cirrhosis of the liver. Chaikin and Schwimmer (1945) noted evidence of increased collateral circulation in 67 of 93 decompensated cases with ascites. Of 70 cases where ascites was absent, but the liver was palpable 4 to 5 fingers below the costal margin, 23 showed evidence of collateral circulation.

In summary, a total of 790 cases of cirrhosis of the liver have been reviewed and of this group it was found that 275, or 34.4 percent, presented evidence of collateral circulatory changes.

Another fairly common manifestation of cirrhosis of the liver that is due, in part at least, to collateral changes is hemorrhoids. Chapman, Snell and Rowntree (1931) found hemorrhoids in 9 of 58 patients who had cirrhosis without ascites, and in 46 of 112 patients with ascites. Hemorrhoids were present in 105 of the 386 patients in the series studied by Ratnoff and Patek in 1942. Rectal discomfort, dyschesia, or bleeding due to hemorrhoids were noted by only two of the patients studied by Fagin and Thompson in 1944. In one case hemorrhoids were the presenting complaint. Physical examination, however, revealed dialated and protruding hemorrhoidal veins in 34 percent of the patients. Eighteen of the 24 who had hemorrhoids also had ascites.

Chaikin and Schwimmer (1945) made rectal examination on 87 patients, of whom 39 had ascites. They noted that 15 out of 46 without ascites had hemorrhoids, while in the group with ascites, 21 patients had hemorrhoids.

The frequency with which hemorrhoids were found in association with ascites have led the authors of the last two references cited to conclude that hemorrhoids are the result not only of portal stasis, but also of pressure exerted by the ascitic fluid upon the inferior vena cava or the hemorrhoidal veins.

The various communications that exist between the portal vein and vena cava have been classified by McIndoe in 1928. He divided these channels into three groups.

Group 1.- At the two situations in the gastrointestinal tract where absorbing epithelium comes in contract with protective epithelium, that is, the cardia and anus. The former represents the site of anastomosis of the coronary vein of the stomach with the intercostal, azygos minor and diaphragmatic veins of the caval circulation, here producing esophageal varices. At the latter, the superior hemorrhoidal veins of the portal circulation anastomoses with the middle and inferior hemorrhoidal veins of the caval circulation.

Group 2.- At the site of an obliterated embro-

logical circulation, that is, the falciform ligament containing the parumbilical veins. The umbilical vein is itself rarely, if ever, a part of the actual circulation, being entirely obliterated a few days after birth.

Group 3.- At all situations within the abdomen where the gastro-intestinal tract, its appendages or the glands developed from it, become retroperitoneal developmentally or adherent to the abdominal walls, pathologically, This includes the duodenum, small intestine, colon, omentum, spleen and pancreas, containing the veins of Retzius, and the liver with its accessory veins of Sappey, both establishing an anastomosis between the portal and caval veins.

In summary, it has been shown that of the 712 cases of cirrhosis of the liver described above, 220, or 30.9 percent were found to have had hemorrhoids. The development of hemorrhoids is due mainly to portal obstruction and pressure of the ascitic fluid upon the inferior vena cava and hemorrhoidal veins.

Fever- In 81 patients with uncomplicated portal cirrhosis, King (1929) found that 14 were afebrile, 56 had temperatures between 99 degrees F. and 101 degrees F., 4 had temperatures between 101 degrees F. and 103 degrees F., and 7 patients had temperatures between 103

degrees and 105 degrees F. After excluding all cases in which a patent cause, such as secondary infection or hemorrhage, was present, Ratnoff and Patek (1942) found that 24 percent of their 386 cases with cirrhosis had a temperature of 11.4 degrees F. or more while under observation. The fever was usually protracted and of low grade. Five patients had a spiking temperature reaching 102 degrees F. each day. Chills and fever, with temperatures as high as 103 degrees F. were noted in 13 patients. Fagin and Thompson (1944) found an elevated temperature in 49 percent of their 71 cases of cirrhosis. The fever was usually low grade and of intermittent character and possibly reflected "active inflammatory and degenerative processes in the liver parenchyma." Lichtman (1942) stated that as a rule the temperature of a patient with cirrhosis of the liver is normal and if fever is present it suggests some complication, such as tuberculosis.

In summary, it has been shown above that a low grade fever is frequently present in supposedly uncomplicated cases of cirrhosis of the liver. Of the 538 cases of cirrhosis described, 194, or 36 percent, were found febrile. It has been suggested that an active inflammatory process in the liver may be the cause, and of course, any other associated inflammatory

disease process.

Angiomata- Williams and Snell (1938) reviewed 15 cases of cutaneous telangiectasis associated with hepatic disease, six men and nine women ranged in age from 35 to 73 years, most in the fifth and sixth decade of life. "Spider naevi" appeared on the face, neck, nasal mucosa, tongue, lips and hands, in most instances antedating, but often increasing rapidly in extent and number with the symptomatic phase of the hepatic disorder. In 10 of the cases there were also familial hemorrhagic telangiectasia. Hepatic cirrhosis was present in five cases, metastatic carcinoma of the liver in two and hepatosplenomegaly of an undiagnosed type in six. Patek, Post and Victor (1940) observed that 48 of 63 patients with cirrhosis of the liver had "vascular spiders". They described the spider as a bright red lesion, characterized by a central point from which radiate fine, hair-like branches for a distance of about one centimeter, usually occurring on the skin of the face, arms, fingers and upper trunk and occasionally on the lower trunk and limbs. They also demonstrated pulsations in the "spiders". Histologic section revealed appearance of a glomus except that it branched into capillaries instead of forming arteriovenous anastamoses. Ratnoff and Patek (1942) noted that

15 percent of their series of 386 patients with cirrhosis were found to have "spider angiomata", and "telangiectasis in 17 percent.

Neurological Findings- Neurological examinations were done on 300 of the 386 patients with cirrhosis of the liver studied by Ratnoff and Patek (1942). Approximately two-thirds of them were found to have no abnormal neurological signs. Forty patients, or about 13 percent, had either the symptoms of peripheral neuritis or absent deep reflexes. Mental changes, were described in 28 of the 386 patients. A toxic delirium was observed in 7 patients, "mania" in 3, and delirium tremens in 3 others. Occasionally Korsakow's psychosis, hallucinations, or delusions were said to be present.

Fagin and Thompson (1944) noted the development of nervous disturbances progressing from restlessness to delirium and coma ending in death in 21 percent of their 71 cases. They also went on to state that in 6 of the 15 patients dying in coma, the development of stupor progressing to coma followed within a few hours the administration of morphine sulfate in dosages of one-sixth to one-fourth grain and apparently was precipitated by the opiate.

Rolleston and McNee (1929) have given an excellent discussion of these neurological changes. They stated,

"The minor degrees of peripheral neuritis are often thrown into the shade by ascites or other effects of cirrhosis in which attention is focused, and so passes undetected. Cramps, muscular tenderness and loss of tendo achilles and knee jerks may occur in cases of cirrhosis admitted for ascites or hematemesis, and are, generally referred to alcoholism. Peripheral neuritis in the early stages of cirrhosis is usually alcoholic and may be due to a combination of varying degrees of alcohol and hepatic insufficiency."

Laboratory Aids to the Diagnosis of Portal Cirrhosis

It is not the contention of the author to give a complete detailed analysis of all the laboratory tests that have been used as an aid to the diagnosis of cirrhosis of the liver. The fundamental principles, as presented by Lichtman (1942), of a few of the common tests used at the present time will be presented, and their value as an aid to the diagnosis will be stressed.

Hematological Examinations- Several cases of Addisonian pernicious anemia have been reported to occur simultaneously with cirrhosis of the liver. McCartney (1933) observed one instance of pernicious anemia among 245 cases of cirrhosis at autopsy. Wintrobe (1936) studied the blood picture of 23 patients who had cirrhosis and noted that anemia was present in every instance. In 10 cases the anemia was macrocytic, in 11 it was normocytic, and in 4 others, hypochromic microcytic in type. Ratnoff and Patek (1942), in their series of 386 cases of cirrhosis, observed two patients with Addisonian pernicious anemia, confirmed at autopsy, one patient with sickle cell anemia, and one with polycythemia vera, which had been treated with phenylhydrazine. Chaikin and Schwimmer (1945), in their analysis of 246 cases of cirrhosis noted that nine patients were admitted with a

tentative diagnosis of pernicious anemia. Hematological investigation, including sternal puncture, was highly suggestive of pernicious anemia. However, gastric analysis following histamine stimulation showed the presence of free acid, and further investigation confirmed the diagnosis of cirrhosis of the liver. These same authors noted the presence of a secondary anemia in 87 patients in this group. They attributed this to recurrent hemorrhage, or insufficient intake, absorption and storage of iron. Twenty-three of these 87 patients were primarily admitted for subjective complaints of dizziness and weakness.

The cause of the macrocytic anemia is not too clear but several explanations for its occurence hav been offered. Wintrobe (1936) reported a reticulocyte response following therapy with liver extract in patients who have cirrhosis with macrocytic anemia, and he suggested that it may be due to the failure of the liver to store the anti-anemic substance of pernicious anemia. Chaikin and Schwimmer (1945), believe it is due to the inability of the liver to synthesize or deliver the anti-anemic principal.

There is a considerable variation in the leukocyte count in patinets with cirrhosis. Rolleston and McNee (1929) believe that leukocytosis did not occur in

patients with cirrhosis in the absence of complications. King (1929) analyzed the white blood cell count of 61 patients with uncomplicated cirrhosis. The leukocyte was less than 6,000 in 31 percent of the cases; between 6,000 and 10,000 in 41 percent of the cases. Seven of the 17 patients with leucocytosis had temperatures ranging from 101 degrees F. to 105 Degrees F. In most instances he found a normal leukocyte response to infection. He also added that the leukocyte count tends to be lower in those patients in whom extreme splenomegaly is present.

In summary of the above, it has been shown that any type of anemia may be present with cirrhosis of the liver. Occasionally, one sees a hematological picture with associated neurological manifestations simulating true pernicious anemia, but only rarely does it prove to be a true Addisonian pernicious anemia. This is probably due to the impaired hepatic function, and the liver is unable to store, synthesize, or deliver the anti-anemic principal. A secondary anemia is not uncommon and this is probably due to recurrent hemorrhages, or inadequate intake or storage of iron. Leucocytosis is very common and is probably due to secondary infection, or the inflammatory reaction within the liver itself.

Serum Proteins- The changes that are seen in the serum proteins in cirrhosis of the liver, and the mechanism whereby these changes have been produced, have already been discussed. It will suffice to say here that in advanced cases of portal cirrhosis there is a reversal of the albumin to globulin ratio, with a compensatory increase in the globulin fraction so that the total serum protein is usually unaltered; however, in terminal stages of the disease the serum proteins may fall far below the normal of 6 to 8 grams per 100 cc.

Urinalysis- According to Lichtman the urinary findings indicate that albuminuria is present in approximately one-half of the cases, cylindruria in approximately one-third of cases and bilirubin in cirrhotics with jaundice. The urobilin and urobilinogen content of the urine is usually increased.

Bromsulphthalein test- This is a dye excretion test and measures the rate at which the reticulo endothelial cells of the liver remove the dye from the blood stream and excrete it into the urine. Persons with normal liver function retain 35 percent at five minutes and only a faint trace or none at the end of thirty minutes. With parenchymal liver damage the dye is retained in the blood stream in concentrations which vary from 0 to 100 percent. This test is invalid in the

presence of jaundice and Townsend (1944) emphasized that a prerequisite for this test is a serum bilirubin of not over 6.0 mgm. per cent.

Nicholson, St. John and Taylor (1945) studied 22 patients with cirrhosis of the liver and found this test showed no retention in 5 cases, while in 12 additional patients the retention was less than 5 percent at the end of 45 minutes. They concluded that the cephalin-cholesterol flocculation test is more s nsitive than this test in a patient with cirrhosis of the liver. Wade and Richman (1945) studied this test on 127 cases of cirrhosis of the liver and found it to be positive in 89.1 percent of the cases. It was excelled only by the cephalin-cholesterol flocculation test. Watson (1944) believes this test should be employed in all cases of cirrhosis of the liver, but thinks it is of less value than the cephalin-cholesterol test or the quantitative urine urobilinogen test.

Cephalin-Cholesterol Flocculation test- This test is based upon the fact that the serum of subjects with hepatic parenchymal damage will flocculate a colloidial suspension of cephalin-cholesterol complex. It probably depends on the capacity of an altered globulin constituent of the serum to become affixed to the colloidial elements of the emulsion.

Nicholson, St. John, and Taylor (1945) employed this test on 22 patients with cirrhosis of the liver and all of these had strongly positive cephalin-cholesterol flocculation tests, even in the absence of an elevation of the serum bilirubin. Chaikin and Schwimmer (1945) employed this test in 131 cases of cirrhosis of the liver and found that a negative reaction was obtained in 14 percent of 57 jaundiced patients and in 58 percent of 74 non-jaundiced ones. In the jaundiced group, 72 percent exhibited 3 plus and 4 plus flocculation, while 14 percent had one plus and 2 plus responses. In the non-jaundiced group, only 19 percent had 3 plus and 4 plus reaction. In their experiment they found this test to be excelled in raliability, only by the cholesterol ester determination. Wade and Richman (1945) found this test to be positive in 125 of 127 cases of proven cirrhosis of the liver. They further stated that of 178 patients with known diffuse parenchymatous liver disease this test was found to be positive in 173 instances. Nearly all were found to be 3 plus or 4 plus. Discrete lesions of the liver gave a positive test in only 53.3 percent of 45 cases. They noted that occasionally "false positive" reactions occur during the course of infections, in the presence of allergic disease, or during the puerperium of the

neonatal period.

Chol sterol Esters- The fundamental principles of this test are not known, but it is believed that the hepatic cells esterify cholesterol. The normal value for this test is from 50 to 70 percent of the total cholesterol. With parenchymal liver dammage these values are considerably lowered.

Chaikin and Schwimmer (1945) used this test on 131 patients with cirrhosis of the liver and considered a figure below 65 percent as abnormal. According to this criterion, 55 percent of non-jaundiced cases gave abnormal results. In the jaundiced group the figures were even more impressive, with 86 percent of cases exhibiting an abnormal percentage of esters; of these, almost one-fourth had ester values below 35 percent of the total cholesterol. It is interesting to note that Spellberg, Keeton and Ginsberg (1942) in producing experimental cirrhosis in guniea pigs on a deficient diet, noted an early drop in the plasma cholesterol esters in all cases.

Hippuric Acid Test- This test is based upon the fact that the liver detoxifies sodium bensoate by combining it with glycine to make harmless hippuric acid, which is excreted rapidly in the urine. Since glycine is synthesized in the liver, certain types of liver

damage show a diminution in the hourly excretion of hippuric acid by the kidney. Normal adults excrete 0.70 to 0.95 gm. or less in one hour. An output of 0.5 gm. or less in one hour is indicative of severe liver damage. In mal-functioning kidneys the test is obviously not valid, but to measure or evaluate the renal function simultaneously, Hoffbauer, Evans and Watson (1945) inject 6 mgm. of phenolsulfonphthalein dye through the same needle after giving the sodium benzoate. The urine specimen is collected at the end of 60 minutes and an aliquot is used to determine the dye excretion, the balance being employed for the determination of the hippuric acid. This is obviously advantageous because it evaluates renal function at the time that such knowlege is most desirable, viz., during the actual hour the hippuric acid test is being conducted.

Wade and Richman (1945) found that of 127 patients with cirrhosis of the liver 83.1 percent had a positive hippuric acid test. They found this test to be excelled by both the cephalin-cholesterol flocculation test (98.5 percent positive) and the bromsulfalein test.

Takata-Ara Reaction- The principle of this reaction is unknown, but is believed to depend upon the

reveRsal or partial reversal of the albumin to globulin ratio, and hence some disturbance in protein metabolism.

According to Lichtman (1942) this test was at first thought to be specific for cirrhosis of the liver; however, future work soon indicated the lack of this specificity. Magath (1938) has made a comprehensive review of the results of the Takata-ara reaction in cases of cirrhosis of the liver and found that positive reactions were obtained in 82 percent of 1,270 cases of cirrhosis gave positive reactions. Lichtman (1942) states that the validity of this reaction is questionable, because positive tests are obtained in other forms of liver disease and in certain conditions in which liver disease is absent.

Van den Berg Reaction- Kracke and Parker (1940) described this test as being based upon the formation of a colored compound azobilirubin when sulphanilic acid and sodium nitrate are added to a solution of bilirubin. When quantities of bile pigment are absorbed or regurgitated into the blood stream, as in obstruction of the common bile duct by a stone, the serum upon testing, gives a direct reaction. When there is an increase in the serum bilirubin in the blood that has not been acted upon by the liver, as in conditions of excessive hemolysis of red cells, no color reaction is elicited until

the serum has been titrated with alcohol. This is an indirect reaction. A third type of reaction, the biphasic reaction, is seen where both types are present simultaneously. In the event there is marked liver damage so that the hepatic cells can no longer convert biliruben Type 1 (the derivative of the porphyrin fraction of the hemoglobin molecule) to bilirubin Type 11, the indirect reaction occurs.

Chaikin and Schwimmer (1945) found the direct Van den Berg to be positive in 9 percent of their 108 jaundiced patients, the indirect type was present in 69 percent and the remaining 22 percent showed the biphasic reaction.

Icteric Index- This is a simple test for determining the amount of bilirubin in the blood serum, and is done by comparing the depth of the yellow color of the serum to a standard potassium dichromate solution. Normal values for this test are between 2.5 and 5 units. Anything above 15 units is usually associated with definite clinical jaundice.

Since the signifigance of this test in determining jaundice has already been emphasized in the section devoted to the physical signs of portal cirrhosis, it will merely be necessary to state at this time that in patients with cirrhosis of the liver the icteric index

usually ranges somewhere between 10 and 25 units; however, values much higher than this are not uncommon.

Medical Management of Portal Cirrhosis

Within the past several years there has been a marked change in the medical management of cirrhosis of the liver, particularly in regard to the role of diet in therapy. This is undoubtedly due to a multiplicity of factors, but the most important can be accredited to a better understanding of the underlying disturbed physiological and pathological changes associated with cirrhosis of the liver and upon more accurate and scientific experimental and clinical observations.

The pathogenesis has been presented in a previous section, so at this time I shall attempt to analyze a few of the recent experimental and clinical observations. For this reason I have divided the section devoted to therapy into two parts. The first will include the results of a few experimental investigations upon animals, and emphasis will be stressed upon those substances which have been used clinically in the therapy of cirrhosis of the liver. In the second part, I shall attempt to present the results of the therapy in the human subject, the rationale for which was based upon the experimental observations in animals. Along with this, other points of interest in therapy will be presented along with the rationale for doing so.

Animal Experimentation

Of recent years an entirely new concept concerning the relationship of alcohol to cirrhosis of the liver has been introduced. Chaikoff, Connor and Biskind (1938) in experimenting with depancreatized dogs maintained with insulin noted that a constant early finding in all of his 16 animals was an early increase in the amount of fat in the liver. In the same year Connor (1938) emphasized the importance of prolonged fatty infiltration of the liver in the development of cirrhosis in both diabetes and chronic alcoholism. This same author a year later published an article that cast more light on the subject of cirrhosis of the liver than any other of its kind. He stated, "Alcohol and the habits induced by the consumption of large amounts of alcohol are the most important factors in the production of a fatty liver which passes on in some cases to cirrhosis." To him it seems evident that when two factors are operating, alcohol and starvation or alcohol plus a protein-fat diet, all of which cause a marked lowering of the respiratory quotient of the hepatic cells, the liver will accumulate unoxidizable fat and the liver cells will be deprived of oxygen and nutrition. The liver becomes an unnatural storehouse for fat and approaches, so far as

oxygen-carbondioxide exchange is concerned, the normal fat storage tissue of the body, in which this is very low. There is complete depletion of glycogen from the liver, the absence of which renders it more susceptible to all poisons of this nature.

Jolliffe and Jellinek (1942) complimented Connor highly upon his observations and conclusions, and stated that it is odd that these observations had not been made before, because it has long been known that fatty liver is one of the most common occurrences in chronic alcoholic and estimated that it is porbably present in 75 percent of patients with chronic alcoholism.

The primary etiologic importance of diet rather than alcohol was subsequently indicated in 1940 when Chaikoff, and Connor produced marked fibrosis and fatty infiltration of the liver in dogs fed a high fat, low protein diet with supplements of "Cowgills" salt mixture, bone ash and vitamin supplements in the form of cod liver oil and rice bran concentrate. These findings were also confirmed by Blumberg and Grady (1942) who produced diffuse nodular cirrhosis in rats maintained for approximately 200 to 400 days on a stock diet supplemented with 3 to 5 cc. of ether extracted wheat germ oil. Similar observations were made by these same authors in rats fed similarly with commercial corn

oil. Similar experiments were again produced by Chaikoff, Eichorn, Connor and Entenman (1943) who produced marked fatty infiltration and cirrhosis in dogs recieving 7 grams of lean meat and 10 gm. of lard per Kg. of its initial body weight, and 1 to 3 gm. of bone ash with each meal. Vitamins A and D were also supplemented.

Concomitantly, experiments began to be carried out which would provide evidence that some vitamin deficiency was the important etiological factor in the production of cirrhosis of the liver. As a result of this a tremendous amount of literature has accumulated in the last few years concerning the relationship of vitamin deficiencies to cirrhosis of the liver.

Gygorgy and Goldblatt (1939) in experiments on rats kept on a basal diet deficient in the Vitamin B conplex and supplemented with vitamin B_1 and riboflavin, or with vitamin B_1, riboflavin and vitamin B_6 observed various pathological changes in the liver. These changes were characterized mainly by parenchymatous and fatty degeneration, focal and massive necrosis, hyperemia and hemorrhage and, in some, by perilobular and condensation fibrosis. They further found that the addition of yeast or "Peters' eluate" (yeast extract) regularly prevented these hepatic changes. From this they assumed that the liver changes are of nutritional origin and should be

correlated with deficiency in part of the nitamin B_2 complex. Rich and Hamilton (1940) observed diffuse portal cirrhosis in rabbits deficient in parts of the vitamin B_1, B_2, B_6, and nicotinic acid. They also emhasized that the animals that did not develop cirrhosis were obtaining choline from yeast.

Cystine has been accredited with procuring cirrhosis of the liver for some time. Curtis and Newberg (1927) demonstrated that the addition of as little as 0.75 percent cystine to an 8 percent diet produced slowly progessive interlobular necrosis in rats and larger amounts causes a progressively greater injury (massive hemorrhagic necrosis) in diminished intervals of time. Similar findings were reported by Earle and Victor (1941) who demonstrated that cystine fed to young albino rats as 10 percent of their diet resulted in portal hemorragic necrosis, fatty infiltration of hepatic cells in all rats surviving the initial acute lesion and cirrhosis of the liver in rats surviving more than two weeks. These same investigators, in the following year varied their diets considerably and then supplemented each with varying percentages of cystine and found that the pathogenesis of the liver lesions are related to the proportion of cystine in the diet but not to the amount of cystine ingested. They also noted that high fat diets

in the fo of 25 percent lard or cod liver oil have some protective action for excess cystine, while butter does not.

Another substance, choline, has been experimented with considerably in the last few years and is, as will be shown shortly, a lipotropic substance, i.e., it removes fat from the liver cells.

Gyorgy and Goldblatt (1941) found necrosis and cirrhosis of the liver in rats fed, for 100 days or more, a diet devoid of Vitamin B complex, but supplemented with thiamine, riboflavin, pyrodoxine and pantothenic acid. The diet was also low in protein (casein 10 percent) and high in fat (lard 20 percent). They found that the addition of cystine to the diet increased the liver damage, but choline reduced the incidence and severity of the liver injury to a limited extent. Blumberg and McCollum (1941) using rats fed a high fat, low protein diet supplemented with the same vitamins as above also produced marked cirrhosis of the liver. They also observed that the addition of l-cystine to the diet did not prevent the cirrhosis, but by adding 1 percent choline hydrochloride to this diet the cirrhosis was prevented. They further found that normal livers were secured by the combination with methionine, or even with cystine. They presumed the beneficial action of choline

to be due to its lipotropic activity, and thus prevents the long continued fatty infiltration which Connor (1939) has emphasized as leading to cirrhosis. Daft, Sebrell and Lillie (1941) observed a fairly rapid production of liver cirrhosis in rats on a low protein, high fat diet with added cystine; however, the addition of choline, methionine and casein, singly or in combination prevented the cirrhotic process.

Webster (1942) used betaine hydrochloride, a substance chemically related to choline, and found it to be preventative against cirrhosis in rats fed on high fat, low protein diets.

Lowrey, Daft, Sebrell, Ashburn and Lillie (1941) demonstrated that vial therapy with choline or with large amounts of casein can arrest the cirrhotic process in rats as indicated by survival, improved general condition, regression of fatty changes, decrease in liver size and improved appearance of the liver cells.

Blumberg, Mackenzie and Seligson (1942) investigated the effect of casein level with a choline-deficient diet containing 70 percent fat. At a 10 percent casein level all of the rats developed cirrhosis, at 18 percent most of the rat snowed slight cirrhosis, while at 24 percent cirrhosis was absent. Ten percent of yeast, in a diet containing 10 percent of total protein, was

also protective. Cirrhosis was produced in young rats on a somewhat similar diet containing 7 percent casein, 20 percent fat, and 0.456 percent cystine. Prevention was secured with 0.713 percent methionine. Methionine was also protective in paired feeding experiments, indicating that a difference in food consumption was not an essential factor. Liver lipids were increased in the cirrhotic rats.

Gygory and Goldblatt (1942) observed rats maintained on a diet low in casein with a moderately high or high content of fat and without choline regularly exhibited hepatic injury (diffuse or focal necrosis and cirrhosis) after between 100 and 150 days. Supplements of cystine were found to have an aggravating effect on the production of cirrhosis, whereas a supplement of choline alone reduced the severity and the incidence of hepatic injury, although not decisively. The combined administration of cystine plus choline or of methionine in adequated doses was found to be highly effective in preventing injury to the liver. They also noted that choline, even when given in combination with liver extract, proved to be ineffective in the prevention of hepatic injury.

Thus, so far, it has been almost unanimously agreed upon that either choline or methionine definitely

protects the liver against hepatic injury induced by high fat and low protein diets, or with low fat, low protein diets. Cystine alone will produce necrosis, but when given in combination with choline or methionine it has no deleterious effect upon the liver. However, as we shall see shortly, these contensions have not passed without opposition.

Spellberg, Keeton and Ginsberg (1942) observed that guniea pigs, placed on a diet containing approximately 20 percent fat, mostly in the form of butter, and modified by the addition of 10 percent dessicated yeast, showed severely fatty livers at necropsy. The fat content of the liver was found to vary from 19 to 39 percent of its total weight. They likewise found that these animals recieving the yeast supplement developed hepatic changes as easily as those who did not recieve the yeast. Furthermore, they found that neither choline or lipocaic influenced the fatty changes in the animals when these were supplements to the diets.

Himsworth and Glynn (1944) from their observations on white "Wistar" rats introduced an entirely new concept in regard to the production of cirrhosis by dietary means. They have presented rather convincing evidence that there can be two distinct lesions produced by dietary deficiencies; namely, massive hepatic necrosis

These same investigators, in the same year, published their results of a comparison of the effect of the following substances on both a high fat and high carbohydrate diet, each supplemented with 8 percent yeast protein. (1) Each basic diet alone. (2) Basic diet plus choline (4 mgm. per rat per day). (3) Basic diet plus 8 percent casein. (4) Basic diet plus methionine (in equivalent amounts to that found in 8 percent casein). (5) Basic diet plus cystine (equivalent to the amount in the 8 percent casein diet). (7) Basic diet plus cystine plus choline.

The results of these experiments showed that complete protection against the development of massive hepatic necrosis on either basic diet is given by including 8 percent of casein in that diet or by adding dl-methionine in the amounts contained in that quantity of casein. Cystine, in the amounts contained in an 8 percent casein diet, has no influence on the development of the lesion, and methionine and cystine together protect as effectively as methionine alone. Choline, in supplements of 4 mg. per rat per day, gives no protection, and the effects of choline and cystine in combination do not differ from those of either alone. From this they concluded that the protection afforded by casein can be adequately explained by the action of

the methionine it contains.

Brunschwig, Nichols, Biegelo, and Miles (1945) in experimenting with dogs subjected to chloroform anesthesia noted that protein molecules containing a sulfhydryl group when given in sufficient amounts protects the liver against hepatic injury, ordinarily induced by this anesthetic. Sodium thioglycollate was found to afford rapid protective action against hepatic injury and they emphasized the fact that this effect parallels that observed with methionine, a sulfur containing amino acid.

Warren and Findley (1945) have published a list of the lipotropic and antilipotropic substances known at the present time and before concluding the results of the literature that I have read pertaining to the animal experimentation upon lipotropic substances I would like to list them as they have.

Lipotropes	Antilipotropes
raw pancreas	cystine
lecithin	cysteine
choline and derivatives	homocysteine
betaine	low protein high fat diet
casein	cholesterol
tyrosine	alcohol
methionine	liver extract
lipocaic	thiamine
cystine plus choline	riboflavin
inositol	pyridoxine
ethanolamine	pantothenic acid
	nicotinic acid
	biotin

General Management of Portal Cirrhosis

A brief history of the old dietary regieme for cirrhosis of the liver and the rationale for its use has been presented by Hoagland (1945), and he has summarized it as follows: "Until the turn of the century, the diets prescribed by most physicians for patients with cirrhosis of the liver were generally low in all constituents. Carbohydrates were avoided because it was felt that excessive intestinal fermentation might arise, and prejudice the patient's clinical condition. Moreover, diets high in carbohydrates gave rise to diarrhea in many patients with chronic liver disease, thus providing another troublesome complications. Protein was avoided because it was believed that a damaged liver should not be further embarrassed by giving it protein to metabolize. Fat, too, was avoided on the basis that it would stir up the bile and thus add an additional load to the liver." He furthermore pointed out a rather "glaring" inconsistency in this method of therapy, in that magnesium sulfate was prescribed at the same time in order to promote biliary secretion and drainage of the liver. Other rationale for these various dietary restrictions were based on the knowlege of the central role of the liver in the breakdown of the con-

stituents of food, and the belief that the liver should be "splinted", as it were, for the duration of the disease.

All of these older theories have been entirely abandoned within the last few years, with the exception of the low fat diet, and these changes have been brought about mainly through a better understanding of the physiological functions of the liver in both health and disease. Our actual knowledge of the hepatic functions are still very meager, but much has been learned within the last few years to justify our questioning the validity of these older theories.

Patek and Post (1941) were among the first to submit to the literature the results of treatment of cirrhosis of the liver by a highly nutritious diet supplemented with vitamin B concentrates. In so doing, they compared their results of 54 patients treated in this manner with those of a control series of 386 patients. They found that following the onset of ascites, 72 percent of the treated series, as compared with 57 percent of the controls, survived 6 months. At the end of the first year, 57 percent of the treated series survived, but only 39 percent of the controls. At the end of the second year, 45 percent of the treated series, as compared to 21 percent of the controls, were still alive.

In addition to an increased period of survival, there were signs of general bodily improvement and presumptive evidence of arrest of the disease process. In a significant number of patients there was a disappearance of ascites, edema, jaundice and of vascular spiders. Certain laboratory data, such as the level of the serum albumin and of the serum globulin, the Takata-Ara test, cephalin flocculation test, and bromsulfalein dye test, reflected corresponding improvement.

Their diet contained a moderate amount of protein and fat. In addition to the protein of the diet (114 gm.) the patients received 50 grams of powdered Brewer's yeast daily, of which the protein content was about 50 percent. They found no evidence of intolerance to fat in the amounts given. The stools did not contain excessive fat. Salt intake was restricted in patients with ascites and edema to the extent of omitting a salt shaker from the tray, and fluids were allowed up to 2,000 cc. per day. in addition the patients generally received intramuscular injections of concentrated liver extract, 5cc. twice weekly, and of thiamin chloride, 5 mgm. daily.

They also tested the effect of the administration of alcohol on four patients who before entering the hospital gave a strong alcoholic background. On admission to the hospital they all presented varied de-

grees o liver failure. After they had shown signs of clinical improvement they were fed alcohol in addition to the nutritious diet and vitamin B concentrates described. Nine ounces of 40 percent alcohol were fed daily as a "fruit juice tonic" for 6, 14 and 18 months respectively. There was no recurrence of their former symptoms or signs, such as jaundice or ascites. The bromsulfalein test, Takata-Ara test, and the serum proteins showed no adverse changes. A fifth patient, a former barkeeper who has resumed his former trade, admits drinking 6 to 8 glasses of beer daily in the past one and one half years since discharge from the hospital.

From this experiment they concluded that cirrhosis of the liver is not necessarily committed to a continuous progressive course.

Fleming and Snell (1942) treated 50 patients with a diet consisting of 350 to 500 grams of carbohydrate, 110 grams protein (chiefly of vegetable origin or derived from milk and egg white) and approximately 50 grams of fat. Vitamin supplements were employed in large doses, such as usually, 30 minims of oleum percormorphum and 9 to 12 fluid ounces of orange juice daily, 2 fluid ounces of liver extract daily or 2cc. of liver extract intramuscularly three times a week, two to four tablets of brewer's yeast with each meal and 4 to 10 mgm. of thiamine chloride daily, administered parenterally or

by mouth. Nicotinic acid was also given in some of the patients. The majority received glucose intravenously while under treatment in the hospital.

Of the 50 patients treated in this manner, 22 percent were free of ascites, or fluid was accumulating so slowly that they might be considered as approaching the state of compensation. This they found to be in distinct contrast to an earlier group of 150 patients who they had treated by diuretic remedies as the principal feature of therapy. In this latter group only 8 percent had recovered at the time this report was submitted for publication.

Chaikin and Schwimmer (1945) treated and observed 112 patients with a highly nutritious diet and vitamin supplements and made a comparative evaluation with 134 patients as a control, who had previously been treated by diuretics, paracentesis and general supportive measures. Of this latter group or control, 54 presented evidence of ascites. Of those that could be followed, 22 died within the first four months after admission, 12 died fourteen months later, and 10 were known to be alive 23 months later. Fifty-three of the 80 non-ascitic patients with enlarged liver, recurrent attacks of jaundice and recurrent hemorrhages died in an average of 9.3 months. Seven appeared in good health three and

one half years after the diagnosis of cirrhosis was made. Twenty of the patients could not be followed up.

In the group of 112 patients that were treated with a high protein, high carbohydrate, low fat and multiple vitamin concentrates, 39 had ascites. Seven of the 39 could not be followed, and the clinical course of the remaining 32 was carefully observed. Fifteen of the 32 died within three months after admission, which is greater in percentage and shorter in duration than in previous groups treated with the old regimen. Six died with nine months and three within nineteen months. Eight with nine months and three within nineteen months. Eight lost their ascites, their nutritional status improved and at the time of this report seemed to be in good health. Of the non-ascitic group, 47 patients were observed during the period of three and one half years and 21 were at that time, in good health. Eleven died of hemorrhage, 5 of hepatic insufficiency, and 10 had recurrent attacks of jaundice with general state of health not considered good.

From this it would seem that a high protein diet with the addition of vitamin concentrates influences, favorable, the course of the disease since 8 patients of 32 had lost their ascites and seemed to be in good health in comparison to 2 out of 44 with the old re-

gimen. It was also shown that the results for the highly nutritious regimen are more striking in the non-ascitic group where 21 of 47 were apparently in good health in comparison with 7 out of 60 with the old regimen.

These investigators concluded, "While the new therapeutic approach to cirrhosis offers a ray of hope; the mortality rate is still high with either regimen, particularly in the ascitic group." They further noted that the best results were obtained in the following groups: (1) patients that were admitted with large livers which probably represented various degrees of fatty degeneration without extensive periportal fibrosis, (2) where multiple liver function tests showed deviation from normal, and (3) where the clinical symptomatology was vague and physical findings equivocal, the so-called latent group.

Goldstein and Rosahn (1945) reported their results of treatment of four cases of severly decompensated patients of cirrhosis of the liver by the use of high protein, high carbohydrate, and low fat, supplements with multiple vitamins, choline and isisitol. They found that choline alone or in combination with inositol produced regression or complete disappearance of the symptoms and signs of all four patients. It appeared to them

that the improvement was the result of the lipotropic activity of these agents and not due to any regression of the fibrotic liver changes.

The choline was administered orally in 6 gram daily dos s for several months, and evidence of toxicity was found. The same was true with inisitol. They also emphasized that inisitol when given in combination with choline does not inhibit the beneficial effects of choline in therapy of cirrhosis, but may be beneficial in that inisitol tends to depress the desire for alcoholic beverages in patients with "alcoholic" cirrhosis.

Barker (1945) published the results of therapy, using a high caloric, high protein, high carbohydrate and low fat diet, supplemented with from 30 to 50 gm. of brewer's yeast powder a day and polyvitamin capsules in numbers sufficient to supply at least twice the estimated normal adult requirement for the vitamins of proven importance in human nutrition (vitamins A, C, D, thiamine, nicotinic acid and riboflavin), on four patients with severely decompenstaed portal cirrhosis. Where hemorrhagic phenomena were observed with prolongation of the prothrombin time, vitamin K was administered either parenterally or orally along with bile salts to promote its absorption. Intramuscular injections of

crude liver extracts were given in cases where macrocytic anemia was present. Along with this each recieved choline chloride, 1.5 grams a day, administered in the form of a 10 percent elixir. Three of these four patients recovered over a period ranging from three to 14 months. Of these three, one of them underwent splenectomy, but was continued on this diet and his post-operative course was uneventful. The other one died following a severe hematemesis.

From this he concluded that this type of therapy is the best that we have at the present time for the treatment of portal cirrhosis.

Hoagland (1945) doubts that the rational treatment of chronic diseases of the liver necessarily calls for a diet which is extremely low in fat. In the first place he thinks it is impracticable to give a diet high in protein which at the same time contains little fat. Moreover, fats are rich sources of vitamins A, D, and E, and certain essential amino acids. Also, diets which are extremely low in fat are equally unpalatable and unappetizing. Finally, there is little evidence that diets with a moderate content of fat are prejudicial to patients with chronic liver disease.

Adjuvant Therapeutic Measures

Hoagland (1945) emphasized the fact that the patient with cirrhosis of the liver should be restricted in their physical activity, and states this is evident from a consideration of elementary principles of physiology. Moreover, it permits careful control of the diet and medication to a degree not possible in the ambulant patient.

Jollifee and Alport (1945) have stressed that the patient with cirrhosis should have intelligent, patient, nursing care. He stated that most cirrhotics have poor appetites and an aversion for food, making the consumption of a full diet a real problem.

The treatment of patient with ascites often times presents a rather perplexing problem to the clinitian. Often, the ascitic fluid disappears following the institution of proper therapy, but in many cases it remains, and causes the patient much discomfort and distress. Diuretics, have, and still are being used by some, but others believe them to be absolutely contraindicated.

Fleming and Snell (1942) stated that toxic reactions, consisting of diarrhea, fever and microscopic

hematuria occur frequently following the use of diuretics, and the forced administration of such agents in cases in which no immediate increase in urinary output occurs often seems to precipitate the onset of the fatal hepatorenal syndrome. The presence of a marked degree of jaundice, gastro-intestinal bleeding and mental confusion is definitely a contraindication to the use of diuretic agents and if they are used there is always the possibility of increasing the degree of acidosis among older patients who have moderate renal insufficiency.

Ivy (1945) stated, "I seriously question whether diuretics or purgatives should be used to counteract ascites if their use can be avoided, because I should suspect the former as being hepatotoxic, regardless of statements to the contrary, and the latter as upsetting an already disordered digestive tract. I should prefer paracentesis, in the recumbent position if the systolic blood pressure is low, to relive abdominal distension. Bowel evacuations should, of course be well regulated; perhaps the best agents for this purpose, when required are bile salts and heavy magnesium oxide.

In contrast to these, Snell (1945) and Barker (1945) both believe that paracentesis should be delayed and diuretics should be used. Barker believed when ascites

is present the daily fluid intake should be limited to 2,000 cc. and the salt intake moderately restricted to the extent of permitting no salt on the tray. As a diuretic he recommends 3 to 4 gm. of ammonium chloride a day by mouth for several days, followed by one or more intravenous injections of mercupurin, 1 to 3 cc. at a time for one to three days in a row. This proceedure can also be safely repeated at seven to ten day intervals. When diuretic measures fail to accomplish adequate relief from ascites, then paracentesis becomes imperative. The intervals between paracentesis can best be gauged by the weight curve, the condition of the abdomen, and the subjective status of the patient. Snell likewise suggested acid-producing salts and organic mercurials diuretics.

As has been seen before, a macrocytic hyperchromic or microcytic anemia is not an uncommon finding in pateints with cirrhosis of the liver. The treatment of this has already been touched upon, but to no extent other than to mention that liver extract is often given as a supplement to the above standard dietary regimen.

Barker (1945) stated that the macrocytic anemia occasionally responds to the oral or parenteral administration of liver extract, but the response is not nearly as encouraging as that seen with pernicious anem-

ia. Likewise the secondary anemia seldom responds to this therapy but requires 0.2 to 0.4 gm. of ferrous sulfate after each meal. Transfusions of course become necessary in those patients suffering large or prolonged hemorrhages from ruptured varices.

Snell (1945) states that the anemia of liver disease is especially refractory to treatment. It may respond somewhat to the injection of liver extract and to iron, but in general it is not much altered until the liver itself regenerates. For this reason, transfusion of blood must be relied on to maintain the patient's hemoglobin until the liver cells have regenerated.

Summary and Conclusions

The etiology of portal cirrhosis is completely obscure. Alcohol has been incriminated with a great deal of justice, but its exact role is still unknown. It is probably due to the fact that the chronic alcoholic develops marked anorexia; consequently, he fails to eat and ultimately suffers from an avitaminosis, plus a lack of specific foodstuffs that are normally synthesized or matabolized in the healthy liver.

Chlorinated hydrocarbons are known to produce cirrhosis of the liver, but the mechanism whereby these chnages are produced is unknown. Their injurious affects are dependent entirely upon the amount of hydrocarbon on to which they were exposed, the duration of exposure and the frequency to which the individual is subjected to the toxic agent. Large toxic doses, repeated at frequent intervals results in marked fatty degeneration to the hepatic cells and death ensues before cirrhosis develops. Small exposures over long periods of time first result in a fatty infiltration of the hepatic cells and ultimately results in a diffuse perilobular fibrosis.

Bacteria and certain paracites are known to produce cirrhosis of the liver. In many instances specific

bacteria have been isolated and cultured from the cirrhotic liver, suggesting either the possibility of a direct inflammatory response to the bacteria or their toxins. Eberthella typhosa, mycobacterium tuberculosis, hemolytic and non-hemolytic streptococci, treponema pallidium and malarial paracites are frequently eluded to as specific etiological factors.

Macroscopic examination of the cirrhotic liver at necropsy may reveal absolutely nothing diagnostically. Approximately one-half of the cirrhotic livers are reduced in size, but this is variable. The color depends entirely upon the microscopic pathology, i.e. the amount of congestion, biliary stasis, fibrosis, necrosis and fat content present. Usually the smaller, atrophic livers are literally studded with small nodules varying in size from less than a millimeter to more than a centimeter in diameter.

The development of these pathological changes in portal cirrhosis appear to be rather complex. The first and most outstanding feature is the appearance of a fatty infiltrate at the periphery of the lobules. Simultaneously there is an infiltration of inflammatory and phagocytic cells in response to the irritant. In the event the etiological factor is removed these changes may disappear completely, thus the process is at first

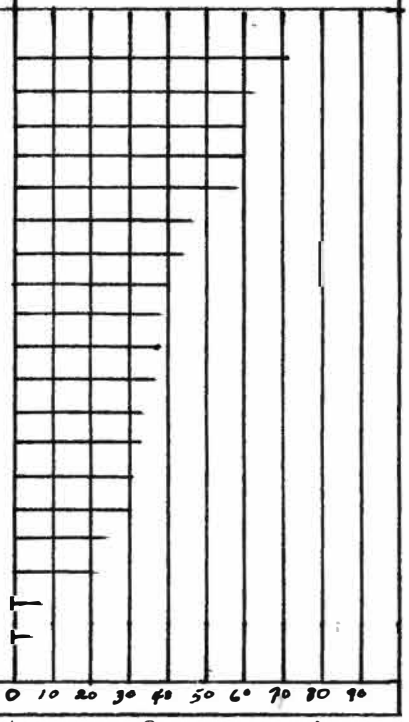
reversible. If the etiological factor continues to operate, there is soon an infiltration of perilobular connective tissue. Eventually, the entire lobule is not only completely surrounded, but also invaded by connective tissue and the architectural pattern becomes more distorted, the central vein is markedly compressed, as well as the terminals of the hepatic artery and biliary canalicules, at the periphery of the lobule. Consequently, the pressure rises in the portal vein which induces multiple pathological changes elsewhere in the body. As the process continues there is a gradual diminution of the less resistant parenchyma and a progressive accumulation of the more durable supportive stroma eventually leading to a small, hard, nodular liver.

Microscopically, the picture seen depends upon the degree to which the cirrhotic process has progressed. The basic histology remains unchanged. Outstanding, is a diffuse fibrosis which, as can be seen in the earlier stages, begins with a typical perilobular distribution but later it may progress to a point where it cuts and invades the lobule in every direction and the normal lobular architecture becomes completely lost. The cytoplasm of the cells show a picture of cloudy swelling, fatty degeneration, focal necrosis, or

hyaline degeneration all of which depends upon the degree to which the cirrhotic process has extended. Inflammatory cells likewise may be present, including plasma cells, lymphocytes, or polymorphonucler leucocytes. In other areas in the liver there may be seen simultaneously, evidence of regeneration as indicated by a hyperplasia of hepatic cells containing many mitotic figures.

The diagnosis of portal cirrhosis is usually made after a thorough evalu tion of the patient's symptoms and physical signs. Laboratory data is helpful in confirmation of hepatic injury, but this is usually not required to establish the diagnosis of portal cirrhosis. For thi reason I have constructed a chart of the most common symptoms and physical signs from th reports that were available in the literature that provi ed these stastics. Obviously, one could not secure the resu ts of the same number of patients for every symptom and sign, and for that reason I have made a special column showing the number of patients which were analyzed by the various investi ators, and indicated the percentage of this group that presented that symptom or sign at some time throughout the course of the disease. The exact percentages have been calculated in each instance.

No. of Cases	Symptoms and Signs	Percentage
704	*Palpable Liver	
1,307	Ascites	
345	*Flatulence	
561	*Anorexia	
844	*Edema	
789	*Loss in Weight	
1,735	*Jaundice	
464	*Cutaneous Angiomata	
866	*Palpable Spleen	
696	*Abdominal Pain	
457	*Nausea and Vomiting	
538	Fever	
619	Urinary Disturbances	
712	*Hemorrhoids	
569	*Change in Bowel Habits	
534	*Hemorrhagic Phenomena**	
1,390	*Hematemesis	
619	Cardio-respiratory Signs	
697	Hydrothorax	



* Frequently the earliest manifestations of cirrhosis.
** Includes epistaxis, gingival bleeding and purpura.

There is no known single laboratory proceedure by which one can make a diagnosis of cirrhosis of the liver, and for this reason several proceedures are necessary before much information is to be gained. In my estimation the laboratory tests to be employed in cirrhosis of the liver may well then be selected with a five-fold purpose: (1) to aid in establishing the diagnosis; (2) to determine the degree to which the cirrhotic process has advanced. (3) to determine the progress or recovery of the

of the hepatic injury in response to therapy; (4) to employ tests which are practically feasible with regard to technical detail, suitability to the individual patient, and economy of materials and sources of error inherent in the proceedures; (5) to provide information as to specific therapy needed by the particular patient at hand.

With the above statements in mind, the laboratory proceedures that I would pursue in the care of a patient with cirrhosos of the liver, and the respective order in which these tests would be made, are as follows:

(1) Complete blood count and serology. From this one can detect the presence of any anemic condition, and if so, the type of anemia present. This is of the utmost importance from the standpoint of therapy. Likewise, if the serology is positiv treatment should be directed toward its eradication as soon as possible. Any marked leucocytosis may lead one to uncover some other obscured inflammatory condition that may be present; however, it must be kept in mind th t th re is frequently present a leucocytosis for which there can be found no apparent cause.

(2) Urinalysis. The findings of albuminuria and casts in the urine, along with other sy ptoms of cirrhosis aid in the confirmation of the diagnosis. Likewise,

one may also discover evidence of kidney disease, as would be indicated by the above two findings plus the the presence of red blood cells and numerous pus cells. Any of these findings would be suggestive of kidney pathology, and would certainly provide evidence that would make the use of diuretics absolutely contraindicated, especially mercurials of any type.

(3) Determination of the total serum proteins and the ratio of the albumin fraction to the globulin fraction of the serum. This is very important from the standpoint of both therapy and extent of the hepatic injury.

(4) Determination of the icteric index. This is a very simple test, inexpensive, and provides adequate information concerning whether the patient is jaundiced or not. Since the degree of jaundice is one of the best criteria for determining the prognosis of the patient, and since the jaundice usually disappears as the hepatic cells regenerate, frequent repitition of this test is advisable.

(5) Determination of the prothrombin time. This is an excellent test to use and absolutely essential, particularly in respect to therapy. Many obscure hemorrhagic tendencies can frequently be controlled if one knows the prothrombin time is greatly prolonged. The test is very easy to perform, of little inconvenience to the patient and unexpensive.

(6) Cephalin-Cholesterol flocculation test. It was shown that this is seemingly the most efficient laboratory test at the present time for the detection of diffuse parenchymal liver damage; therefore, its value lies mostly in the aid to early diagnosis and following the response to therapy. The test is simple to perform, but it takes about 24 hours for the test to be completed.

(7) Determination of the cholesterol esters. This test is apparently equal to the cephalin-cholesterol flocculation test, and provides confirmation of that test. It does have the disadvantage in that the proceedure for carrying out the test is quite lenghty and requires a preliminary determination of the total serum cholesterol.

The treatment of a patient with cirrhosis of the liver is usually a long tedious process. The patient should be hospitalized immediately and given the best of nursing care. Following this attention should be directed toward the restoration of the normal physiological processis in the body. In the event the patient is markedly anemic, he should be transfused repeatedly with whole blood until his blood count is within normal range. Following this, iron, in the form of enteric coated ferrous sulfate tablets should be given to maintain this normal level. In the event a hyperchromic macrocytic anemia is present, 1 to 3 cc. of crude liver

extract should be given parenterally three times weekly until definite response is elicited. It is usually found that any anemia seen with cirrhosis of the liver is quite refractory to treatment, and too much should not be expected from this therapy. In the event the serum proteins are low, plasma or parenterally administerid amino acids should be given immediately. This serves not only to restore the serum proteins to normal, but frequently results in marked diuresis and disappearance of edema and ascitic fluid if present. Here again we have a condition that is very refractory to treatment, but every possible effort should be attempted to restore their normal levels. Where the patients exhibit bleeding tendencies and the prothrombin time is prolonged, vitamin K should be given parenterally. Any evidence of secondary infection should be given its immediate specific therapy.

Throughout this time the patient should have been placed on a highly nutritious diet, rich in proteins and carbohydrates, but relatively low in fat. This diet should be supplemented with vitamins A, D, thiamine hydrochloride, niacin, pyrodoxine and riboflavin. Lipotropic substances should be used, but with caution. In my estimation, these substances are being used too promiscuously. It has been shown that yeast and choline

when given alone are strongly lipotropic and have even produced hepatic necrosis when given in conjunction with a low protein, low carbohydrate, and high fat diet. It seems very logical to assume that the early fatty infiltration seen in cirrhosis is a protective mechanism for the hepatic cells. Now by giving these strong lipotropes, the fat immediately disappears from the liver and this protective mechanism is lost and the hepatic cells suffer. It likewise seems logical to assume that if this action were delayed until the liver once again has its glycogen and amino acid stores re-established, and other physiological processes restored to normal, the removal of this liver fat would not result in this damage to the hepatic cells.

Evidence for this is seen where methionine has been used in the treatment and prevention of hepatic necrosis and cirrhosis. Methionine is one of the weaker lipotropic substances known at the present time, yet experimentally it seems to be the most effective in protecting against the cirrhotic changes. The cost of methionine is too outlandish to permit its administration as such, but casein, relatively rich in methionine is not, and hence offers an adequate source.

Further evidence for this is also supplied when one considers the fact that cystine alone is known to produce

necrosis nd cirrhosis of the liver, not by its lipotropic ction, but by its antilipotropic action. Yet when this substance has been given in combination with choline or yeast, it afforded complete protection to the hepatic cells. This suggested to me that the cystine may have a buffering action when given in conjunction with eith of these two strongly lipotropic substances.

For these reasons my choice of lipotropic substances would be either n abundant supply of casein, or choline chloride given in conjunction with cystine. Adequate amount of these substances would be provided y giving 2.0 grams of each substance daily divided into three doses.

In the presence of ascites fluids should be restricted to a maximum of 2,000 cc. per day, and the salt intake limited to the extent of not including a salt shaker on the tray. If ascites and edema still persists after the above diet has b en well established, it would be necessary to resort to diuretics. Acid producing salts, such as ammonium chloride, should be given in dosages of one gram four times daily. In the event these prove to be ineffective and there is no renal damage organic mercurial diuretics may also be used. When this fails, it is necessary to resort to abdominal paracentesis.

Recent reports indicate that this method of therapy is far superior to older methods; however, this method

seems to be effective where there are no other marked changes in the liver other than fatty infiltration, producing hepatomegaly. Where the liver has become markedly infiltrated with connective tissue and reduced in size as a result of the contraction of this scar tissue, all types of therapy seem futile.

In my opinion there will never be any pharmacological product that will cause a regression of the cirrhotic process in the liver after these advanced changes have appeared. If there were such a substance that would remove this connective tissue from the liver, it would undoubtedly endanger the integrity of the connective tissue elsewhere in the body.

FINIS

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