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Etiology of cirrhosis of the liver

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Section I

The liver is the largest gland in the body, and performs a number of different functions. It is essential to life. Its removal results in death within two days at the most. It is unique in that it receives a double blood supply. Arterial blood comes to it through the hepatic artery. Venous blood comes to it through the portal vein. The blood in the portal vein comes from the entire gastro-intestinal tract, so that anatomically the liver is placed as a barrier in the blood stream between the abdominal organs and the heart. These structural relationships by themselves suggest that the liver has the function of removing toxic substances that may have been absorbed into the blood in the intestines. The liver also plays an important role in protein and carbohydrate metabolism, and in the metabolism of fats. It forms bile and in so doing forms and excretes bilirubin and bile salts. It stores vitamins and other substances necessary for normal function of the body. The liver forms substances necessary in the coagulation of blood. Also, it has a part in regulating the fluid balance of the body.

The liver takes up the simp e sugars from the blood and stores them as glycogen so that the body may have a source of carbohydrate that can be called upon in

time of need. The amino-acids that are produced in the gastro-intestinal tract during digestion are absorbed into the blood and a large proportion of them are removed by the liver and temporarily stored in that organ. The liver may deaminize the amino-acids or use them in the production of proteins.

The liver may form acetone or ketone bodies by oxidation of lipids. This occurs during fasting, or when the diet is composed principally of fat. In this way energy is produced when the supply of glycogen is low. Another function of the liver is the secretion of bile. The liver is the chief producer of prothrombin which is essential in the clotting process. Detoxification of various poisons that travel in the blood stream is carried on in the liver. The liver is also important in the production of fibrinogen, in the storage of iron and copper and formation of vitamin A from carotene.

The liver to carry on its various functions must have an ample supply of carbohydrates, vitamins and other substances. One of the important functions of the liver is to detoxify poisons that may enter the blood. It can do this only when it is not in a deficient state. If it is in a deficient state when poisons are in the body it can not detoxify them and the liver thus is damaged by the poisons. (1)

The liver, the largest gland in the body, is situated in the upper and right parts of the abdominal cavity, occupying almost the whole of the right hypochondrium, the greater part of the epigastrium, and weighs from 1.4 to 1.6 kilograms in the male and from 1.2 to 1.4 kilograms in the female. It is relatively much larger in the fetus than in the adult. In the fetus it consists of one-eighteenth of the entire body weight. In the adult it makes up about one-thirty-sixth of the total body weight.

The right lobe of the liver is much larger than the left lobe in a proportion of six to one. The quadrate lobe is situated on the under surface of the right lobe. The caudate lobe is situated upon the posterior surface of the right of the liver, opposite the tenth and eleventh thoracic vertebrae.

The blood supply of the liver is quite different from that of other glands in the body. It has two sources of blood. The hepatic artery which comes from the celiac, a branch of the aorta is one source and the other is the portal vein, which arises from veins that drain the blood from the abdominal part of the digestive tube, except the lower part of the rectum. It also drains blood from the spleen, pancreas and gall bladder. Hepatic veins commence

in the substance of the liver, in the terminations of the portal vein and hepatic artery. It drains into the vena cava. (2)

The substance of the liver is composed of lobules held together by an extremely fine areolar tissue in which ramify the portal vein, hepatic ducts, hepatic artery, hepatic veins, lymphatics and nerves; the whole being invested by a serous and fibrous coat. The lobule of the liver is a polygonal prism which in cross section has five, six or seven sides. Running through the center of the lobule, in its long axis, is the central vein. At the periphery of each lobule are branches of the portal vein (interlobular vein), the interlobular bile ducts, branches of the hepatic artery, and the lymphatics which form a network about the portal vein and its branches.

The cells of the liver are arranged in a more or less regular formation of cords which form columns extending radially from the central vein to the periphery of the lobule. The central veins of the liver lobules unite to form a collecting vein, and these in turn form the hepatic vein which drains to the vena cava. The cords are slightly branched and may anastomose with nearby cords. The sinusoids are irregular tortuous blood spaces which connect the ends of the interlobular portal

veins with the intralobular central veins. They also receive blood from the branches of the hepatic vein. Parts of the lining of the sinusoids are made up of the phagocytic stellate cells of v. Kupffer.

Between two adjacent liver cord cells, lies a thin bile canaliculus. The bile canaliculi run through the length of the liver cell cord and receive short lateral branches which extend between the sides of adjacent liver cells. They collect and connect via the hepatic duct and common duct to the small intestine.

The lobules of the liver are partially separated by the very thin strands of dense connective tissue called periportal connective tissue. This is part of the dense connective tissue sheathing the intrahepatic portions of the portal vein, bile duct and hepatic artery. The periportal collagenous connective tissue continues directly into the dense network of reticular fibers which surround the sinusoids. This network of fibers supports the liver parenchyma. (3)

Cirrhosis is a disease of the liver in which fibrosis spreads from the portal spaces and encloses varying numbers of the lobules. The sequence of events in cirrhosis is believed to be first, a degeneration of the liver cells in the periphery of the lobules caused

by poisons carried in the portal vessels. Areas of degeneration and necrosis are seen throughout the liver. This process may be preceded by fatty infiltration, or accompanied by fatty infiltration. The second stage is regenerative hyperplasia of the remaining liver cells and bile ducts with proliferation of the interstitial tissue and contraction. The liver in the meantime may first become enlarged then shrink in size and become nodular with a tawny appearance.

The most simple and useful classification is based on the clinical differentiation between portal biliary types. The first is portal cirrhosis with toxic cirrhosis and pigment cirrhosis. The second is biliary cirrhosis of two distinct types. One is infective hypertrophic and the other is obstructive cirrhosis.

In portal cirrhosis the liver is usually atrophic and often deformed. Frequently the organ is enlarged due to a pre-existing fatty infiltration. Biliary cirrhosis is so named because it originates in the small bile passages. Jaundice is an outstanding feature. (4)

The liver plays an indispensable part in the metabolism of the body and in certain digestive processes, including the elaboration of bile. The liver is

essential to life. When it is removed by ordinary surgical methods the animals die in a few minutes. With a developed collateral circulation, the animals may survive hepatectomy for thirty-six to forty hours, if they are injected frequently with sugar solutions. Diseases that destroy the capacity of the liver to carry on its functions will cause serious consequences to the person affected.

The liver is a "silent" organ with a wide margin of safety. The symptoms of disease depend largely upon the ultimate exhaustion of hepatic reserve, the final inability of the liver to regenerate new liver cells in sufficient amounts to compensate for those that are damaged or destroyed, and upon the accident of connective tissue replacement gradually divorcing the hepatic cells from the porta venous radicles. Indefinite symptoms may be present at first, such as vague pains and tenderness in the right upper quadrant, "indigestion", especially after heavy or fatty meals, malaise, headache, pruritus, urticaria. Jaundice may or may not be a symptom. The liver may become enlarged and ascites may result as a final condition before death. (6)

One of the diseases of the liver that often remains silent until well developed is cirrhosis of the

liver. In far advanced stages of the disease, the result is often death because the condition is irreversible. The logical study of such a disease is of the early stages or perhaps the cause, and not the stages that are recognizable, but can not be helped in many cases. This paper then, takes up the etiology of cirrhosis of the liver.

Cirrhosis of the liver was known to the ancients some two thousand years ago, but up to the present time, the cause has been obscure. As long ago as the sixteenth century, cirrhosis was associated with inebriety. (7) The name cirrhosis, meaning yellow or tawny, was first used by Laennec to describe that form now known by his name. The name has persisted and is now synonymous with sclerosis or fibrosis of the liver. (8)

Section II

Laennec's cirrhosis occurs in males more than twice as frequently as in females. There were 267 males and 119 females in this series. The ratio of males to females among the several nationalities is approximately three to one. The predilection of cirrhosis for males has long been attributed to their higher incidence of alcoholism. Of the 16,692 persons certified to have died of alcoholism in the United States between 1934 and 1938, 87.9% were males and 12.1% females.

Although characteristically a disease of late, middle life, Laennec's cirrhosis may occur at any age. In 84% of the series, the first symptoms appeared between the ages of thirty-five and sixty-four years. O. C. Ratnoff and A. J. Patek, Jr., cite an incidence of cirrhosis in a two year old girl, and in a seventy-six year old carpenter. The peak of incidence for females occurs from forty-one to forty-four years and for males from forty-five to forty-nine years. Since the number of persons in the population falls sharply in the late groups, it is essential to make a correction for the age distribution of the general population. The corrected age morbidity incidence for cirrhosis is seen to reach its peak between the age of fifty to fifty-five years.

In Mohammedans and the natives of India and Egypt, it is thought to be due to the action of spices, curries, and other stimulating articles of food, such as ginger. This may be explained as depending on the irritating effects of acetic, butyric, lactic acids or other acids manufactured as the result of intestinal fermentation. Cirrhosis of this kind is sometimes described as due to auto-intoxication or as autochynous. A certain degree of fibrous replacement may result from atrophy of the liver cells, and gastro-intestinal catarrh may give rise to the formation of irritating bodies which when absorbed find the liver in a condition of diminished resistance and are then able to set up changes. (9)

Eight hundred sixty-five charts on which the diagnosis of cirrhosis of the liver appeared were reviewed from the files of the Babies Beth Israel, New York, Mount Sinai and Presbyterian Hospitals, all of New York City. Sixteen and nine-tenths per cent were of Italian descent and twenty and seven-tenths were of Jewish descent. (10)

Hepatic disorders are common in Syria and the Lebanon. Cirrhosis of the liver is seen more commonly at the American University of Bernet among clinic patients than among private patients. It is more frequent

in farmers than in city dwellers, especially in farmers from villages in the neighborhoods of Sidon and Tyre.

Conditions in which cirrhosis is most common is seen in the difference of diet. The diet of the people consists largely of cereals, olives, citrus fruits, grapes and figs. Milk is used only for the sick, the rest is sold. Their diets are often low in protein and Vitamin A. The average farmer smokes, but rarely touches alcohol. They use some red and green peppers.

Bacterial and protozoal infections and helmenthic infestations are very common. Malaria and dysenteries are common in farmers much more so than in city dwellers. Yenikonshian is convinced that chronic malaria and dysentery, especially in combination, are important factors in the cause of cirrhosis. He has studied seventy cases. (11)

Records of the Massachusetts General Hospital from 1921 to 1935 studied by W. R. Richardson showed a heavier incidence of cirrhosis in native born Italians than those born in the United States. (12)

Section III

The commonest type of cirrhosis of the liver is that known as alcoholic cirrhosis, because it is so frequently associated with over-indulgence in alcoholic beverages. (13) As long ago as the sixteenth century, cirrhosis was associated with inebrity. The French in the eighteenth century referred to such a liver as gin-drinkers liver, also because of its association with people who drink liquor. (14)

In the United States, following the passage of the nineteenth amendment, there was a decided drop in the incidence of cirrhosis of the liver. The following statistics show the drop that occurred. In 1916 there were 160 cases of cirrhosis in 31,261 hospital admissions. In 1917 there were 156 cases of cirrhosis in 22,680 admissions. In 1918 the figure dropped to 87 cases of cirrhosis in 29,527 admissions. However in 1919, the figure rose slightly to 98 cases in 27,819 admissions. The year 1920 found the number of cases of cirrhosis at only 19 in 27,862 hospital admissions. Such a drop in the incidence of cirrhosis of the liver seems quite conclusive that alcohol plays an important part in the etiology of cirrhosis of the liver.

T. B. Mallory, M.D. (15) reports a case of cirrhosis in a forty-two year old male. He drank from one to two pints of hard liquor a day for many years. He also had syphilis and was treated with arsphenamine which also could have been a cause of the cirrhosis. Diagnosis was made at autopsy of cirrhosis of the liver. (16)

John Talbott reported a case of a fifty-one year old female with cirrhosis of the liver. She drank from six to eight shots of whiskey a day. The patient was found to have an avitaminosis, which vitamins helped. She admitted that her diet had been very poor. (16) In this case the lack of a proper diet, which is often found in alcoholics, may have been an important factor in the etiology of the cirrhotic condition of her liver. A liver of a person who does not eat the proper diet may be deficient of certain dietary factors important in the protection of the liver.

Kerr and Briggs (17) report three cases of portal cirrhosis. Patient number one admitted having been a moderate drinker most of his life. He took alcohol in the form of wines and beer. He also was a liberal eater and for a long time was obese. The second patient had used whiskey and beer in moderation for many years. Patient number three had history of yellow fever at the age of twenty. He took arsenic and mercury for a period

of one year after the excision of a bubo on the back of his neck. He was obese, a heavy eater and a heavy drinker, taking about a quart of whiskey daily over long periods of time. In many livers in the pre-cirrhotic, a condition of fatty infiltration may be found. Two of these patients were obese. Kerr and Brigg concluded that alcohol may injure the liver cells in the periphery of the lobules, and that other poisons are present in alcohol. Alcohol acts individually by causing an inflamation of the gastro-intestinal tract and thus sets free substances such as fatty acids that are toxic to the liver.

A. E. Boycott (18) states that the association of cirrhosis of the liver with chronic alcoholism is plain enough. There are however, many difficulties in the way of believing that the liver damage is caused directly by the use of alcohol. Hurst (19) showed that manganese slats are particularly effective in the production of cirrhosis in rabbits for experiments. It occurred that possibly in their diets, drunkards might take more manganese than ordinary people. Such foods might be particularly tasty addiments with which the fading appetite may be encouraged. After the examination of such foods, it was concluded that there was not

enough manganese present in the foods to be of any danger. The one exception was in the case of certain fish foods as shell fish or scallops.

J. Freidenwald (20) made an extended investigation of the effects of alcohol in animals. This was given in the form of whiskey or of absolute alcohol suitably diluted, by stomach tube to one hundred rabbits. Acute alcoholic poisoning lasting a few days and chronic effects of more than four year's duration were studied. A great majority of the animals showed fatty changes of the heart, liver and kidneys. These effects were temporary. They were not found in the animals whose treatment with alcohol had been discontinued a short time prior to their examination. In one rabbit was cirrhosis with ascites. He concluded that such lesions as cirrhosis did not result from alcohol. Some of the livers on pathological examination showed bands of connective tissue running along the interlobular lines. Genuine cirrhosis was not satisfactorily produced in rabbits.

F. Epplen (21) states that alcohol alone can produce cirrhosis of the liver in animals if it is given over a long enough period. He thinks it possible that a particular type or degree of gastro-enteritis must be produced by alcoholism before cirrhosis can

develop. Hepato-toxic poisons may be formed and absorbed by the gastro-intestinal tract when it is in this condition.

E. M. Hall and W. A. Morgan (22) made a study of sixty-eight cases of subacute or progressive alcoholic cirrhosis selected from among 120,000 autopsies at the Los Angeles County Hospital. At least eight per cent of the patients had chronic alcoholism. Only one out of the sixty patients denied the use of alcohol. The patient with chronic alcoholism suffered low intake of carbohydrate, diminished storage of glycogen, fatty replacement of the liver and deficient intake of vitamins. These conditions render the liver especially vulnerable, so that continued abuse by alcohol is followed by necrosis of the liver cells and fibrosis, which in the susceptible patient, after years results in cirrhosis of the liver. The clinical impressions have long been present that excessive consumption of alcoholic beverages is conducive to the development of Laennec's type of cirrhosis of the liver, in spite of the general failure to produce this lesion experimentally by feeding alcohol to laboratory animals. N. Evans and P. A. Gray (23) report that autopsy records of typical cases of Laennec's cirrhosis (portal cirrhosis or atrophic)

from the Los Angeles County Hospital have been examined in an effort to gain further insight into the etiology of this lesion. Two hundred and seventeen cases of Laennec's cirrhosis were observed. When chronologically arranged, these cases show a definite rising incidence. The beginning of this rise coincided with the repeal of the national prohibition law. The incidence since the repeal is three times as high. Observation shows that of preponderance of male over female, two and one-half to one. Most of the cirrhosis occurred from the fourth to the fifth decade of life. The peak is reached in the sixth decade for the female. In the forty-six cases, twenty two per cent gave a clear cut history of chronic alcoholism.

In five other cases the abuse of alcohol was questionable. Syphilis was the next most frequent associated condition, being present in twenty-six or twelve per cent of the cases.

Sir Humphrey Rolleston (24) lists ingested poisons as one of the sources of toxins to the liver. In practice, it is noted easily that the abuse of alcoholic drinks is a frequent precursor of hepatic cirrhosis. On 250 necropsies on confirmed drunkards who died suddenly from the affects of alcohol, only

six cases of cirrhosis were found. The question, why do some escape, if alcohol is a cause of cirrhosis, was asked. In those days, experimental alcoholic cirrhosis could not be produced. Only fatty liver and some necrosis could be produced experimentally. Alcoholic cirrhosis could not be produced experimentally by alcohol. Thus, something else was expected to contaminate the alcohol, or that other alcohols were present besides ethyl alcohol. It was thought that potassium sulfate put in beer and wine might produce it. Alcohol or alcoholic drinks produce a gastro-intestinal catarrh and thus lead to the production of poisons that when acting on the liver simultaneously with bacterial poisons so lower the resistance that cirrhosis results from the latter.

The distribution of cirrhosis does not run hand in hand with that of alcoholism. In hot countries alcoholic excess more often tends to produce a rapid reaction in the liver such as hepatitis, while in cold climates, cirrhosis is more common. It was also conceived by Rolleston (25) that in alcoholic mothers, the liver of the offspring may be influenced so that these livers would be most susceptible to poisons.

After the fact is established that chronic severe fatty infiltration of the liver would in time become cirrhosis, the search for etiologic agents narrows

down to the conditions which will produce the first stage, fatty infiltration. Fatty infiltration occurs in a large number of diseases and is incidental to poisoning by phosphorus, carbon tetrachloride, chloroform and alcohol. (26)

The occasional cirrhosis which has been noted for many years in diabetes mellitus has been explained. In this disease, fatty infiltration is due to the lack of proper sugar metabolism and incomplete oxidation of the fat. The storage of fat in the liver is accompanied by a markedly reduced respiratory quotient. With a low respiratory quotient, it is assumed that very little carbohydrate, if any, can be utilized. Two factors bring about the same condition in chronic alcoholism itself. Alcohol interferes with the carbohydrate metabolism and fat oxidation, because of its activity on a cell, as a tissue toxin and because of starvation or lack of carbohydrate in the diet. Sugar is withheld from the metabolic cycle.

The liver becomes an unnatural storage place for fat and lowers the respiratory quotient. There is then a complete depletion of glycogen from the liver, the absence of which renders it more susceptible to all poisons of this nature. Liver cells are deprived of oxygen and nutrition. Fibrous tissue develops,

partly as a direct result of relative anoxia and partly as a reparative process following cell death. When the liver is completely infiltrated, the patient's tolerance is broken and he has lasting intoxication on small amounts of alcohol. C. L. Connor (27) concludes that starvation or partial starvation and the continuous use of large amounts of alcohol produce a fatty liver from which a patient may die before cirrhosis develops. A person who is on a balanced diet and who drinks, does not develop cirrhosis.

Experimentally, it is generally accepted that alcohol alone will not produce cirrhosis of the liver. However, when administered in combination with other toxic substances, cirrhosis has been produced. R. S. Boles and J. H. Clark (29) reported fifty-eight cases of cirrhosis in 228 cases and twenty-six cases of fatty changes. They concluded that alcohol cannot be regarded as a specific factor in the production of cirrhosis.

Cirrhosis has not been produced by pure alcohol in experiments or there is conflicting results. The cirrhotic effects of alcohol in the liver may be, according to F. Mann and Johnston (30), a result from obnoxious by-products or it may be from damage to the mucosa of the gastro-intestinal tract with the subsequent absorption of untoward products of metabolism or admission of bacteria or their products.

Mallary and Parker (31) have advanced the role of copper as a contamination in alcoholic beverages in experimental cirrhosis. It must be concluded that cirrhosis is possibly only indirectly related to alcoholic consumption and that many factors, together with anatomic and constitutional irregularities, are important in the etiology.

T. B. Mallory (32) reports a case of cirrhosis from the records of the Massachusetts General Hospital. The patient had no previous illness and was accustomed to drinking about two to three glasses of whiskey, wine or beer daily.

The first effect according to T. L. Elthausen (33) is to produce hyperfunction from irritation of the hepatic tissue. This later changes to a hypofunction. The essential factors in the production of experimental cirrhosis is the repeated administration of hepatic toxins in sufficient doses to produce necrosis of some of the parenchymatous cells without causing death of the animal. Agents causing fatty infiltration alone do not produce cirrhosis. The localization of lesions within the hepatic lobule depends upon the dose of the toxin and upon the susceptibility of the individual animal at the time of administration. Following necrosis of hepatic parenchyma, two types of response

to injury can be observed. One is regeneration of hepatic cells from similar pre-existing cells. The other is sclerosis of a replacement proliferation on the part of the framework of the liver. This starts with round cell infiltration at the site of necrosis and is succeeded by accumulation of fibroblasts.

Among substances injurious to the liver are two classes. (34) The first is comprised of alcoholic beverages. It has been shown that a single large indulgence results in a temporarily reduced capacity of the liver to metabolize lactic acid. Also the power of the liver to excrete bilirubin is impaired. In England and Germany, cirrhosis of the liver is more prevalent in urban than in rural populations corresponding to the consumption of alcoholic beverages. For this same reason, the disease is more common in men than in women. The only exception applies to prostitutes. In the United States during the first years of the prohibition there was a marked decline in incidence of cirrhosis.

In laboratories, the majority of observers were unable to produce cirrhosis of the liver by alcohol alone, but could if they combined it with another toxic substance. This shows either that alcohol is in itself a weak hepato-toxin producing necrosis only in conjunction with toxin in the body or brought in from without.

Its role then is to render the liver more susceptible to the action of other toxic agents.

The second group of substances is inert colloids such as india ink and trypan blue. India ink injected into a rabbit produced a reduced activity of the liver.

Section IV

It has been shown by a number of workers that repeated administration of carbon tetrachloride in dogs produces, after some months, changes in the liver closely resembling portal cirrhosis. (35) Observations have been made on fifty adult albino rats. Chemically pure carbon tetrachloride was administered by the subcutaneous route. The animals were killed at various intervals. After a single toxic dose of carbon tetrachloride, there is little evidence of change in the liver, except for a diffuse congestion which appeared between the fifth and twenty-fourth hour. Hydropic and fatty degeneration then appeared in the liver cells of the central and midzonal regions of the lobules. The extent of degeneration depends on the size of the dose. The damaged areas are invaded by leucocytes and especially by histiocytes. The Kupffer cells of the unaffected parts become more prominent and perhaps contribute to the increased cellularity. By the third day, removal of damaged and necrosed liver cells is proceeding. Repair is going on actively, chiefly through mitotic division of healthier cells. Repair is completed by the fourteenth day. If repeated doses are given, the liver shows marked fibrosis.

Some conditions appear to be necessary for the production of 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 continuously 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 preceding dose. If experiments are interrupted between the sixth and twenty-first day, the cirrhotic changes invariably leave. Beyond this period the changes tend to become more stable and by the fourteenth dose, cessation of administration was not followed by a return to normal. Carbon tetrachloride in small amounts produces marked lobular degeneration and necrosis of the liver, followed by repair, but if continued, it is followed by cirrhotic changes.

Cirrhosis of the liver, as indicated from the above experiments, results from the effects of toxins upon a liver that is in a susceptible state. This susceptible state is a condition in which the liver has not recovered from damage wrought by some previous disease or toxin. It was noted that if the liver was given enough time to recover, cirrhosis would not develop. If, however, toxins were administered before recovery, a cirrhotic condition would develop.

Many chlorinated hydrocarbons have a toxic action on the liver. Of these chloroform and carbon tetrachloride are the best known. It is used in industry and for cleaning. Many cases of acute poisoning have now been recorded following the inhalation of fumes of carbon tetrachloride. Carl H. Greene (36) reported a case of cirrhosis in a patient that had been exposed to the fumes of carbon tetrachloride over a prolonged period of time. S. M. Lambert (37) produced hepatic injury in animals experimentally by inhalation, orally, and intravenously by the use of carbon tetrachloride in the treatment of hookworm disease.

Frank C. Mann (38) studied cirrhosis produced by carbon tetrachloride. These experiments have been of value in indicating some of the factors responsible for this characteristic lesion. The administration of sublethal doses of carbon tetrachloride produces acute necrosis of the liver. Recovery from such a lesion usually occurs promptly. If the drug is administered repeatedly before recovery from the preceding dose has occurred, marked cirrhosis is produced. The result of this experiment again leads to the conclusion that a toxin given to the liver before it has had a chance to recover from a previously damaged condition results in a cirrhotic condition.

B. V. Lyon (39) reported a number of cases of acute poisoning following the use of a shampoo containing carbon tetrachloride. The toxins probably entered by absorption through the skin, or the vapors were breathed.

Since the advent of cinchophen poisoning in the treatment of arthritis, there has been noted an occurrence of cirrhotic livers with cases of arthritis. Rheumatoid arthritis causes considerable pain, which can be relieved by cinchophen. This drug was put in the hands of the public. Its indiscriminate use has resulted in many cases of poisoning.

L. Block and D. H. Rosenberg (40) reported seven cases in which the pathologic changes occurred chiefly in the liver, and consisted of an extensive destruction of the parenchyma, resembling the acute or subacute yellow atrophy produced by other known toxic agents. 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.

S. D. Conklin (41) believes that the toxic effects of cinchophen is derived from a splitting of the guino-line nucleus which gives rise to a free

benzine ring. He states that pre-existing gall bladder or liver disease with jaundice, malnutrition, pregnancy, chronic alcoholism are thought to be predisposing. Neither length of time the preparation is administered or the size of the dose appears to predispose. Here again, effects of a toxin on the liver depends upon the condition of the liver at the time.

Weiss (42) stated in his review of cases of cinchophen poisoning, that toxic manifestations have no relation to the amount of the drug ingested. For example, one patient had a reaction on fifteen grains of cinchophen and another had a reaction on seventy-five grains of cinchophen.

E. Abinowitz (43) reported cases that took from forty to ninety grains of cinchophen daily for a period of eighteen years without untoward effects. He suggests that certain predisposing factors exist which sensitize the liver parenchyma to the toxic action of cinchophen.

Weiss (44) reported eighty-nine cases of hepato-toxic reactions due to cinchophen poisoning. Fifty-two recovered and thirty-seven were seen at autopsy.

R. B. Clarke and F. B. Settle (45) reported a case of cinchophen poisoning. The patient had an attack of pain in the right upper quadrant and jaundice.

Cirrhosis was later found. They concluded that cirrhosis is evidence of severe injury to the liver.

J. Davidson (46) produced liver necrosis and cirrhosis experimentally by coal tar. Tar was applied to the ear of rabbits. The animals lost weight. The effect varied on the liver according to the individual susceptibility of the animal and to the method of application. A combined application and injection did not cause especially severe symptoms. The results showed that coal tar causes necrosis of the liver cells. The acute changes are similar to those found in acute yellow atrophy in the human subject. The chronic changes, including regeneration of the liver, closely resemble atrophic cirrhosis. These observations suggest that the changes observed in acute yellow atrophy, subacute yellow atrophy and atrophic cirrhosis of the liver are different stages of one process. The regenerative tissue is still susceptible to the irritant. The arrangement of the cells in the regenerated tissue is irregular and in some instances, adenomatous growth occurs.

L. V. Gardner and E. D. Cummings (47) used rabbits experimentally in their study of silicotic cirrhosis of the liver. Two series of eight rabbits each, were injected with 1.3 grams of silica particles.

The first set was injected with particles the size of 6 to 12 microns. The other group was injected with particles the size of 1 to 3 microns. In the first animal killed at eighty-four days, the portal areas already showed thickening by proliferation of cellular connective tissue and also the number of small bile ducts was more evident than in a normal liver. The next animal killed at nine months showed that the portal connective tissues were greatly thickened at the expense of the parenchyma.

The next two animals were killed 656 days after the dose was given. The portal connective tissue had increased tremendously and large groups of lobules had been completely destroyed and replaced. The liver cells were infiltrated with fat.

In the rabbits given particles of sizes from 6 to 12 microns, there was no reaction in the liver. The largest particles were held back in the lung. The importance is the factor of particle size in the reaction.

The introduction of organic arsenic compounds has been followed by an increase in liver injury. C. W. Baldridge (48) reported twelve cases of cirrhosis. Ten were syphilitic and two were non-syphilitic. Treatment was with arsphenamine and mercury. Clinical

evidence of the disease of the liver was not found in any case before anti-syphilitic treatment.

Butter yellow, p-dimethylaminoazobenzine, has in the last three or four years been used in experiments to study the production of hepatic changes. J. W. Orr (49) added butter yellow to the food of 200 white rats and the course of histological changes in the liver was followed in 136 rats, which were killed at intervals throughout the experiment.

The usual sequence was proliferation of connective tissue cells in the portal systems. There was extension of granulation tissue from the latter into the parenchyma, with degeneration of the contiguous liver cells, a typical regeneration proliferation of bile ducts and liver epithelium leading ultimately to non-architectural nodular and microscopically hob-nailed liver. Butter yellow, if broken down, does not act as a liver irritant.

Numerous reports of the effects of phosphorus on the liver have been published. (50) Small doses of phosphorus given to rabbits by mouth and continued through many months, produced a marked interstitial proliferation with nodular granulation in the liver. It was found that connective tissue increased about the ducts following chronic phosphorus poisoning. Animals

that died early showed only fatty degeneration and necrosis of the liver cells. This condition, however, is commonly followed by cirrhosis of the liver.

One of the characteristic effects of arsenical poisons is the injury produced in hepatic cells. Necrosis results if the injury is severe. Following chronic arsenic poisoning, proliferation of the fibrous tissue was evident. Chronic lead poisoning was produced in four rabbits. The experiments lasted from forty-two days to five months. Degeneration and necrosis of hepatic cells were followed by perilobular connective tissue proliferation and atrophy of hepatic cells. The livers were indurated and contracted.

In an experiment E. M. Hall and E. M. Mackay (51) fed twenty-one rabbits on a diet containing two miligrams of normal copper acetate in each gram of food. The duration of the experiment was from twenty to one hundred five days. None of the twenty-one rabbits showed cirrhosis of the liver. Five of the rabbits which failed to show cirrhosis showed varying degrees of necrosis.

Any previous condition which causes a decreased glycogen storage affects the liver's ability to affect toxic destruction of hepatic cells, and its ability to influence the regenerative capacity.

Experimental liver cirrhosis by poisoning with manganese, chloroform, phenylhydrazine, bile and quinidine was produced by E. Weston Hurst and P. E. Hurst.(52) They found that manganese chloride given subcutaneously destroys the peripheral cells of the liver lobule and leads to extensive cirrhosis. Its effects are greatly enhanced by repeated intravenous injections of living bacillus coli. Phenylhydrazine rarely causes cirrhosis. Bile injection does not cause cirrhosis nor does it have any effect on the liver.

Section V

A normal reaction is to ask how the liver, known for its resistance to injury and for its reparative and regenerative capacity, could have been brought to such a state. According to A. M. Snell (53) a change in the conception of the nature of cirrhosis has taken place during recent years, which furnishes an answer, as yet not entirely complete or satisfactory for this question. It is now believed that cirrhosis is a deficiency disease, at least in the sense that nutritional errors lay the ground work for hepatic injury. There are certain factors influencing the vulnerability of the liver to toxins and its capacity for repair following exposure to these substances. The evidence of nutritional factors in the maintenance of the normal composition and the structure of the liver.

Cirrhosis as studied on experimental animals clearly indicates that it begins as a progressively destructive process involving individual hepatic cells. Fatty degeneration, atrophy and necrosis are the original lesions. The hepatic lobules are destroyed in whole or in part. This process is followed by regeneration of hepatic cells to form new tissue, which may be irregular

in size and shape, and by invasion of the lobules by connective tissue arising from the portal spaces.

Studies on experimental animals also have demonstrated clearly two points of great importance. It seems to be relatively difficult to induce this process of necrosis in hepatic cells except in a liver which is made abnormal in its chemical composition by dietary factors, or to keep the liver from regenerating itself if a proper diet is supplied. The liver may show marked cirrhotic changes and gross examination and yet, once regeneration is complete, may be functionally normal and capable of maintaining the health of the animal. Cirrhosis of the liver then must depend not on some hepato-toxic substance alone, but upon the time the hepato-toxic factor is acting.

The next step in this process of logic was to see what factor or factors tend to maintain the normal chemical pattern in the liver and thus serve to protect the organ against those endogenous and exogenous toxins to which it may be exposed. It has been demonstrated by many workers that increased levels of glycogen in the liver not only protect against hepatic poison but increase the rate of oxidation. Hepatic content of fat has been shown to have an opposite effect. In fact, the higher the lipid content of the hepatic cells, the

more vulnerable they seem to be. It appears that if the content of fat is high, even a good level of glycogen does not seem to protect the hepatic cell from injury. The composition of the diet in respect to fat and carbohydrate is therefore extremely important in regulating the level of fat and glycogen in the hepatic cell.

There are three well known factors that increase the lipid content of the liver. These factors are under-nutrition, an insufficiency in the intake of carbohydrate and protein, and high intake of fat. The role of the protein in the protection of the liver has been recently appreciated. It has been noted that the incidence of necrosis of the liver following administration of chloroform to experimental animals fed a high protein diet before exposure, was decreased by fifty per cent. There is much evidence to indicate that some component of the Vitamin B complex asserts a specific protective effect on the parenchyma of the liver. When this factor is absent, changes ranging from simple necrosis and fatty infiltration of liver cells, or actual cirrhosis may develop. Further studies revealed the development of this type of cirrhosis and that an increase in the amounts of the Vitamin B slowed the process.

Alcohol alone will not produce cirrhosis in experimental animals. It is, however, capable of

producing extensive fatty infiltration of the liver, especially in animals maintained on diets high in fat. Possible hepatic lesions develop most readily among human beings who do not eat as they drink.

The incidence of cirrhosis is high in countries where highly spiced and seasoned foods are used widely, and in localities where intestinal disease of bacterial origin are widespread. It is likely that intestinal disease produces hepatic damage by two separate mechanisms. One is by impaired nutrition due to indifferent absorption of the protein, vitamins and other essential substances from the diet and the second is from the production of toxins in the intestinal tract which overtax the detoxifying function of the liver.

The first experimental indication that long continued presence of large amounts of fat in the liver gives rise to fibrosis was obtained in completely depancreatizing a dog kept alive with insulin. L. C. Chaikoff and K. B. Euhorn (54) in an experiment fed high fat diet to seventeen dogs. Fifteen of the dogs showed early fatty infiltration as well as actual fibroblastic proliferation and diffuse cirrhosis. The remaining two showed nodular cirrhosis.

The first deviation from normal was an accumulation of fat within the liver cells. This was accompanied by hyaline atrophy or coagulative degeneration affecting cells adjacent to the portal veins. Next connective tissue fibers from the portal spaces and then without regard to pattern diffusly in liver tissue.

There was a complete absence of infections of inflamatory processes. The conclusion was that continued fatty infiltration resulted in cirrhosis.

Chaikoff and Connor (55) produced fatty infiltration and cirrhosis of the liver in depancreatized dogs maintained on insulin. The first experimental indication that a continued presence of large amounts of fat in the liver gave rise to fibrosis was obtained in the completely depancreatized dog, was observed at an interval of one and five-tenths years after pancreatectomy.

M. A. Spellberg, R. W. Kecton and R. Ginsberg (56) did an experiment on guinea pigs giving them thoroughly mixed, fresh basal diets and water ad libitum. Supplements of carrots and carrot greens were weighted out. The guinea pigs received pure ascorbic acid dissolved in water. Some of the animals were then allowed to die of scurvy.

The most significant change was fatty degeneration. The amount of fat in the liver bears a relation

to the length of time that the animal survives on the diet. Only one pig developed a stage of fibrous tissue proliferation. The animals with the greatest fat deposits showed the least fibrous changes. These were probably not as far along in the process.

In seven rabbits used in the experiment, the stage depended upon the length of time that the animals had been fed the diet. Rabbits which lived over two hundred days invariably showed a liver with gross, irregular surfaces. Microscopically there was a striking increase in fibrous tissue. Some large bands of connective tissue were invaded with numerous multiplying bile ducts.

In order to test the role of the B complex in the process of production of cirrhosis, rabbits were used and given a diet of casein, hydroginated cotton seed oil and dextrin. Cirrhosis was produced in rabbits and a fatty liver in the guinea pigs when the animals were fed an apparently adequate diet containing approaching twenty per cent fat (butter fat). Supplements of desicated brewers yeast, alpha tocapherol and synthetic vitamin K did not lessen fatty degeneration.

A reduction of the fat in the basal diet to five per cent by exclusion of butter and use of skim

milk caused marked reduction of liver lipids. A replacement of butter fat with cotton seed oil did not cause a decrease in liver fat, but the substitution of a hydrogenated vegetable oil (crisco) caused a significant drop in liver fat.

It has been suggested that the liver has difficulty in metabolizing certain types of fats. When these become lodged in the parenchyma, permanent damage results. There was an early drop in plasma cholesterol esters in the experimental rabbits.

In an experiment, W. C. von Glalin and F. B. Flinn (57)to study the effect of yeast on the incidence of cirrhosis used arsenic because it was so effective in the production of cirrhosis. Rabbits were used and fed regulated diets and yeast. Four rabbits were fed the standard diet without the addition of lead arsenate and yeast. Their livers were found to be free of cirrhosis. Another group of rabbits was given the standard diet and yeast. Their livers were also free of hepatic lesions. Another group was given the standard diet with lead arsenate. Two of the rabbits survived for twenty-six days. The connective tissue of the portal areas was increased. The bile ducts were also beginning to proliferate. Rabbits living a longer time showed

more changes but none were very great. The other group of rabbits were fed standard diet, lead arsenate and yeast. These rabbits showed less change than the others. There was no apparent relation between the glycogen content and cirrhotic livers. This last finding is contrary to the findings and ideas of most of those who have studied cirrhosis of the liver. It however, is commonly agreed that vitamins have an important part in addition to the protection of the liver. This fact was somewhat proved in this experiment.

Wm. Antopol and K. Unna (58) experimented with the effect of riboflavin on the liver of rats. After six weeks on the riboflavin free diet, the weights of the rats fed p-dimethylaminoazobenzene became almost stationary. Most of them died in six to eight weeks. All rats fed ten miligrams of riboflavin three times a week continued to gain weight throughout the experiment and presented a normal healthy appearance. In another group of rats, the riboflavin was removed after one hundred sixty days and their weight went down. The protective affect of riboflavin in the rats receiving ample amounts of casein and choline in the basal diet consisted, therefore in retarding the occurrence of liver damage resulting from butter yellow for a period of five months. During this period all animals receiving no riboflavin developed liver damage.

K. Suguira and C. P. Roads (59) found that p-dimethylaminoazobenzene will produce cirrhosis of the liver after only sixty days and cancer at the end of one hundred fifty days. Rats in the first thirty days feeding on butter yellow, had livers that showed no great changes grossly. At the end of forty-five days of butter yellow feeding, some livers had surfaces with more or less well defined nodules, which revealed early cirrhosis and adenomatous hyperplasia of the bile ducts. At the end of sixty days most of the livers revealed irregular surfaces with more or less well defined nodules. Histologically, there was extensive proliferation of the fibrous connective tissue with lymphocytic infiltration.

Rats that had butter yellow removed from the basal diet showed livers that would not return to normal after sixty days. Another group of rats were maintained on butter yellow and the basal diet for definite periods of time. Then the carcinogen was removed from the diet and feeding was continued on the basal unpolished rice eighty-five per cent and fifteen per cent supplements of whole yeast. The results showed that yeast feeding produced striking inhibition of liver changes. Cirrhosis or cancer was absent in the livers of the rats if butter yellow had been removed from the diet in less than

forty-five days. If the preliminary feeding of butter yellow exceeded eighty-five days, liver changes resulted in one hundred per cent of the cases.

Thiamine deficiency is often present in patients with hepatic cirrhosis. A history of low vitamin intake is usually obtained. It is used in the treatment of hepatic cirrhosis. In giving cirrhotic patients thiamine, R. H. Williams and G. W. Bissel (60) found that they could not phosphorylate the thiamine as do normal patients.

N. Jolliffe (61) states that neuropathological and clinical identity of polyneuropathy and beri beri are the same. It is a basic nutritional deficiency in alcoholic neuropathy. The vast majority of modern investigations are in agreement that the basic etiological factor is a Vitamin B_1 deficiency. In beri beri heart patients, there was often noted an associated cirrhosis of the liver.

The regular production of hepatic cirrhosis and cancer by the oral administration of dimethylaminoazobenzene and butter yellow to rats was reported by Kinosita. C. J. Kensler and K. Suguna (62) in experiments showed that a riboflavin deficiency coincides with the susceptibility of the carcinogenic effect of

butter yellow. None of the animals that received fifteen per cent of the diet as yeast showed any gross or microscopical evidence at two hundred days. This picture was comparable with that shown by rats given the supplemented basal diet with butter yellow for thirty days.

John W. Orr (63) during experiments with butter yellow noted a cirrhotic stage of the liver. The first naked eye changes seen in a rat killed after eleven weeks showed the liver with a granular surface. The appearance recalled those of the various grades of human subacute necrosis and multilobular cirrhosis. On section, the nodular appearance was repeated, with loss of the normal lobular pattern. At the end of the second month, the rat livers showed changes limited to the portal tracts. Spreading out from the portal systems were cellular strands containing some or all of the following elements; lymphocytes, histiocytes, plasma cells and mononuclears. At the end of the third month, peripheral granulation tissue extended further into the lobule and in many places became continuous from one portal system to another. He concluded that butter yellow produced cirrhosis of the liver, but that before the cirrhosis became irreversible, carcinomatous changes took place.

H. R. Fraser (64) reported a case of an eighteen year old boy who had a Vitamin D deficiency associated with cirrhosis of the liver. While the child was in utero, the mother was chronically ill with weakness, anorexia, bronchitis and repeated attacks of vomiting. He was on a diet definitely short of minerals and vitamins for the first two years of his life. The patient at the age of nineteen years. Autopsy showed a liver that was very irregular and presented a hob-nail appearance. On section there was a marked increase of interstitial connective tissue which appeared to be continuous with the capsule.

Section VI

There is great diversity of opinion regarding the etiology of the disease. In a general way, it is believed to be the result of various toxic and infectious agents which cause a destruction of liver cells and proliferation of connective tissue. (65) Other factors besides alcohol, such as acute infections, as measles, scarlet fever, typhoid and pneumonia, substances such as copper, lead, arsenic, silver, bacterial toxins, especially of intestinal origin, condiments such as chilies and spices and a deficiency of Vitamins A and D and protein in the diet all have at one time or another been suspected.

A consideration of the etiology of cirrhosis involves the recognition of its composite structure of liver cell relationship to the closely allied reticulo-endothelial system (Kupffer cells), probably functioning as a unit. Injury to the liver cells is known to occur in acute infectious diseases as typhoid, pneumonia, diptheria and septicemia of all kinds. To these agencies must be added the subacute and chronic effects of local and distant infections of tuberculosis, syphilis and the infestation of animal parasites. In addition, the

specific role of specific organic poisons such as alcohol, phosphorus, chloroform and manganese. Menne and Johnston (66) conclude 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.

H. E. MacMahon (67) reported five cases of streptococci hepatitis, in four of which he demonstrated streptococci 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 hepatic cells and of fibrous tissue such as is characteristic of 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 eight and one-half months following the operation. Pronounced cirrhosis was found

This experiment very definitely indicates that certain strains of streptococci are injurious to the liver.

J. C. Adami (69) noted in the ordinary liver in which cirrhosis was absent, that bacterial forms visible are almost all corpses, and even long action of strong carbolized fuchsin will not lead them to become stained. In cirrhosis, on the other hand, areas can be made out in which diplococcic-like bodies stain deeply. Either they have only recently been killed or they have entered the organ or they are alive in an attenuated state far to weak for culture. The presence of these weak forms indicates that the liver has lost some of its power of self-protection.

Professor L. Hektoen (70) used a bacillus of the colon group and one belonging to the pseudo-diptheria group and succeeded in producing a well marked perilobar cirrhosis of the liver in guinea pigs. He states that pressure of the resulting fibrous tissue causes necrosis of the hepatic cells, which in turn leads to renewed connective tissue proliferation.

L. J. Owens (71) states that it has been shown that the liver cells and endothelial cells of the liver are phagocytic in action toward bacteria. The liver probably receives more bacteria than any other tissue in

post morten, and numerous streptococci were demonstrated in the liver. It was regarded as a chronic hepatitis due to streptococci of moderate virulence. This caused a diffuse progressive destruction of hepatic cells resulting in cirrhosis. Guinea pigs and rabbits inoculated via the portal vein with streptococcus scarlatinae showed localized and diffuse areas of hepatic necrosis. Conclusions are that streptococci may cause hepatic necrosis resembling that of acute yellow atrophy, and that it may develop into cirrhosis.

V. H. Moon (68) reported three cases of cirrhosis in one family. Scarlet fever preceded the development of the cirrhosis in each case. In one case, hemolytic streptococci were cultivated from the substance of the liver at post mortem examination. A blood culture made a few hours prior to death was negative. This indicated that the streptococci found in the liver were not incidental to a terminal septicemia. The streptococci found in the liver were inoculated into young rabbits by various routes. The animals lived from three to fifteen days, and in eleven of the twelve rabbits, hemolytic streptococci were re-cultivated from the livers. Marked degeneration and necrosis and very little inflammatory reaction were present in the liver.

the body. A. L. Grover (72) injected rabbits with staphylococcus aureus and the colon bacillus. He found that repeated injury of the liver cells results in their ultimate destruction and replacement by scar tissue. Owens found that there are frequent associations of syphilis with nodular cirrhosis of the liver. The fact that syphilis was present in forty per cent of nineteen cases of nodular cirrhosis indicates that it is an etiologic factor in the production of the hepatic lesion. The occurrence of alcoholism in cases with syphilis indicates that the combination of the two factors may produce the lesion.

In haemic infections, micro-organisms tend to accumulate in the spleen, and if not rapidly destroyed, produce toxins which travel to the liver and there may produce changes analogous to cirrhosis. Thus, in malaria, the spleen is greatly enlarged and cirrhosis of the liver in malarial subjects may in part be due to the poisons manufactured in the spleen. In chronic splenic anemia a terminal cirrhosis of the liver with jaundice sometimes occurs (Banti's disease). The portal vein in the adult has two main sources, the gastro-intestinal veins and the splenic vein.

Rolleston (73) 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 cirrhosis. It has been found that colon bacillus almost constantly are 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 in acute hepatitis and cirrhosis result.

It was suggested that cirrhosis may be set up by the specific fevers, typhoid fever, measles, smallpox and pneumonia. Theoretically, the toxins of these 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. (37)

The conditions favoring the development of permanent cirrhosis after infections are congenital susceptibility, want of resistance on the part of the liver, and the presence of other factors such as alcoholism.

Experimentally, a certain amount of hepatic fibrosis has followed prolonged poisoning with vegetable, mineral and bacterial poisons. The intoxication must be induced gradually and continued for a considerable period. If the poison is employed in too large

amounts, the results are those of acute poisoning, with degeneration and necrosis of the liver cells, focal or diffused as in phosphorus poisoning. In the same way, the injection of bacterial poisons into the circulation when carried on rapidly, gives rise to necrotic changes in the liver cells around the intralobular veins; when the process is less intense and more prolonged a certain amount of cirrhosis results.

In haemic infection, the liver changes are often extremely acute and give rise either to supporation or to widespread degenerative changes allied to acute yellow atrophy. In less acute haemic infection, the supporting fibrous tissues show proliferation and an accumulation of leucocytes in the portal canals and in the peripheral parts of the lobules of the liver. (37)

R. M. Pearce (74) gave dogs injections of serum from rabbits which had been immunized to dog's red blood corpuscles. Some of the dogs so treated died in from four minutes to forty-eight hours. In these, there was diffuse necrosis of the liver. In the livers of those which lived forty-eight hours or longer, proliferation of endothelial cells and on connective tissue cells was seen. In five days there was marked regeneration of hepatic cells with proliferation of endothelial

cells and of connective tissue cells. In five days there was marked proliferation of granulation tissue. In one dog thirty-six days after injection of the serum, the liver was firm and had a finely granular surface. On section, distinct pseudo-lobulations were seen. Histologically, there was marked perilobular fibrosis with lymphoid infiltration and proliferation of bile ducts. The reparative process was most active in the region of the portal spaces and resulted in diffuse cirrhosis. He did not claim that this experiment explained the origin of cirrhosis in man, but that it proved that cirrhosis results from a reparative process following parenchymatous injury. (13)

Section VII

It has been demonstrated by investigators that alkaline extracts of the anterior pituitary are capable of increasing the fatty content of the liver. This could not be done, however, if the adre ls had previously been removed. Waren C. Corwin (75) showed that alkaline or saline extracts of the anterior lobe was as well as adrenotropic factors markedly increased. The liver fat content was increased in twenty-four hours. It was also found that thyroidectomy prevents the increase of fat on the liver. Conclusions are that fat deposition is mediated from the anterior pituitary via the thyroid and adrenals. Possibly an upset in the relationships of these glands could lead to the deposition of fat in the liver.

During observations of the effects of complete hyposphysectomy on the induction of hypertension, I. H. Page, I. Graef and J. E. Sweet (76) noted that nodular livers were present. Dogs at post morten examination were found to have nodular hepatic cirrhosis. Fatty changes in all were present but not remarkable. Cortical atrophy of the adrenals was also present.

On analysis of the hypothalamic lesions, positive correlation is noted with respect to the occurrence of fatty cirrhosis and the finding of extensive defects in the hypothalamus. (77) The defects seemed attributable to the operation, however, the hypothalamic lesions were not nearly so extensive in non-cirrhotic dogs. Obesity was generalized and and correlation to fat deposits in the liver are possible. Obesity was found in all of the cirrhotic dogs.

Diet was excluded because dogs kept on the same diet showed no defects. It is well known that the hepatic disturbances begin after the onset of neurologic manifestations, even years after neurological symptoms. Non-cirrhotic dogs showed no hypothalamic degeneration. Eleven dogs used showed lesions in the hypothalamus.

In the progressive lenticular degeneration there is bilateral degeneration of the lenticular nuclei of the brain which is invariably accompanied by cirrhosis of the liver by various means to see if lenticular degeneration would occur.

Manganese poisoning in man presents, like hepato-lenticular degeneration, the peculiar combination of degeneration in the basal ganglion of the brain with

cirrhosis of the liver. (78) The condition is not uncommon among miners and others who work with ores containing the metal, especially when this involves the production of considerable amounts of dust. The percentage of total contacts affected is not very high. This showed that individual susceptibility is a factor in its genesis. Experiments with manganese on various animals were carried out. Rabbits are relatively much more susceptible to the poisonous action of salts of manganese than are guinea pigs, although in the rabbit large doses produce severe degeneration in both liver and kidney. In both species, smaller and often repeated doses act chiefly or entirely upon the liver. In guinea pigs, after one or two large doses, massive necrosis is not very common and the affected areas are scattered irregularly throughout the liver. With repeated large doses it is easy to produce a very definite atrophy of the liver parenchyma, unaccompanied by an inflammatory or fibroblastic reaction. Cirrhosis, however, follows tardily and many months must elapse before the occurrence of considerable fibrosis. The distribution of fibrous tissue tends to be intralobular rather than perilobular and the resulting histological picture does not compare closely with that found in cases of human cirrhosis. In neither species did the central nervous system show any changes.

The introduction during the course of manganese poisoning in the guinea pig of a bacterial factory has a profound effect upon the resulting lesions. Attempts to produce cirrhosis with chloroform in guinea pigs were not very successful. In the guinea pig the effect of phenylhydrazine on the course of manganese poisoning is to greatly increase the amount of necrosis according to the dose of the former. The necrotic areas are either central or periportal in distribution. In the experiments of longer duration, cirrhosis definitely is more extensive than with manganese alone. No evidence has been obtained of any connection between liver cirrhosis and cerebral changes which might throw light on hepato-lenticular degeneration.

There has been in most cases of Bant's disease, associated cirrhosis of the liver. It is now thought that the enlargement is secondary to cirrhosis.

Section VIII

In a review of eleven cases of cirrhosis at the University of Nebraska Hospital, five patients gave a history of drinking alcohol. Two patients gave a history of a preceding infection. One patient may have received toxic substances from his occupation which is painting.

The first patient was a forty year old Bohemian butcher who gave a history of drinking for twenty-five years. He was poorly nourished. A thirty-eight year old white male gave a history of heavy drinking of alcohol for twenty years. A thirteen year old school girl had measles and developed jaundice and died in three months of cirrhosis. A forty-two year old white male had cirrhosis but gave no history that indicated any factors except his occupation, that of a painter.

A sixty-seven year old woman, who was apparently well, developed cirrhosis. There was no apparent factors given in the history that might have served as a cause for cirrhosis. A forty-three year old white male gave a history of drinking in excess. He ate poorly and worked in a brewery and as a bar tender. A fifty-four

year old insurance salesman who developed cirrhosis gave a history of alcoholism. A thirty-three year old female at autopsy showed a toxic cirrhosis.

A sixty-one year old male, who had a great deal of marital trouble, gave a history of drink only a few beers. He developed jaundice and then cirrhosis. A fifty-nine year old female develo ed cirrhosis following attacks of jaundice. Another female, age forty-six, developed cirrhosis after several attacks of jaundice.

Alcohol, here again, is associated with cirrhosis. These people, however, were not very well nourished.

To produce an experimental picture similar to the usual type of portal cirrhosis, it is, according to F. Mann (79) necessary to repeatedly administer sublethal doses of a toxic agent which produces acute necrosis of the liver.

From the literature it may be easily alcohol is not a cause of cirrhosis in itself. It is known that most heavy drinkers, or at least a large number of them, are poor eaters. Through an inadequate diet, a deficiency in certain factors such as vitamins, may be present. Under conditions in which the liver lacks the

necessary factors for protection, cirrhosis can develop. It has been proven that riboflavin affords protection for the liver against poisons. When the liver was well supplied with riboflavin, a much greater quantity of poison and a much greater length of time was needed to produce cirrhosis of the liver. A person who drinks and at the same time eats a properly balanced diet will not develop cirrhosis of the liver. Thus, when the liver is in a deficient state, the pressure of a toxin will cause cirrhosis. One may conclude that cirrhosis is a deficiency disease.

Of course, it may also be concluded that bacteria and parasites may cause cirrhosis of the liver. After an attack by a certain disease which was followed by cirrhosis of the liver, the bacteria of the disease were found in the liver. In cases that cirrhosis did develop, the bacteria were not found.

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