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Incidence of cirrhosis of the liver in diabetes mellitus

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THE INCIDENCE OF CIRRHOSIS OF THE LIVER IN DIABETES MELLITUS

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Introduction:

Both diabetes mellitus and cirrhosis of the liver are anchient scourges of man. Since the liver of the diabetic is affected by the altered metabolism, the question arises whether or not there could be a causal relationship between these two entities in some cases. In hemochromotosis, where iron deposition in pancrease and liver has caused destruction of many of the islets of Langerhans and in turn has resulted in the laying down of connective tissue in the liver, cirrhosis and and diabetes coexist in a high percentage of cases, a fact universally appreciated. There is a rare syndrome called lipoatrophic diabetes in which a generalized complete lipoatrophy occurs in the subcutaneous and other fat deposites. It tends to be insulin resistant, but does not lead to ketosis. Intense hyperlipemia is seen, perhaps leading to the subcutaneous xanthomas associated with this disorder. Such patients are euthyroid though the basal metabolic rate is increased. Hepatomegaly is a constant feature. Here again diabetes and cirrhosis coexist in a high percentage of cases.(29)

But when one turns to other more common varieties of cirrhosis, opinion is divided on the possibility of a connection between these two disease processes. The consensus of early workers was an emphatic no. More

recently, however, workers in the field are more apt to state that a definite association between certain forms of cirrhosis and the diabetic process does exist. In this paper I would like to examine the evidence anew, largely skipping hemochromotosis, which is not controversial.

Definition of terms:

Dorland's Illustrated Medical Dictionary defines diabetes mellitus as; "A metabolic disorder in which the ability to oxidize carbohydrates is more or less completely lost due to faulty pancreatic activity, especially of the islets of Langerhans, and consequent disturbances of normal insulin mechanism. This produces hyperglycemia with resulting glycosuria and polyuria, giving symptoms of thirst, hunger, emaciation, and weakness; and also imperfect combustion of fats with resulting acidosis, giving symptoms of dyspnea, lipemia, ketonuria, and finally coma." Diabetic metobolism is characterized chiefly by decreased glucose utilization by both periphery and the liver. At this time the decrease at the periphery is felt to be due to the inability of glucose to enter the cells rapidly--an alteration of cell membrane decreasing transfer rate with insulin lack is postulated. There is no barrier to the entrance of glucose into the liver cells. In the liver,

however, there does appear to be a decrease in hexo-kinase which catalyzes the reaction glucose $\rightarrow$ glucose-6-PO_4, and a concommitant increase in the exzyme, glucose-6-phosphatase, which catalyzes the reverse reaction. Thus the glucose-6-phosphate which is present in the liver cells is converted to glucose which escapes into the blood stream to such an extent that not enough sugar is left behind to carry out normal metabolic activities. The most important deficiency perhaps is the underutilization of the hexose mono-phosphate shunt, in which TPNH is regenerated. TPNH is necessary in the next step of importance--incorporation of acetate into fatty acids, resulting with TPNH deficient in a decrease of this process. In order to supply the energy needs of the body, there is increased catabolism of protein (to amino acids) and fat(to ketone bodies). So much Acetyl-CoA is formed that the Krebs cycle is swamped. (The cycle may actually be slowed due to the fact that beta oxidation of fat requires DPN as does the Krebs cycle). Thus the ketone bodies, acetoacetic acid, acetone, B-hydrosybutyric acid are formed from the excessive acetyl-CoA. The final defect is increased gluconeogenesis which is a natural result also of the large amounts of acetyl-CoA and the increased glucose-6-phosphatase which favors a reversal of glycolysis.

(12), (25), (28)

Cirrhosis on the other hand is defined as: "A disease of the liver, marked by progressive destruction of the liver cells, accompanied by regeneration of liver substance and an increase in connective tissue." Cirrhosis then is to a large degree a pathological diagnosis. It is divided on its supposed pathogenesis and microscopic appearance into a number of subgroups.

The most common of these is Laennec's cirrhosis, often called fatty nutritional, alcoholic or portal cirrhosis. It is apparently due to chronic, repeated injuries to hepatic cells. The liver, though usually reduced in size, may be considerably enlarged. The involvement can be divided into three phases. The first stage gives the large, yellowish, greasy liver. Microscopicly it shows hepatic cells bulging with fat. Periportal fibrosis is mild to moderate in intensity. In the second stage, fat has disappeared from half of the livers. The periportal fibrosis is now present up to a marked degree. The late stage shows a small, atrophic liver with little or no fat. Fibrosis is marked. Microscopically, connective tissue bands divide the hepatic cells into irregular lobules-- the normal architecture of the lobule may be completely lost. Numerous small bile ducts shoot through the

tissue.

Postnecrotic cirrhosis is another of these types. The name suggests the suspected mechanism of production of this entity. Though not as frequent, this type is seen at variable intervals following infectious hepatitis. The liver is small and is characterized by large nodules unevenly scattered through the liver parenchyma. The nodules are separated by thick, dense, greyish septa of fibrous tissue. This entity is also seen as a late complication of cystic fibrosis. Overlapping between the picture given by portal and post necrotic cirrhosis may occur.

Obstructive biliary cirrhosis is a third type, resulting from a prolonged obstruction of the bile ducts--commonly extrahepatic, occasionally intrahepatic. The liver which is normal or slightly enlarged has a smooth or slightly granular surface deeply pigmented with bile. The moderate fibrosis is largely perilobular. The bile ducts are distended with inspissated masses of yellowish brown bile. An infiltration of lymphocytes, plasma cells, and neutrophils at times, are found around the prolipherating bile ducts.

Cardiac cirrhosis is associated with the prolonged passive hyperemia seen in chronic congestive failure.

The entity appears to be favored by repeated bouts of decompensation. Hypertension of the portal circulation over a sufficiently long period appears to be an essential factor. The liver is of normal or reduced size, with a mildly nodular surface and thickened capsule. Fibrosis occurs in the portal areas as well as centrally. There is little cellular infiltration.

A marked degree of cirrhosis may be seen in acquired syphilis. At least one form of this is due to the healing by scarring of multiple gumma. Parasitic cirrhosis, common in the Far East and secondary to such liver flukes as Clonorchis Sinensis, occurs but hardly seems pertinent in a discussion of diabetes and will be dropped from further consideration along with the syphilitic form. (1)

Richard MacDonald (18) believes that the pathogenesis of the major types of cirrhosis are based on the same general process. His work at Havard was based on radioautography for the detection of prolipherative cells in rats under various experimental conditions, and also special stains of human livers in patients suffering from a variety of cirrhotic conditions. He feels the first step is one of marked distention of the hepatic cells, especially Kupffer cells. This distention may be due to fat or may be merely hydropic swelling of

the cells under a toxic influence or an injury. This swelling causes an obstruction of the sinusoidal lymph and blood flow. If nutrients are completely cut off from a small area, focal necrosis develops. The usual course of events is the prolipheration of new vascular and lymphatic channels to supply the ischemic area. The capsular area is frequently the first involved since it is the area most poorly drained and nourished. These vascular channels start at the central veins and head outward. Next, the portal veins become involved. Shunts may be formed between the two systems. In the early stages of this process all changes are completely reversible. If the liver loses its load of fat or if the swelling of cells due to a poison such as CCl_4 or an infection such as infectious hepatitis, goes down, the vascular channels which are beginning to form disappear without a trace. This occurs until the point of no return is reached in which actual fibrous bands are formed. These result from venous channels which have lost their lumens. The process stimulates a variable amount of bile duct prolipheration. It is this further prolipheration which is apt to embarrass circulation to such an extent that zones of focal necrosis are seen. Once the proces is well extablished endothelial strands

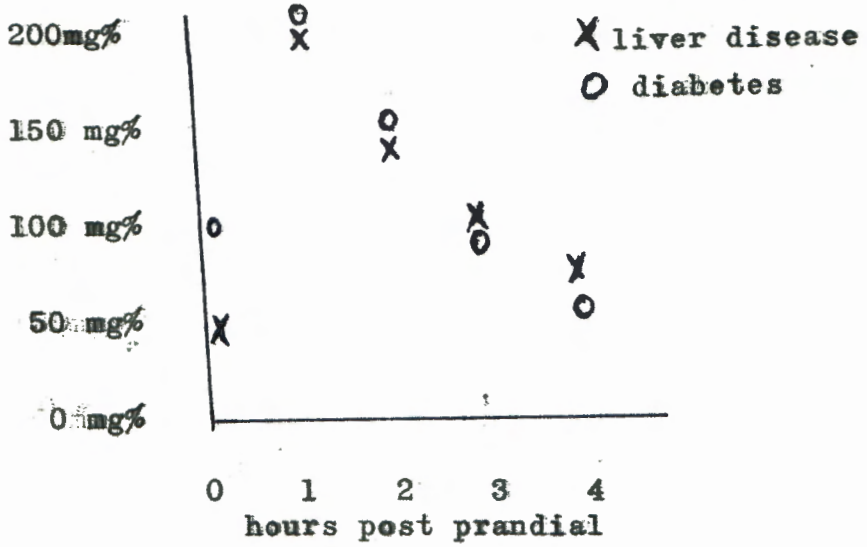
grow out to encircle liver cells which eventually disappear, replaced by dense bands of fibrous tissue. It is these bands originating from new vascular channels which destroy the architecture of the liver producing such patterns as lobules which have no central vein. The presence of such nodules gave rise to the notion of regeneration as a cardinal feature of the process of cirrhosis in the past--a notion rendered unnecessary by the mechanism presented. If not every portal or central area is involved (a likely state of affairs in infectious hepatitis) one expects to get larger nodular areas--the picture seen in post necrotic cirrhosis. Thus different etiologic agents by effecting different groups of hepatic cells can produce different pathologic pictures through very similar mechanisms.

Diagnosis:

How are the entities of cirrhosis and diabetes diagnosed? In the final analysis the diagnosis of cirrhosis depends of the microscopic picture of liver. So in an autopsy series, there is no difficulty with the diagnosis. It is not as satisfactory in the living individual in the absence of a liver biopsy. Such features as persistant hepatomegaly with persistantly, grossly abnormal liver function tests were used in one series. (4) Any error here is likely to be in letting

actual early cases of cirrhosis slip through ones fingers undetected.

The diagnosis of diabetes is usually no problem. It is made on the basis of fasting blood sugar, glucose tolerance curve etc. But it becomes difficult in the mild diabetic with liver disease. For liver disease can cause hyperglycemia, giving a glucose tolerance curve which resembles that of the mild diabetic. Criteria used by Frankel, et.al.(10) for diabetes in the face of liver disease were a fasting blood sugar above 200mg% or a failure to return below 160mg% in two hours time on the tolerance curve. They were not sure of the adequacy of their own standards. The first



portion is probably sound; the second not. Subsequent study (29) has shown that though in both the early

diabetic and the curve of liver disease, the glucose level will reach around 200mg% at one hour and both levels will decrease more slowly than normal, eventually reaching low levels by about four hours. But the fasting blood sugar is characteristicly low in liver disease but elevated in diabetes which should permit one to differentiate the two. If the onset of diabetes preceeds that of cirrhosis, this problem is bypassed.

Possible relationships beteen diabetes, cirrhosis:

What are the possible interrelationships between two disease processes, namely cirrhosis and diabetes? The first relationship is that of the common ancestor to use evolutionary parlance. Man did not evolve from the ape as we know it today, but supposedly from a common missing link. The situation in hemochromatosis,-- the liver and pancreas become fibrotic leading to liver cirrhosis and diabetes respectively through some fault in iron metabolism which allows excessive amounts of iron to accumulate in the tissues--is perhaps of this type. The second might be termed 'brinkmanship'. The body's defences are so swamped trying to cope with a given entity, say diabetes, that a second factor, say hepatitis, has a pushover job, and it in turn results in the scarred liver of cirrhosis. A third possibility

is closely akin to the foregoing one. In this the very nature of a community (say it is diabetic) is such that its exposure rate (say to serum hepatitis through use of contaminated syringes) is higher to a given agent which leaves as a sequella the associated entity (cirrhosis). The last possibility is that of the direct effect. Diabetes causes a sufficiently fatty liver so that the circulation to hepatic cells is embarrassed, initiating the process of cirrhosis. But before one can decide if any of the above factors are indeed operative in the problem under consideration, one must turn to the evidence one has in the literature.

Much of this evidence will deal with statistics--the incidence of this in that. Before one goes on one must state that statistics without a little common sense attached can lie quite proficiently. This is especially true when an entity such as cirrhosis which has a number of etiologies and types is treated as a single unit. The actual relationship may be missed because an increase in one type is accompanied by a decrease in another, giving a net change of zero in the statistics. The interesting situation may even develop statisticly that there is a significant incidence of A in B but not B in A. To illustrate, hemolytic anemia

in sickle cell trait but not sickle cell trait in hemolytic anemia, though when seen together, the sickle cell trait is the direct cause of the anemia. This because of hemolytic anemia in the area sampled is caused by malaria in the vast majority of cases, an entity which the trait protects against. Using this illustration as a guide, one sees that if an entity is statisly significantly related to another entity, the reverse relationship must be significant also, though statistics may not show the reverse relationship. Also eventhough a causal relationship exists between the two entities, which is cause and which is effect cannot be told through statistics. Thus warned let us proceed.

Presentation of statistical evidence

In 1871 Claude Bernard on discovering that the liver played a part in glucose metabolism, first suggested that the liver might be involved in the production of diabetes mellitus. A scattering of cases reporting cirrhosis in cases of diabetes began appearing in the literature. With the discovery of the pancreas and later of the roll played insulin from the islets of Langherhans, attention was directed away from the liver to the periphery. But not until there had been a slow accumulation of information pertaining to the subject.

By the early nineteenfifties a number of studies had been run on the incidence of cirrhosis of the liver in diabetes. Unfortunately, in most of them there was no use of controls, but merely crude rates. The importance of this ommission can be seen in the following data.

Incidence of cirrhosis in diabetes

Grabe 1951	0.25%
Falta 1944	0.40%
Marble	0.44%
Joslin	0.51%
Wilder 1940	0.70%
Frankel, et al 1950	1.01%
Lohr and Reinwein 1952	1.04%
Noorden and Isaac 1927	2.60%
Weichselbaum 1911	6.0 %
Heiberg 1914	7.1 %
Hartman 1957	9.6 %
Schleusner	12.7 %

(3) (14) (16) (27)

These series show a considerable variation. This is almost the exact range given for the incidence of cirrhosis in the general autopsy population which has varied from 0.66% to 12% depending on the series. (3) It makes considerable difference whether ones clientel

come from skid row or from a middle class neighborhood. Epidemics of hepatitis also leave their mark. In looking at these early figures, the consensus had to be, there is no relationship between diabetes mellitus and cirrhosis of the liver. This was the statement to be found in the textbooks. The reverse side of the coin the incidence of diabetes in cirrhosis was not much more impressive. During this time reports scattered through the literature on particular cases stated such findings as a case of cirrhosis with ascites in which the ascites disappeared after the coexistant diabetes was brought under controll with insulin.(13) Other cases reported that the levels of glucosuria in diabetes gradually fell as cirrhosis in the same cases became increasingly severe.(5) The consensus remained that outside of hemochromatosis, cirrhosis had no effect on diabetes. (3) (10)

Then the picture began to change. In 1950 Reinberg and Lipton (23) made a study of the association of Laennec's cirrhosis with diabetes mellitus. They also came to the conclusion that there was no relationship between the two entities. 5.7% of their diabetic patients had liver cirrhosis. Their control group, a small portion selected between random dates of their total autopsies, had 6.4%. The incidence in the total autopsy

autopsy population was actual lower, close to 5%. With their data they published the age of death in the diabetic and control cirrhotics. This data is presented below.

Age of death in cirrhosis of the liver

	diabetes	controls
0-9	0	0
10-19	0	0
20-29	0	0
30-39	1	4
40-49	3	17
50-59	8	7
60-69	12	4
70-79	8	3
80-89	1	2
90-99	0	0

Just glancing at these figures it appeared that the ages at which these two groups of patients had died was significantly different. So I calculated the means , the standard deviations ,and the standard error of the difference between the two means. The mean of the control series falls right at the fifth decade. The mean age of the diabetics is 0.8 decades higher. The standard deviations in both are close to

one decade. The standard error of the mean in each of these turns out to be 0.165 decades; the standard error of the difference of the two means to 0.232. This divided into the difference between the means of these two series or 0.8 gives a number greater than 3. In other words fate does not even have one chance in a hundred of selecting two such series from a like population. Or cirrhosis in diabetes is somehow different likely from cirrhosis in the general population.

In 1958 MacDonald and Mallory (19) published a series in which they found the concommitant occurance of these two diseases to be that expected by a chance association. But they observed a difference in the types of cirrhosis associated with the diabetic and with the population in general. A brief summary of their data, based on some 10,000 autopsy cases, is seen below.

Type of cirrhosis	Incidence of cirrhosis in diabetes	Incidence of cirrhosis in non diabetes	X^2
post necrotic	2.5	1.3	4.31
portal	4.2	7.3	5.57
hemochromatosis	1.5	0.5	5.57
biliary	1.9	1.5	
cardiac	1.0	0.9	
undetermined	2.7	1.9	
total	13.8	13.4	
fatty livers	14.0	10.6	

One can see from the X^2 values they obtained, that in the postnecrotic , fatty nutritional (portal), and hemochromatosis patterns, the differences in incidence are significant between the 2-5% level. One should note that in the diabetic group the type of cirrhosis was undetermined in a higher percentage.

Jaques (14) published a series of 177 patients dying of diabetes mellitus. He reported the incidence of portal cirrhosis in this group and a group of controls matched in age and sex. He graded his cirrhotics from 1 to 4 depending on severity. Grade one was mild periportal fibrosis; grade four a marked destruction of the normal architecture of the liver along with marked fibrosis.

Incidence of portal cirrhosis -- 177 cases

grade of cirrhosis	diabetes		controls	
1	13	7.3%	5	2.8%
2	10	5.7%	6	3.3%
3	5	2.8%	3	1.6%
4	1	.5%	1	.5%

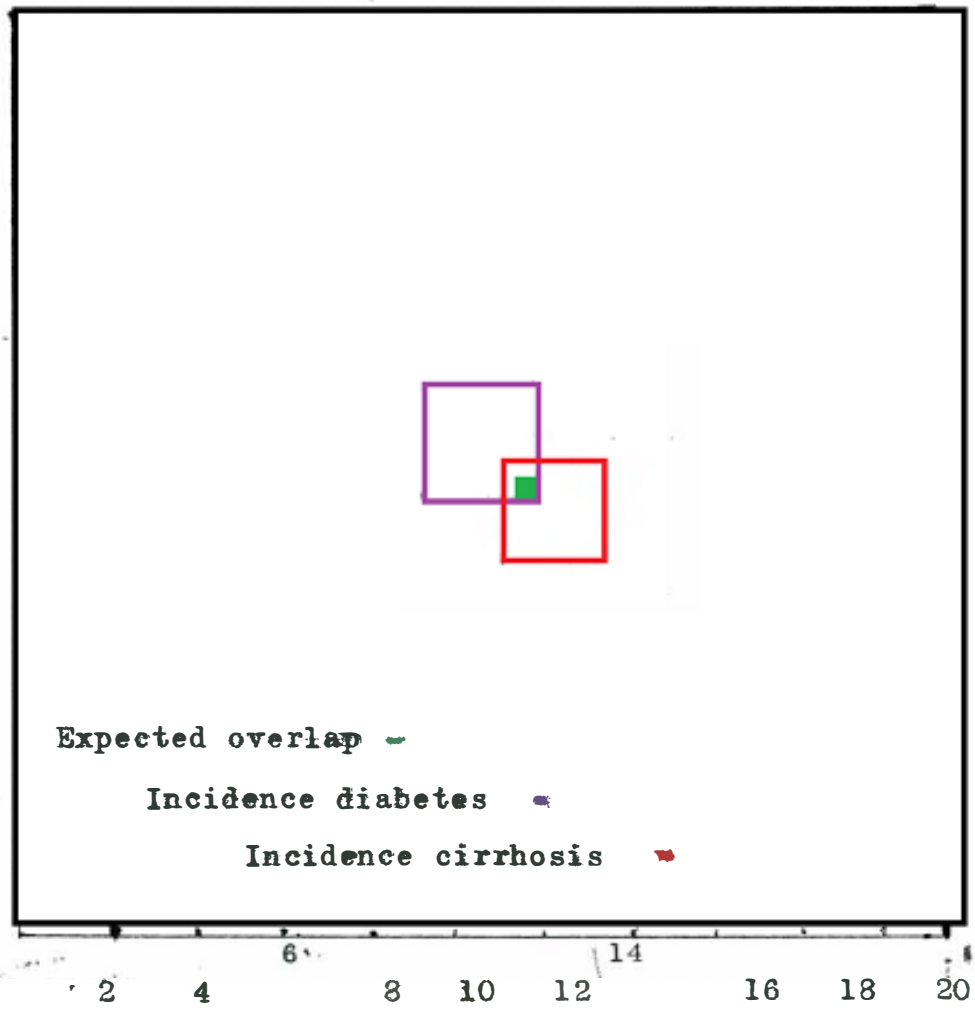
The X^2 here is 5, certainly statisticly significant.

In 1955 Bell (2) followed with an analysis of 932 autopsies on subjects with portal cirrhosis. Patients with hemochromatosis were left in his series. He breaks down his data as follows:

	No. autopsies	diabetics%	cirrhotics	%diabetic
male				
below 40	12956	.65	76	4.0
above 40	31752	2.32	557	11.8
female				
below 40	9479	1.04	45	2.0
above 40	15618	4.98	254	6.7

This data is presented graphicly on the next two pages. In males he obtained five times more cirrhosis in diabetes than his general autopsy population showed. Even excluding hemochromatosis the incidence is three times that of the general population. The total incidence of cirrhosis was much less in females. In them little gross difference was picked up between the normal and the diabetic populations.

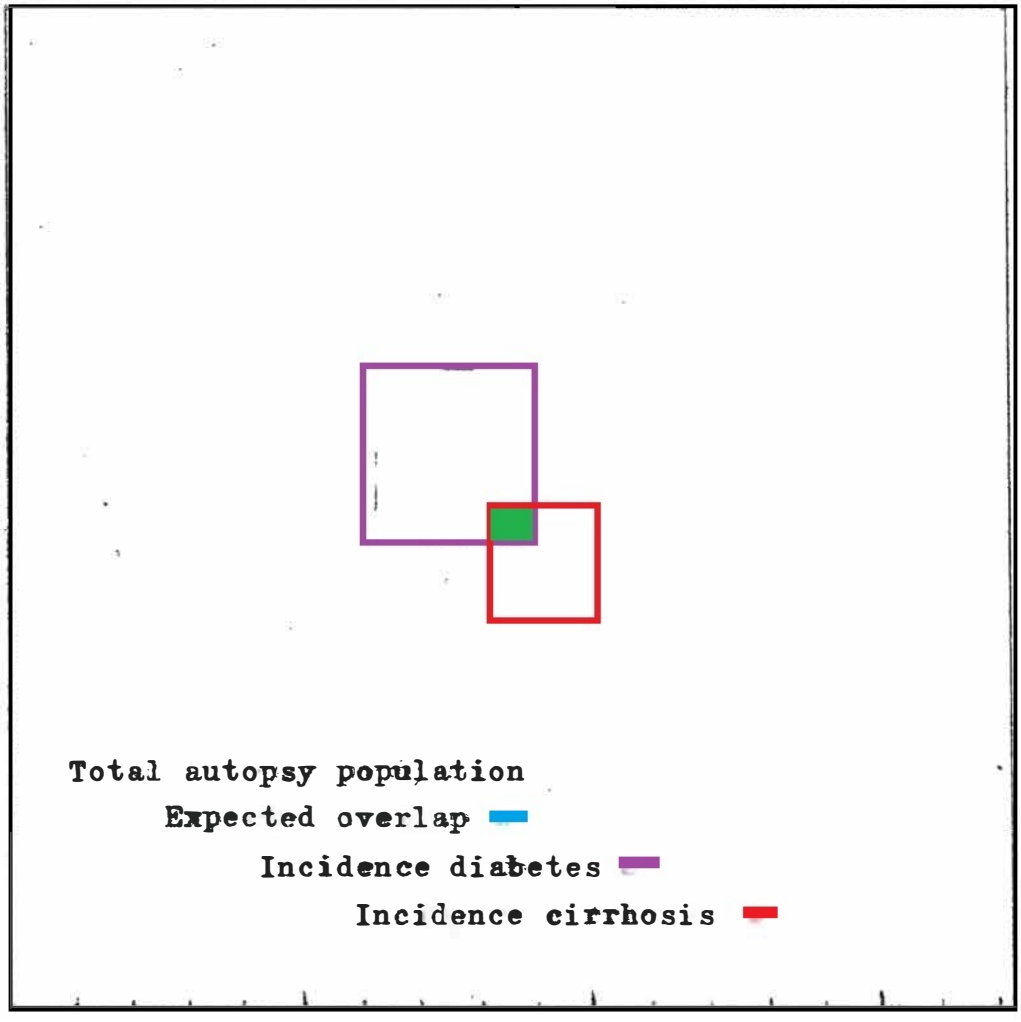
Then in 1961 Bloodworth (3) published the results of some 27,050 post-mortem exams at Ohio State University. He had an overall increase in incidence in his series. But during the first seven years and the first 5,000 autopsies, cirrhosis in the diabetic patient remained at the same level it did in the general population. When he took his last 5,000 autopsies, from 1955 on, he finds that the total incidence of cirrhosis has risen in both populations, but in the diabetic this increase was much greater. Through 1944, the incidence of cirrhosis in control and diabetic population was around 1.2%. After 1955 this figure in the diabetic



Area directly proportional to number of autopsy cases

1 sq. unit. 100 cases

Data after Bell male population



Area directly proportional to number of autopsy cases

1 sq. unit 100 cases

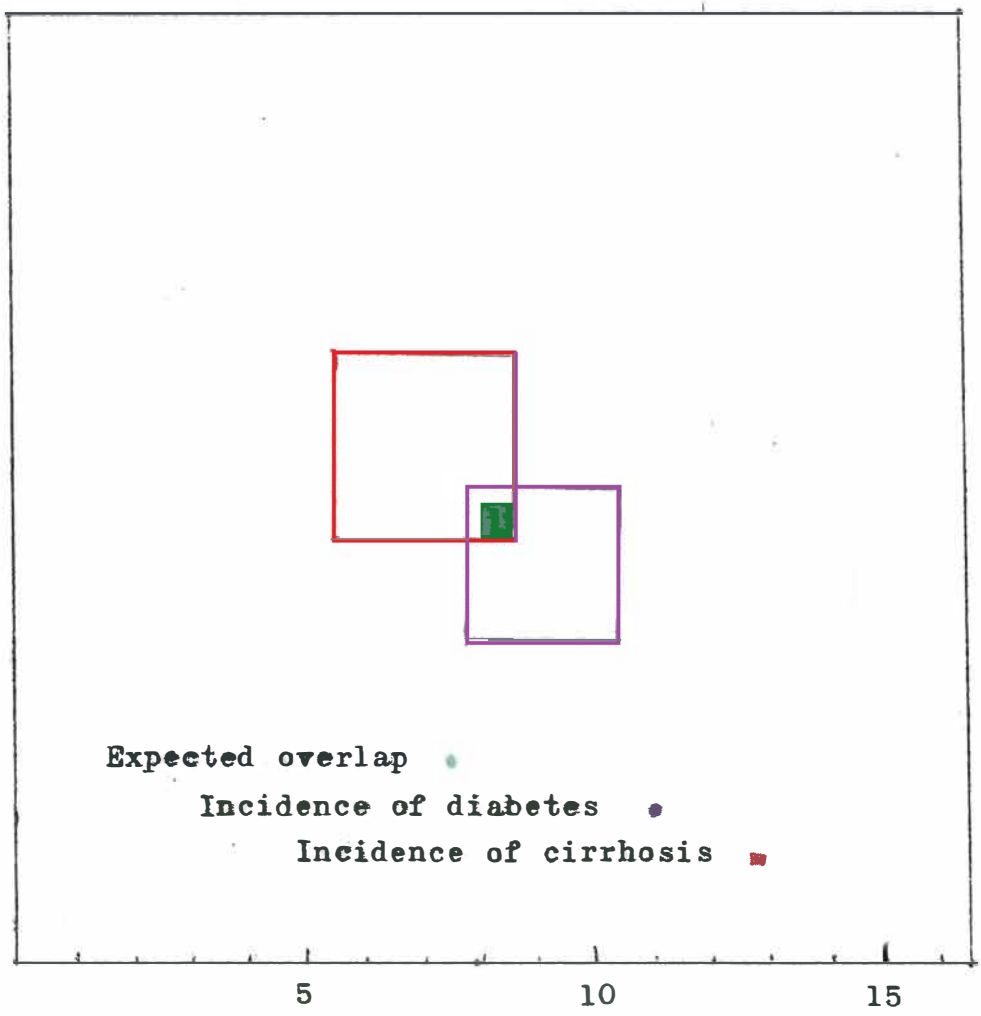
Data after Bell female population

was increased to 12%, twice that of the general population. This data is summed up graphicly on the following page.

Around 1950 the technique of the liver biopsy began to be applied to this question. In that year McMurray and others came up with a series of 10.7% of their diabetics had cirrhosis. Leevy and others followed with a series of 26.6% the same year. Kalk (16) choosing diabetics with hepatomegaly, found in 1955, that 32% of these patients showed some signs of cirrhosis. Patients with hemochromatosis were excluded. Even though these were selected patients, the series supports Reinberg's contention that the incidence of cirrhosis in the diabetic is five times that suspected clinically. (23)

Summary of significant data:

Now to review the facts gleaned from the literature, based on the assumption that the data presented was reliable. There is a significantly higher incidence of cirrhosis in the diabetic as compared to the population at large. This increased incidence appears to be of relatively recent onset and dominates in the male population. The greatest increase (exeluding hemochromatosis) appears to be in the post necrotic



Area directly proportional to number of autopsy cases

1 sq. unit 100 cases

Data after Bloodworth --- 1937-1960

type of cirrhosis. Though the fatty nutritional or portal type pattern has been as prevalent in the non diabetic, the disease in the non diabetic is fatal at a significantly lower age.

Discussion:

How is one to explain these facts? After the discovery of insulin the life expectancy in the diabetic has increased quite markedly. Could this have anything to do with the results found? The increased age per se likely plays a very minor part if any. For cirrhosis is not at all correlated with the length of time a patient has had diabetes. Almost all the cases of cirrhosis reported in the literature had developed in diabetics who have had their disease less than twenty years. In fact cirrhosis is just as likely to be the presenting diagnosis as diabetes. Nor does cirrhosis appear to be influenced by the severity of the diabetes. A large portion of patients develop their cirrhosis in the prediabetic stage. (8) (10) (14) Kalk (3) found in his studies, that the pattern in such individuals was predominantly one of post necrotic cirrhosis.

This brings us to our next question. What is the roll played by infectious hepatitis. A sequence of events, hepatitis cirrhosis diabetes, has been postulated. Poche (21) blames all the rise seen in

cirrhosis in diabetes of late on infectious hepatitis. He states that the diabetic patient is more susceptable to hepatitis and that the course of the disease is more severe leading to cirrhosis as a sequella much more frequently. Perhaps this severity extends to the prediabetic stage. And then insulin injections have been implicated in outbreaks of serum hemolagous hepatitis spread from one diabetic to another through the use of contaminated syringes. (24) In one such epidemic in an English hospital needles, but not syringes, were changed between patients. The vacuum created when the needle is removed from the syringe sucks serum up into it. This probably has not been a frequent enough occurence to affect the statistics to any significant degree. Could another mechanism play some part? Infectious Hepatitis certainly does not have a sufficient direct effect on the islets of Langerhans to produce diabetes. (26) In the normal individual some 80% of the of the pancreas must be destroyed to reduce insulin levels sufficiently to produce the symptems of diabetes. What effect does the decreased functioning of the liver have on a patient with a diabetic tendency though? Many compounds are detoxified solely by the liver. Most of the hormones are among these, including some of the ones

such as growth hormone which are diabetogenic. (29) So it is certainly possible that hepatitis and its sequella cirrhosis aggravate any diabetic predisposition present.

Thus infectious hepatitis plays a significant roll in the cirrhosis of diabetes, through multiple mechanisms. But the story does not end here, for it ignores portal cirrhosis. Jaques (14), who found a high incidence of this entity in his diabetics, states that there is history of hepatitis in any of them. Also the age difference is left unexplained.

Among its other names, portal cirrhosis has been called alcoholic cirrhosis. This name due to the fact that a history of chronic alcoholism is a prominent feature in the history of a high percentage of these individuals. The name is now frowned on because it suggests an etiology which may have nothing to do with many of the cases. (8) On a world wide basis simple dietary insufficiency seems to be the major factor. Even in the alcoholic, there are those who feel that the poor nutrition seen in these individuals is the actual culprit and not the alcohol per se. Returning to the work of Reinberg and Lipson (23), one finds that they noted a difference in their diabetic and non diabetic populations with portal cirrhosis--a difference which might or might not be real. Using the criteria

of repeated hospital admissions for alcoholism or an admitted consumption of over one pint of whiskey per day, they discovered that 24% of their diabetics were chronic alcoholics as opposed to 78% of the non diabetics. The hooker here was that they had no drinking history on 60% of the diabetics and on 10% of the non diabetics. So conceivably the two groups might imbibe equal amounts. This difference if real is somewhat difficult to understand. It would be more comprehensible if cirrhosis was associated to a greater degree with the brittle type of diabetes. In other words in a disease requiring close control at an early age, restricting the opportunity for excessive alcoholic consumption. In the adult or maturity onset diabetes, one would expect that the drinking habits were established before the age of onset, and would be hard to break even though diabetes climbed into the picture. The adult diabetic does tend towards obesity. This might have a slight curbing effect on the individuals ethanol intake--alcohol is notoriously fattening. It would be more logical to attribute a decrease in alcoholic consumption in the prediabetic individual, if it exists, to a difference in the metabolism of alcohol. Individuals who get severe hangovers after drinking are less likely to become heavy users or alcoholics. The hangover in turn depends

on the build up of acetaldehyde from the ethanol, ie its metabolism. This must remain a mere hypothesis in the absence of supporting data. On the other hand if the diabetes had no effect at all on cirrhosis, a normal drinking population should give a normal cirrhotic population and that includes a like age distribution. Now diabetes certainly increases the work load on the liver. It is this very reason why the whole question of its relationship to cirrhosis was raised in the first place. In the diabetic alcoholic then, one would expect an earlier onset of cirrhosis not the reverse as seen in the previous part of this paper. Therefore, one must proceed under the assumption that the diabetic portal cirrhosis is indeed a different from that seen in the non diabetic population in some cases at least. This brings up the problem of fatty infiltration of the liver.

Earlier in the paper a mechanism was discussed whereby fatty infiltration itself could cause cirrhosis. (18) In fairness one must state that as recently as 1958 a number of prominent pathologists were openly dubious of the idea that fatty infiltration alone could cause cirrhosis. (3) One must again turn to the literature to discover what it has to say about the fatty liver in the diabetic, in an effort to decide this question.

As early as 1784, Mead commented on the fact that fatty infiltration of the liver occured in diabetes. Hepatomegaly with fatty infiltration was first considered a significant entity in childhood diabetes-- by Marble and others in 1938. 1077 patients were reviewed; 60 of these having massive hepatomegaly reaching down to the umbillical level. All of the cases having hepatomegaly were under poor control-- 54 having had severe bouts of acidosis and 42 having had frequent attacks of hypoglycemia. Half of them were diabetic dwarfs. This hepatomegaly occured on an average of six years after the diabetes was diagnosed. Autopsies on patients who died showed livers which were large and greasy and of yellowish hue. Fat stains showed fat droplets in the hepatic cells; the conclusion was fatty infiltration. The question on whether or not a significant amount of glycogen was present or whether an absolute increase in the number of hepatic cells occured was left open. But I could find only two cases of brittle diabetics who had progressed on to cirrhosis. (14) Though over 90% of these patients develope a serious complication before they have had their disease twenty years, cirrhosis is not a significant one.

The early investigators were not particularly

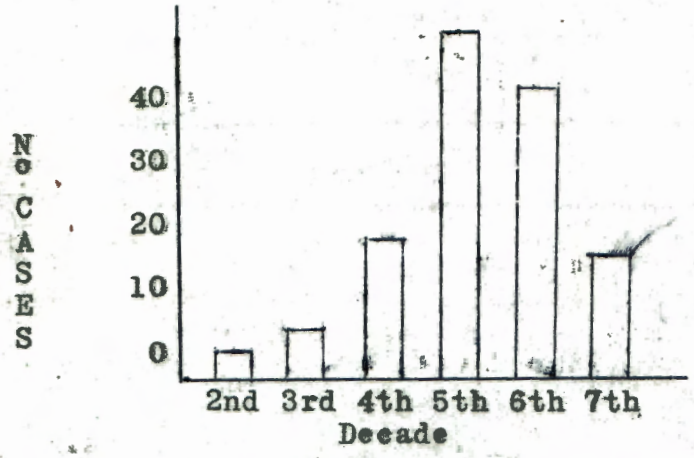
excited about fatty infiltration of the liver in the adult diabetic. For they did not find an incidence much greater than in the general population, though known to occur. Hansen found only one patient with a large liver among his 231 adult diabetics. In 1950 Frankel (10) stated that the incidence of hepatomegaly and fatty infiltration in adults is quite low. Yet it was well known that uncontrolled diabetes in the adult, namely acidosis, was a different story altogether, certainly capable of causing hepatomegaly with a fatty liver. (9) Reinberg and Lipson (23) report that 19.4% of their diabetics had fatty livers while the figure for their controls was 15.1%. However, in the diabetics in comma or in acidosis, fully half were found to have fatty livers. In general the liver function tests in such individuals showed only transitory abnormalities, which disappear gradually as the diabetes is again brought under control. The liver usually decreased in size. The commonest abnormality is an increased BSP retension. In the few cases where liver function remained abnormal, the liver often remained large. (4) (6).

Simple obesity is certainly present in a high proportion of the adult type diabetics. 40% are overweight at the time the diagnosis of diabetes is made

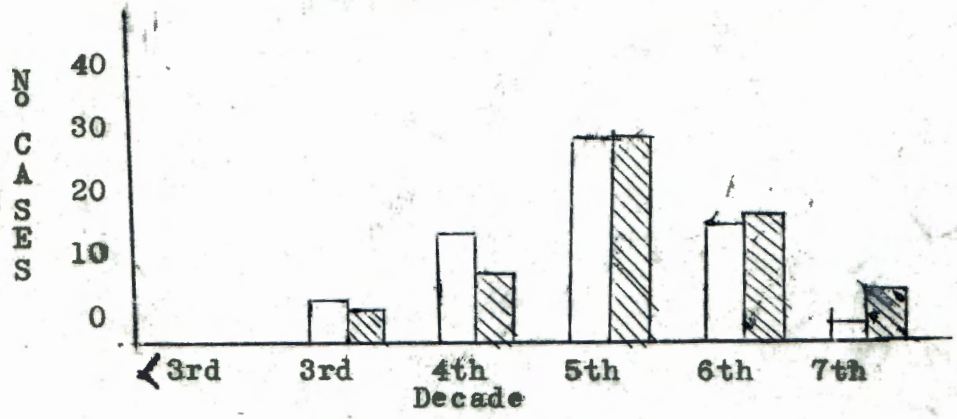
and more than half of those who have had the disease for any length of time are overweight. The greater the obesity, the greater is the chance that diabetes will develop. An individual who is 10% overweight has 1.5 times the chance a normal individual has of developing the disease. When this increases to 25% overweight, the chance has risen to the high value of 8.3. (29) Gross obesity alone may cause a fatty infiltration of the liver.

Goodman (11) writing in 1951 felt that the very obesity which is associated with the diabetic was obscuring a large percentage of the enlarged livers in them. For in the stocky, obese individual, the liver rides high and is difficult to palpate. He used a percussion method, trying to outline both upper and lowereborders of the liver, using an absolute flat note as end point. By using this method, he found 44.5% of the livers were enlarged--the largest in patients who were acidotic. But just plain gross obesity in many of these diabetics was associated with a good sized liver.

Kalk (16), in doing his biopsies on diabetics, found that 49 out of his 102 cases showed fatty infiltration of the liver. His findings are presented below.



Age of diabetic at time of examination



Diabetics with fatty livers

age examined

age onset

Bloodworth also found a high incidence of fatty liver. (3) It is worthy of note Jaques (14) found his diabetics had a significantly higher percentage of fatty livers. It is these authors who found a definite increase of cirrhosis in their diabetics. Kalk and Bloodworth were strongly of the opinion that in some of their cases at least, the fatty infiltration per se was causing cirrhosis. Kalk divided his fatty livers

into an active group and a nonactive group, which differed in that the active group showed a focal infiltration of inflammatory cells microscopically. The glucose-6-PO_4 was elevated in this group also, as it is in hepatitis. He felt that it was this group which was in the process of progressing on to cirrhosis.

The fatty liver is now excepted as a frequent part of the diabetic picture. And though it plays a role in diabetic cirrhosis, it could hardly account for the increased incidence of cirrhosis in the diabetic in recent years. For one has to make the assumption that either the control of the diabetic has deteriorated in the last few years or diabetics today are just fatter than they used to be. Neither seems likely. One does not like to think that control of the diabetic has lessened while our knowledge has been increasing. And with the emphasis on the importance of weight control in helping regulate the diabetic, one does not expect that the incidence of obesity would go up.(9)

At the beginning of the discussion, it was brought out that the life expectancy had greatly increased since the introduction of insulin, but cirrhosis did not appear to be related to the increased life span. Could it instead be due the insulin. Insulin will cause a regression in the size of the liver in a patient who

is out of control. This is not sufficient to remove all possibility of guilt from its doorstep. For it has the property of stimulating lipogenesis-- not particularly desirable in an already overly obese individual. Then in vitro experiments on glucose utilization by rat liver slices showed the following conversions. (27)

	glycogen	CO_2	fatty acids
normal rat	36	5.3	0.53
Alloxan diabetes	1.3	1.9	00
" " plus 48 hr insulin	113	19	5.5

Thus there was at least a transitory increase in fatty acids in the slices with insulin.

The biguanides do not stimulate lipogenesis and may prove to be the drug of choice in the mild obese diabetic. Liver glycogen is also decreased with this drug. (29) The role of insulin in the production of cirrhosis must remain pure conjecture for lack of further evidence.

Conclusion:

Biliary cirrhosis and cardiac cirrhosis do not appear to be related to diabetes mellitus in any way. Infectious hepatitis has a particular affinity for the diabetic, increasing both in incidence and in severity and resulting in an increase in the post hepatic form

of cirrhosis. Perhaps gamma globulin should be given routinely to the diabetic who is exposed to the disease in hopes of at least lessening the severity of the hepatitis, should it develop.

The evidence for the relationship of portal cirrhosis is not as clear cut, though there does appear to be a difference in the diabetic with this entity and the population at large. Its production is likely a by product of fatty infiltration of the liver. It may be that weight control and good control of diabetes are most important here. Perhaps biguanides will prove to be useful in these patients. At present that old and sometimes quite difficult exercise of pushing ones self away from the table may be the best treatment.

Certainly the overall evidence for cirrhosis along with the fatty liver in the diabetic is strong enough, so that these possibilities should be kept in mind when the next adult diabetic steps into the office.

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