ALCOHOLISM AND LIVER-FUNCTION TESTS

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Bailie in 1793 and Addison in the early part of the 19th century recognized some association between alcoholism and cirrhosis of the liver.[1]

According to Jolliffe and Jellinek[2] cirrhosis is 6·8 times as frequent in alcoholics as in a non-drinking population; the incidence of cirrhosis is, however, low, even in severe alcoholics, and numerous alcoholics are found with completely normal livers. According to Zieve and Hill[3] there is no definite relationship between alcoholism and liver function in healthy, well-nourished and gainfully employed individuals. Relatively large amounts of alcohol may be consumed without evident abnormality of hepatic-function tests.

Where alcoholic excess leads to hospitalization, functional abnormalities are encountered, and varying numbers of these individuals, by continuing their excesses, eventually develop fatty livers and portal cirrhosis. Spree drinkers are less likely to develop liver damage than continual topers. This is probably explained by the fact that spree drinkers eat reasonably well in the intervening periods. Sherlock[1] suggests that there may exist an inherent individual susceptibility to alcohol. The type of beverage consumed does not appear to influence the liability to develop cirrhosis. The exact relationship between alcohol and cirrhosis remains conjectural and there are probably several contributing factors.

Relationship between Alcohol and Cirrhosis

Alcoholic cirrhosis is probably caused by a combination of nutritional factors and, in some instances, by a direct toxic effect on the liver.

Added caloric intake in the form of alcohol leads to increased choline requirements which may not be met. Cirrhosis in animals is more readily produced by an increased caloric intake in the presence of a fixed amount of lipotropic substances. Evidence exists that in alcoholic cirrhosis a relative choline deficiency exists, and a state of nutritional imbalance ensues.

The anorexia, associated gastritis, and other gastrointestinal disturbances so often found in the alcoholic, lead to decreased absorption of protein and vitamin B. In addition, the alcoholic, after spending much of his earnings on drink, has very little left to purchase protein-rich foods. This results in a deficiency of protein intake, and evidence exists that in the presence of a low protein intake liver disease is more common. This factor can therefore be referred to as a state of 'nutritional deficiency'.

The third factor, a direct toxic effect on the liver, may result from toxins being more easily absorbed from the damaged intestinal mucosa. Certain alcoholic beverages may contain toxic substances which may possibly exert a direct effect on the liver, or alcohol may aggravate defined and undefined hepatotoxic substances.

Alcoholism

'Alcoholism' can be defined as a state of periodic or chronic intoxication, detrimental to the individual and society, and produced by the repeated ingestion of alcoholic beverages. Its characteristics are: (1) Compulsion to continue taking alcohol, (2) early development of tolerance to alcohol,

(3) psychic dependance on the effects of alcohol, and (4) somatic dependance on alcohol, resulting in withdrawal symptoms when abruptly withheld.

The development of means to continue drinking becomes an important motive in the alcoholic's existence. Once the mechanism of true addiction has been established, the only way in which the patient can maintain some degree of functional efficiency is to continue drinking.

The withdrawal symptoms most commonly encountered are: (1) Restlessness, (2) severe feelings of apprehension, (3) depression, (4) irritability, (5) lack of concentration, (6) insomnia (often intolerable), (7) nightmares, (8) tremor of tongue and extremities, (9) *grand mal* seizures, (10) nausea and vomiting, (11) diarrhoea, and (12) increased pulse rate.

Clinical study of the problem of alcoholism over the past 10 years has led one of us to hold strongly the hypothesis of an inborn tendency to the development of addiction. One in 1·78 of the patients admitted to Northlea and Mount Collins sanatoria gives a family history of alcoholism. Almost universal is the history of a rapidly developed tolerance to alcohol resulting in a reputation for being able to 'take one's liquor without getting drunk'. Hangover is practically unknown before the development of compulsive drinking. The tremendous release from tension, even after comparatively small amounts of alcohol (noted by many), is a feature reported by nearly all patients before alcohol became a problem.

In view of the association between alcoholism and liver disease, it was decided to carry out a battery of so-called liver-function tests on an unselected group of 40 volunteer male patients admitted for treatment for alcohol addiction to Northlea Retreat, Johannesburg.

MATERIAL AND METHODS

Initial tests on the group investigated were carried out within 48 hours of admission and the tests were repeated (when possible) at monthly intervals. The group was a true random group, completely unselected beside the fact that all required admission to hospital suffering from the acute effects of a recent bout of drinking.

Characteristics of the Group

1. The average age of the members of the group was 38·1 years, individuals ranging from 25 to 45 years of age.
2. The average length of time lapse between the first drink and the advent of daily drinking was 9·6 years, with a range of from 2 to 18 years.
3. The average lapse of time between commencing daily drinking and admission was 12·9 years with a range of from 5 to 18 years.
4. All the patients in the group were admitted showing signs of dehydration to some degree.
5. 71·6% of the group volunteered that early in the drinking history their capacity to take alcohol was greater than that of their drinking friends.
6. 77·6% of the group stated that they became intoxicated and incapable on comparatively little alcohol since the beginning of compulsive drinking.
7. 21% of the group showed evidence of alcoholic peripheral neuritis.
8. 82% showed some hepatic enlargement ranging from 'palpable' to 5 fingers below the costal margin.
9. Only 2% of the group took regular meals during drinking bouts and the same percentage took breakfast regularly.
10. 98% of the group admitted to alcoholic palimpsests at some stage or other of their drinking history.
11. Only one patient manifested any degree of clinically apparent icterus.
12. All the patients fell into our definition of the alcoholic, viz.

(*a*) Once having had a certain amount of alcohol, a compulsion to consume more alcohol developed.
(*b*) Withdrawal signs appeared on the withholding of alcohol.
(*c*) Some aspect of their lives (physical, general environmental, domestic, or economic), was seriously affected by their drinking.

The laboratory tests carried out on all patients in this investigation were as follows: Thymol turbidity, thymol flocculation, colloidal red flocculation, cephalin cholesterol flocculation, Takata-Ara reaction, zinc sulphate turbidity, total lipids, blood cholesterol (total, free, and esterified), serum proteins, electrophoretic protein analysis, alkaline phosphatase, pseudo-cholinesterase, bilirubin (total and direct), Van den Bergh reaction, bromsulphalein dye retention, mucoprotein, polysaccharides of mucoprotein, ratio of polysaccharides to mucoprotein (PM ratio), packed-cell volume, sedimentation rate, prothrombin index, and urinary urobilin.

The techniques and normal values adopted for the above tests were as previously described.[4,5]

The protein electrophoretic analyses were carried out on the Antweiler electrophoretic apparatus: Mucoprotein and polysaccharides of mucoprotein were carried out according to the method of Simpkin *et al.* and Shetlar *et al.* respectively.[6,7] The sedimentation rate and packed-cell volume were carried out according to the method of Wintrobe and Landsberg.[8] Prothrombin index was estimated by the two-stage technique of Quick.

RESULTS

Table I shows the percentage of abnormal tests found on admission of our patients to the sanatorium. Since the majority of these patients were discharged within a month of admission, no attempt is made to compare the results on admission with those subsequently carried out.

TABLE I. PERCENTAGE OF ABNORMAL LIVER-FUNCTION TESTS IN THE GROUP OF ALCOHOLICS ON ADMISSION

Test	%
Thymol turbidity	5·0
Thymol flocculation	12·5
Colloidal red	17·5
Cephalin cholesterol	12·5
Takata Ara	5·0
Zinc sulphate turbidity	32·5
Total lipids	15·0
Total cholesterol	11·0
Percentage esterified to total cholesterol	0
Total protein	62·0
Albumin	24·0
Globulin	3·0
Gamma globulin	11·0
Albumin, globulin ratio	16·5
Alkaline phosphatase	7·5
Pseudo cholinesterase	12·5
Bilirubin, total	5·0
Bilirubin, direct	15·0
Van den Berg reaction	20·0
Bromsulphalein dye retention	9·0
Mucoprotein	65·0
Packed-cell volume	36·0
Sedimentation rate	43·5
Prothrombin index	9·0
Urobilin	73·5

The following are summaries of and comments on the results of the tests:

Thymol Turbidity, Flocculation Tests, and Takata-Ara Reaction

Only a small percentage of our patients showed ab-

normalities of these tests. The colloidal-red test was the most sensitive in this group and the thymol turbidity and Takata-Ara reaction, the least sensitive. Only one patient showed a maximally positive result for the Takata-Ara reaction, and the mean average level for the thymol turbidity test (2·2 units) was well within the range of normality.

Approximately a third of our patients showed a raised zinc sulphate turbidity test and in 3 there was definite elevation of this test—32, 25, and 22 units respectively. The mean level for this test was just slightly above the upper limits of normal (13·3 units).

Total Lipids

Two patients showed marked elevation, 2 showed only slightly raised levels, and one showed a moderate increase. The mean level on admission was well within the range of normality (567 mg. per 100 ml.).

Total Cholesterol

Four patients showed elevated cholesterol levels and 2 of these showed levels above 300 mg. per 100 ml. Four out of 37 patients showed levels which are on the low side of normality. The mean average figure was well within the range of normality (218 mg. per 100 ml.).

Percentage of Esterified to Total Cholesterol

Not a single patient showed any disturbance of the ratio of the esterified to total cholesterol.

Total Protein

A very high percentage of our patients (62%) showed levels of total protein which were on the low side of normality. This test was the third most sensitive in our series. The mean level of protein on admission was 6·6 G. per 100 ml. against a normal mean of 7·6 G. per 100 ml., but only slightly below our accepted lowest limits of normality (6·8 G. per 100 ml.). Three of our patients showed levels below 6·0 G. per 100 ml.

Albumin

The average level for serum albumin (3·6 G. per 100 ml.) was well below our normal mean of 4·5 G. per 100 ml. Nine patients (24%) showed levels below 3·5 G. per 100 ml., our accepted lowest limit of normality.

Globulin

The mean level for serum globulin was well within normal limits, and only one patient showed a definite elevation of serum globulin.

Gamma-globulin Turbidity

Four patients showed elevation of this test and in the case of 2 patients there was a definite elevation, (2·0 and 2·7 G. per 100 ml. respectively). The mean average level was well within the range of normality (1·07 G. per 100 ml.).

Albumin-globulin Ratio

Despite the high percentage of patients who showed a low total protein and serum albumin, only 6 patients (16·6%) showed a reversal of the albumin-globulin ratio on admission.

These protein results therefore probably reflect a low intake of protein rather than evidence of liver dysfunction.

Protein Electrophoretic Analysis

The significant feature of the electrophoretic protein pattern was a reduction in the percentage of albumin (48% as against a mean level of 55%), and an increase in the alpha$_2$ globulin (9·2% as against 6·5%). The gamma-globulin level shows only a minimal increase over our mean level of normality, and is well within the normal range.

Alkaline Phosphatase

Three patients showed only slightly elevated alkaline-phosphatase levels. The mean level on admission was well within the range of normality (8·3 units).

Pseudo Cholinesterase

Only 2 patients showed levels which were well below the normal range, and 3 patients showed levels just below the accepted normal levels. The mean average level was 92% of normal activity.

Bilirubin

Direct. Six patients showed levels above 0·2 mg. per 100 ml. and one of these showed a level of 2·5 mg. per 100 ml. The mean level was 0·27 mg. per 100 ml.

Total. Only one patient showed a definite hyperbilirubinaemia (3·7 m.g per 100 ml.) and one other patient showed a level of 1·4 mg. per 100 ml. The mean bilirubin level on admission was 0·39 mg. per 100 ml.

Van den Bergh Reaction

Only one patient showed a prompt direct reaction and 7 other patients showed an indirect reacting bilirubin.

Bromsulphalein Dye Test

Two out of 22 patients studied on admission showed a dye retention above 5% (dose: 5 mg. per kg. body weight after 45 minutes)—7% and 8% respectively. The mean dye retention was 3·17%, a figure well within the accepted range of normality.

Mucoprotein Level

This test showed the second highest percentage of abnormalities in our series; 65% showed definitely elevated levels and only 4 patients showed levels corresponding to our mean of 80 mg. per 100 ml. The mean level on admission was 130 mg. per 100 ml. Not a single person had a low level. In a further paper now in preparation by us, an interesting, but as yet unexplained, phenomenon was observed. Mucoprotein estimations were carried out on admission of chronic alcoholics in relapse. High figures were invariably obtained. On withdrawing alcohol an immediate further increase to levels in the vicinity of 200 - 300 mg. per 100 ml. were recorded. Then followed a gradual return to normal levels but, on the administration of even relatively small amounts of alcohol, an immediate rise to high mucoprotein levels was again observed. It is suggested (by us) that a diagnosis of alcoholism may be made in those patients who are not suffering from malignant disease or inflammatory conditions, but show abnormal liver-function tests with a high serum-mucoprotein level.

Polysaccharides to Mucoprotein Level (PM Ratio)

Only one patient had an abnormal result of 0·23 which is indicative of parenchymal liver damage.

Urinary Urobilin

Of our cases 74% showed on admission the presence of urobilin in the urine. This was the most frequently abnormal test encountered in our series.

Packed-cell Volume

Thirteen out of 36 patients (36%) showed some evidence of anaemia and one patient was polycythaemic. The mean packed-cell volume was 45·8%. Five of the 13 patients with anaemia showed packed-cell volumes below 40%, and the polycythaemic patient had a packed-cell volume of 55%.

Sedimentation Rate

The mean sedimentation rate was 15 mm. in 1 hour. Twenty-two of 39 patients investigated had rates within normal limits. In 2 patients extremely high sedimentation rates of over 50 mm. per hour were encountered.

DISCUSSION

Voegtlin *et al.*[9] investigated a large group of chronic alcoholics, all from the middle and upper classes of society, whose state of general health was surprisingly good. Of them 9·6% were entirely free from laboratory evidence of liver dysfunction, 16·3% showed minor abnormalities of one test only, 53·3% showed minor abnormalities in 2 or more tests, 17·3% showed minor abnormalities of 1 or more tests, but with 1 test markedly abnormal, 2% had evidence of severe liver dysfunction, and 1·3% had severe liver damage with obvious jaundice. They found the most sensitive liver-function test to be the bromsulphalein test, and the next most sensitive the total serum bilirubin. However, since 20% of their normal controls showed abnormalities of these latter tests, they question whether in their series those patients who showed equivocal abnormalities (i.e. one test only abnormal), might not be false positive reactions.

In addition, abnormalities in urinary urobilinogen excretion and alkaline phosphatase were frequently encountered. Abnormal results for cholesterol, free and esterified, one-minute bilirubin, albumin-globulin ratio, and flocculation tests were rarely encountered. The prothrombin index, in their opinion, was an unreliable index of liver function in the chronic alcoholic.

Cates[10] studied liver-function tests in proved alcoholic cirrhotics and found that the most frequently abnormal tests in this group were the bromsulphalein test, the proteins, and the albumin-globulin ratio, whereas in a group of 17 acute alcoholics (non-cirrhotics), serum albumin and globulin were within normal limits, only 4 patients showed evidence of bromsulphalein-dye retention and only one showed disturbances in esterified cholesterol. Cates suggests that early and perhaps temporary impairment of liver-function tests may be detected by the bromsulphalein dye-retention test.

Popper and Schaffner,[11] in reviewing over 200 cases of fatty livers in the medical literature, found the most frequent abnormal test to be bromsulphalein dye retention in 70% of cases. In 35% the cephalin cholesterol flocculation test and alkaline phosphatase were increased. The gamma globulin was slightly elevated whilst bilirubinaemia and reversal of the albumin-globulin ratio were present in 25% of patients. The thymol-turbidity test was increased in only 20%. Reduced cholesterol esters or prolonged prothrombin times were found only exceptionally, and the serum-cholesterol level tended to be low.

In nutritional cirrhosis they found the bromsulphalein test usually abnormal, and albumin, cholinesterase, and total cholesterol were reduced in the majority of cases. The gamma globulin was increased in more than 50% of cases. When hepatocellular damage was severe, the percentage of esterified cholesterol was low, urobilinogen was increased, and the cephalin cholesterol—but not necessarily the thymol-turbidity test—was increased.

Cates[12] states that liver damage, as revealed by the bromsulphalein-dye retention test, may occur from alcohol and may disappear if the damage is not too severe.

The bromsulphalein-dye test is sensitive enough to pick up various degrees of liver damage, either with physiological dysfunction alone or associated with pathological changes.

Beazell *et al.*[13] investigated 10 healthy young adult males who consumed 'as much as possible' whisky over a 4-hour period and who became maximally intoxicated. Ten hours later the serum van den Bergh reaction, and tests for phosphatase, hippuric-acid excretion, bromsulphalein clearance, urine bilirubin galactase, and fructose-tolerance were carried out. In no case was there any evidence of a variation from the normal in these tests.

Buck[14] studied 7 male alcoholics with fatty livers. He states that incipient cirrhosis in alcoholics is characterized by fatty infiltration and enlargement of the liver. He found that it is in such cases that spontaneous remissions occur when alcohol is withdrawn and a satisfactory dietary régime established.

The cephalin-cholesterol test was positive in 3, the thymol-turbidity test in 2, a moderate to marked hypoalbuminaemia was present in 5, abnormal bromsulphalein retention in 7, and a mild macrocytic anaemia in 4.

Lepehne[15] found a positive cephalin-cholesterol test in 38% of alcoholic patients, 30% showed positive urobilinogen tests and 21% showed bilirubinuria (using the methylene-blue test), though none of the patients were clinically jaundiced.

Nadeau *et al.*[16] state that, of the numerous liver-function tests available to the clinician, the bromsulphalein test has proved to be the most reliable index in the screening of the slightest dysfunction (usually unnoticed by clinical examination). More than half of 178 alcoholic patients showed an abnormal dye retention using the standard 5 mg. per kg. method.

Phillips and Davidson[17] investigated 18 chronic alcoholics who died, and found that 16 showed pronounced bilirubinaemia, and only 1 patient had a normal icteric index. There was a pronounced decrease in prothrombin concentration. The cephalin-cholesterol test was usually markedly positive, and the alkaline-phosphatase test was normal.

It appears quite evident from the literature cited above and from the pattern of abnormal liver-function tests obtained in our series of cases that liver-function abnormalities are often encountered in chronic alcoholics. In our series, the most frequently observed abnormal tests were the presence of excessive urobilin, a high initial mucoprotein level and low total-serum protein. However, the 'true' tests of liver function, viz. the bromsulphalein-dye retention test, cholinesterase, reversal of albumin-globulin ratio, a reduction in the percentage of esterified cholesterol, and bilirubinaemia were only disturbed in a small percentage of our cases. Elevated gamma-globulin levels are very characteristic of cirrhosis of the liver, and yet in our series only a very small percentage of patients showed abnormal values, using both a chemical turbidity method and electrophoresis.

The most sensitive liver-function test, the bromsulphalein-

dye retention test, was only slightly abnormal in 9% of cases. Mucoprotein levels are usually reduced in portal cirrhosis[18] and in our series the reverse was found. Of our patients 65% showed markedly elevated levels, and not in a single case was a low level encountered.

Only one of our cases had the typical biochemical profile of cirrhosis of the liver—with a fatal outcome in this patient. In the large series of Voegtlin *et al.*[9] only 2 patients out of 300 had biochemical characteristics of portal cirrhosis.

Our results seem to suggest that a characteristic type of liver dysfunction is present in chronic alcoholics that is probably a pathological entity other than portal cirrhosis. These observations bear out what we have previously published,[19] namely, that apparently only those patients whose livers are predisposed by other factors respond to the chemotoxic action of alcohol by the development of cirrhosis of the liver.

Our results seem to conform with the views of Voegtlin *et al.*[9] and with Lepehne[15] who states that liver dysfunction in alcoholic patients can be largely transient, that even serious damage as found by liver biopsy can subside in a month, that the occurrence of cirrhosis is surprisingly rare, and that this develops only if several different factors are present.

Spellberg[20] sums up the position when he says that the statement that liver injury is significantly more frequent amongst chronic alcoholics is undoubtedly true, but whether alcohol as such or whether nutritional factors are the underlying cause is another question. Evidence suggests that diet is probably the more important factor, since:

1. Chronic alcoholics of many years standing may show normal livers, both from a functional point of view and anatomically.

2. Total abstainers, especially in countries where malnutrition is common, suffer from chronic liver disease.

3. In animal experiments continuous large doses of alcohol produce a mild fatty liver which may be prevented by an adequate protein diet.

Alcohol may contribute to the development of a fatty liver, either primarily or secondarily by interfering with the utilization and/or absorption of some of the food substances ingested. The large, soft, fatty liver is a common finding in the early alcoholic. Doubt still exists, though, as to whether the fatty liver is a precursor of human cirrhosis.

Liver dysfunction in our series, as revealed by liver-function tests, suggests that the impaired function in chronic alcoholics is not caused by cirrhosis, but is secondary to fatty deposition in the liver, and is temporary and reversible by abstinence, rest, and an adequate protein and vitamin intake.

SUMMARY

1. A battery of liver-function tests was carried out on 40 volunteer male alcoholic addicts.

2. The most frequently abnormal tests were increased urobilin, raised mucoprotein levels, and a low total protein. Abnormal bromsulphalein-dye retention, reversal of albumin-globulin ratio, and elevated gamma-globulin levels were rarely encountered. Only 1 patient was clinically jaundiced and not a single patient showed a low percentage of esterified cholesterol to total cholesterol.

3. On withdrawal of alcohol a further rise in the mucoprotein was observed; this was followed by a gradual return to normal levels. On subsequent administration of alcohol, even in relatively small amounts, an immediate rise of the mucoprotein level was again observed.

4. Our results suggest that a characteristic type of liver dysfunction is present in chronic alcoholics which is distinct from that found in portal cirrhosis.

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