LIVER DAMAGE IN ADDICTIVE ALCOHOLICS

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ALMOST 125 years ago Addison (1836) suggested the existence of a causal relationship between alcoholism and cirrhosis of the liver and more than 100 years ago Rokitansky noted accumulation of fat as the earliest effect on the liver of over-indulgence in alcohol (cited from Connor, 1938). Though the relative importance of infective hepatitis and alcoholism as aetiological agents in liver cirrhosis may vary a great deal in different countries, "alcohol and infective hepatitis are at present the only two unequivocal aetiological factors" (Annotation, *Brit. Med. J.*, 1957). It is usually accepted that over-indulgence in alcoholic drinks often produces liver dysfunction—maybe in an indirect manner —which though reversible at first, tends to become irreversible as over-indulgence is continued and prolonged (Leevy, Cunniff, Walton and Healey, 1954). The terminal phases are characterized by cirrhosis, hypertrophic at first and then contracted, with ascites and eventual death. When individuals whose drinking habits lead them to this state need hospital treatment, they seem to find their way into general hospitals rather than into mental hospitals. Among them may be alcoholics of the type described by a World Health Organization Expert Committee as "habitual symptomatic excessive drinkers" (W.H.O. Rep., 1952) or "non-addictive alcoholics", and those excessive drinkers whose alcoholism manifests itself in their "inability to stop" continual daily drinking in the face of dangerous consequences (W.H.O. Rep., 1955).

Yet liver cirrhosis is a relatively late complication of alcoholism and supervenes in only a certain proportion of alcoholics. Haggard and Jellinek (1950) estimate that liver cirrhosis does not occur in more than about 8 per cent. of "chronic alcoholics". On the other hand, according to these authors fatty infiltration of the liver constitutes the most common physical disturbance of chronic alcoholism, occurring in 75 to 80 per cent. of chronic alcoholics.

In this country, alcoholic patients entering mental hospitals taking a special interest in alcoholism hardly ever show clinical evidence of liver damage. Their

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https://doi.org/10.1192/bjp.105.440.748 Published online by Cambridge University Press

main problems associated with their alcoholic habits are psychological or social, rather than physical or somatic disturbances. Almost all these patients belong to the type of alcoholic termed "alcohol addicts" characterized by "loss of control" over their alcohol intake once they have started to drink on a certain occasion. These people do not usually suffer from marked physical disturbances but often they have long-standing psychological difficulties—feelings of inadequacy, inability to cope with tension and frustration, etc.—from which they have sought to escape by taking alcoholic drinks. In contrast to the non-addictive alcoholic who "can avoid drunken behaviour whenever the social situation requires it" (W.H.O. Rep., 1952), the addictive alcoholic has usually run into serious difficulties in the sphere of his social adjustment, at work, at home, etc., which often precipitate his hospital admission.

The admission of a steady stream of addictive alcoholics, who in spite of a long-continued history of over-indulgence in alcohol coupled with gross neglect of their food intake showed little clinical evidence of physical damage, raised the question whether the laboratory could detect abnormalities in liver function and in vitamin B_1 balance in these people. Vitamin B deficiency may be precipitated in alcoholics by various factors, such as dietary inadequacy, defective absorption and possibly an increased need for thiamine caused by the high calorie value of alcohol. The series of investigations here reported was therefore undertaken.

Case Material

The patients were addictive alcoholics newly admitted to Warlingham Park Hospital.

The investigation began early in 1953 and although it was continued for a number of years, only the results obtained in 1953 and 1954 are now analysed. At first, blood analyses only were done, but early in 1954 the bromsulphalein clearance test described by Goodman (1952) was included. The patients examined in 1953 had had vitamin B_1 as part of their routine treatment on admission and before the laboratory tests; those examined in 1954 had not had any treatment before the tests were carried out. This, together with sex differences, divided the patients into groups, as shown in Table I.

Table I

Distribution by Age, Sex and Year of Admission of 118 Alcoholics

Year	Group	Number	Age Range	Mean	S.D.
1953	Males I	47	27–68	46·1	9·9
1954	Males II	42	23–64	41·9	10·1
	Total ..	89	23–68	44·1	10·2
1953	Females I ..	17	38–75	52·0	9·2
1954	Females II ..	12	41–66	53·2	7·5
	Total ..	29	38–75	52·5	8·6

Both female groups were older than both male groups, the differences being statistically significant ($p < \cdot 05$ in each case). The age difference between the two male groups was also statistically significant. This suggests that men seek treatment earlier or start drinking younger than women, and that as time went

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on men were seeking treatment at an earlier stage. From the clinical point of view, however, all the 118 patients were a homogeneous group. Almost all were in good physical condition. None had clinically detectable cirrhosis or ascites, although the liver was enlarged in 15 patients. One patient—a woman—had had at some unascertained time a liver biopsy and had been told that she had "a 50 per cent. cirrhosis". Our tests showed that she had liver damage but not cirrhosis. About 20 patients had mild symptoms or signs of polyneuritis; one elderly woman had beri-beri, two others showed mild signs of pellagra. There were two cases of Korsakoff's syndrome. All were "alcoholics" as defined by the Alcoholism Sub-Committee of the W.H.O. Expert Committee (W.H.O. Rep., 1952), almost all were "alcohol addicts" with "loss of control". Socially, they were mostly of the professional and middle classes and all had long histories, on the average 10–15 years, of alcoholic over-indulgence which had eventually brought them in need of special treatment. About four-fifths had neglected their food intake for several years (on the average 4–5 years) before admission.

Tests and Criteria

Table II gives the tests used and the criteria for assessing abnormality.

Table II

Investigation of Alcoholics: Biochemical Tests Used and Criteria of Abnormality

Tests			Abnormal if
Serum:			
Van den Bergh, direct and indirect			Positive
Bilirubin			>0·5 mg. per cent.
Proteins:	Total		<6·0 g. per cent.
	Albumen		<4·0 g. per cent.
	Globulin		>2·5 g. per cent.
	A/G ratio		<1·5
	Electrophoresis:	Albumen	Low
		α-Globulin	Raised
		β-Globulin	Raised
		γ-Globulin	Raised
Alkaline phosphatase			<5 or >10
Cholesterol:	Total		<150 or >250 mg. per cent.
	Free/Ester ratio		>0·5
Takata-Ara test			Positive
Cholinesterase			<50 units
Bromsulphalein clearance test			<4 ml./kg./min.
Blood:			
Urea			>45 mg. per cent.
Cocarboxylase			<5 μg./100 ml.
Pyruvate			>1·5 mg./100 ml.

Techniques

With the exception of the B.S.P. clearance test (Goodman, 1952), which was newly adopted for this investigation, all the techniques were those in daily routine use in our laboratory.

Proteins were estimated by the biuret method. Globulins were separated in 26·7 per cent. ammonium sulphate.

Electrophoresis was done in the Antweiler micro-Tiselius apparatus on only 25 sera, partly owing to limitations of time and partly because it was our usual practice not to carry out electrophoresis when the serum globulin was less than 2·5 g. per cent. The Takata-Ara reaction was carried out by the technique of Ragins (1934–35) but the increasing use of electrophoresis gradually led to the abandonment of this test which was not showing many positive results.

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Other techniques were as follows:
Alkaline phosphatase: King and Armstrong (1934) whose normal range was adopted;
Cholesterol, total, free and ester: a modification of the method of Schoenheimer and Sperry (1934);
Cholinesterase: in Warburg manometers at 30° C. using acetylcholine as substrate; one unit is the amount of esterase liberating 1 μl. of CO_2/ml. of serum/minute;
Urea: Archer and Robb (1925);
Cocarboxylase: Kay and Murfitt (1956);
Pyruvate: Friedemann and Haugen (1943).

Collection of Blood

Puncture of an arm vein was effected with minimal stasis to distend the vein and then, whilst blood was flowing freely in the vein, 30–40 ml. of blood were collected and distributed in appropriate receptacles. Most of the males and females of Group I walked to the hospital laboratory for venepuncture about 2–3 hours after breakfast. All the patients of Group II were bled in bed after overnight fast, prior to carrying out the B.S.P. clearance test.

Results

Excluding for the time being abnormalities in urea, cocarboxylase and pyruvate results, abnormalities in one or more tests were found in 86 (72·8 per cent.) of the 118 patients. These were distributed among the groups as follows:

Table III

Investigation of Alcoholics: Number in Each Group Who Showed Abnormalities

	All Cases	With Abnormality	Per cent.
Males I	47	29	61·7
Males II	42	33	78·6
All males	89	62	69·7
Females I	17	13	76·5
Females II	12	11	91·7
All females	29	24	82·8
All cases	118	86	72·8

There is an obvious tendency for the members of both sexes in Group II to show more evidence of abnormality than those in Group I.

The distribution of abnormal results according to tests as well as groups is shown in Table IV.

With the exception of the Takata-Ara reaction, all the tests used appeared to be able to detect substantial proportions of abnormal values which can be attributed to hepatic dysfunction. No single test detected all the patients likely to show abnormalities. Even the B.S.P. clearance test gave low values in only 17 (31·5 per cent.) of the 54 patients tested by it. Of the same patients, 28 (51·9 per cent.) showed abnormalities in their proteins, 19 (35·2 per cent.) in their phosphatase, and in all, 44 (81·5 per cent.) showed some abnormality or other. The presence of a raised β-globulin in 48 per cent. of the 25 sera tested by electrophoresis suggests that this abnormality, which is associated with a toxic disturbance of the liver, is likely to be the most frequent evidence of reversible hepatic damage associated with alcoholism. Every test detected abnormalities in some patients who showed no abnormalities by the others. All the tests in the battery are therefore necessary. They seem to be concerned with different aspects of hepatic function, each of which may react differently to alcoholic onslaughts.

https://doi.org/10.1192/bjp.105.440.748 Published online by Cambridge University Press

TABLE IV

Investigation of Alcoholics: Summary of Results of Tests

Type of Abnormality	Numbers of Cases Showing Abnormalities				Total	As Per cent. of Cases Tested
	Males		Females			
	I	II	I	II		
Hyperbilirubinaemia ..	2	3	1	0	6	5·1
Proteins:						
Low total	1	9	2	5	17	14·4
Low albumen	8	10	3	8	29	24·6
High globulin	11	7	7	3	28	23·7
Raised α-globulin ..	0 (10)	1 (5)	0 (6)	1 (4)	2 (25)	8·0
Raised β-globulin ..	1 (10)	4 (5)	3 (6)	4 (4)	12 (25)	48·0
Raised γ-globulin ..	1 (10)	2 (5)	1 (6)	0 (4)	4 (25)	16·0
Phosphatase:						
Low	8	12	1	1	22	18·6
High	1	4	2	2	9	7·6
Cholesterol:						
Low total	14	4	0	0	18	15·2
Raised F/E	6	4	0	0	10	8·5
Cholinesterase:						
Low	8 (38)	4 (41)	1 (12)	1 (12)	14 (103)	13·6
T.A.R. positive	1 (45)	0 (15)	3 (15)	—	4 (75)	5·3
B.S.P. clearance:						
Low	—	11	—	6	17 (54)	31·5
Number of cases in groups	47	42	17	12	118	

Tests not applied indicated by —.

Numbers in parentheses are the numbers to whom tests were applied, when less than group total.

It is of further interest to examine the distribution of the number of abnormalities shown by each case in the groups. This is done in Table V.

TABLE V

Investigation of Alcoholics: Distribution of Number of Abnormalities Found per Case According to Groups

Groups	Number of Abnormalities Per Case								Total Cases
	0	1	2	3	4	5	6	7	
Males I cases ..	18	12	9	4	2	1	–	1	47
Males II cases ..	9	13	10	4	4	–	2	–	42
Females I cases ..	4	6	4	2	1	–	–	–	17
Females II cases	1	2	3	4	–	2	–	–	12
All groups: cases	32	33	26	14	7	3	2	1	118
As percentages ..	27·2	28·0	22·0	11·8	5·9	2·5	1·7	0·9	100

There is an evident tendency for the maximum number of cases in the different cells to shift towards the right in passing from Group I to Group II and from males to females, suggesting that there was more evidence of hepatic dysfunction in Group II than in Group I, and in females than in males. The latter results corresponded with the clinical findings. There were usually more

https://doi.org/10.1192/bjp.105.440.748 Published online by Cambridge University Press

marked bodily disturbances in the female patients, who also more often showed clinical evidence of peripheral neuritis and of hypovitaminosis.

Taking all the 118 cases together, a distribution curve can be plotted as in Figure 1.

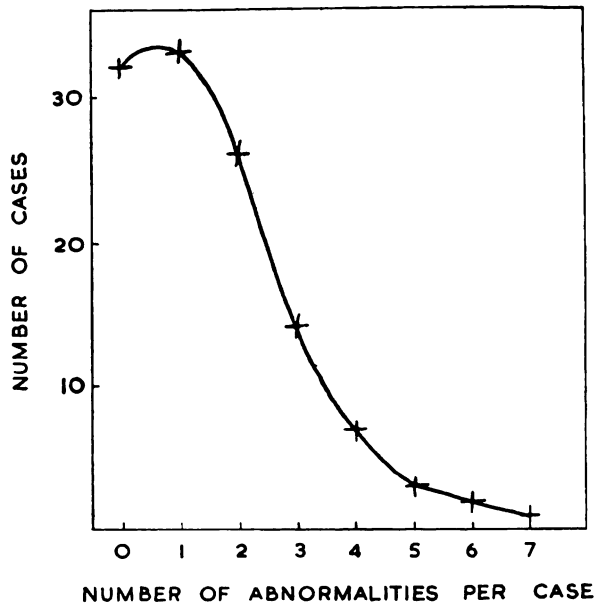


FIG. 1.—Investigation of alcoholics: distribution curve of cases showing different numbers of abnormalities.

The resemblance of this curve to that of natural distribution suggests that the selection of criteria is approximately correct. Re-examination of criteria showed that the omission of some could give a true curve of natural distribution. We are to conclude, therefore, that alcoholics of the clinical type studied, having little or no clinical evidence of hepatic dysfunction, nevertheless do show a high proportion of abnormal results in the battery of tests used, and are to be regarded, therefore, as having liver dysfunction in varying degrees.

This conclusion is supported by the results obtained in re-examinations after abstention from alcohol by, and treatment of the patient. Twenty-five patients who showed abnormalities at the first testing gave improved or even normal results at the second. From this we may infer that their liver damage was of the reversible type. These findings correspond to those of Leevy *et al.* (1954) who noted a disappearance of all evidence of liver disease in patients with fatty livers on discontinuance of drinking and maintenance of a good dietary intake.

Two men of Group I came to necropsy. Both showed fatty changes in their liver, but no cirrhosis. Their blood chemistry when admitted was as follows:

(*a*) Aged 68. Van den Bergh reaction and serum bilirubin, normal; serum proteins: total 6·4 g. per cent., albumen 3·7 g. per cent., globulin 2·7 g. per cent., A/G ratio 1·4/1; T.A.R. negative; serum cholesterol: total 135 mg. per cent., free 40 mg. per cent., ester 95 mg. per cent., F/E ratio 1/2·4; serum alkaline phosphatase 4 units; serum cholinesterase 34 units; urea 36 mg. per cent. The cholesterol, albumen, phosphatase and cholinesterase were all low and consistent with liver dysfunction of reversible type. There was no anaemia. Death occurred 11 weeks after the test.

(*b*) Aged 57. Van den Bergh and serum bilirubin, normal; serum proteins: total 6·4 g. per cent., albumen 3·8 g. per cent., globulin 2·6 g. per cent., A/G ratio 1·5/1; T.A.R. negative;

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electrophoretic pattern normal; serum cholesterol: total 164 mg. per cent., free 41 mg. per cent., ester 123 mg. per cent., F/E ratio 1/3; serum alkaline phosphatase 5 units; serum cholinesterase 43 units; urea 16 mg. per cent. Six weeks later, although the albumen and cholinesterase had improved, the cholesterol and phosphatase had fallen. Death occurred ten months after the first test.

Cocarboxylase and Pyruvate Results

The patients of Group I of both sexes had had vitamin B_1 treatment when their blood was examined. Of the men, 42 were tested and none showed an abnormally low cocarboxylase value. Indeed, a number showed abnormally high values—evidence of more than adequate medication. Of 15 Group I women examined, 4 had abnormally low cocarboxylase values. In one case thiamine deficiency was confirmed by an abnormal response of the blood pyruvate to glucose administration. In spite of an adequate cocarboxylase level, 14 of 46 men and 5 of 16 women all of Group I had high blood pyruvate levels, suggesting that the mild exercise they had taken to reach the laboratory had overtaxed their not fully-recovered cocarboxylase mechanism.

The patients of Group II had not had vitamin B_1 treatment and were all bled fasting and in bed. All had normal pyruvates. Two men and 5 women had abnormally low cocarboxylase values.

These results indicate that this type of alcoholic is prone to add thiamine deficiency to his liver dysfunction.

Summary

The results of the battery of tests used in examining the blood of a group of 118 alcoholics, male and female, coming for treatment in a mental hospital, indicate that in spite of the absence of clinical signs, alcoholics are prone to show abnormal blood chemistry indicative of hepatic dysfunction, and in some cases of thiamine deficiency. To detect abnormalities adequately a battery of tests such as the one used is essential.

Addendum

Further to the results discussed above, the tests have been carried out as a routine procedure in more than 350 patients admitted until 1957 to Warlingham Park Hospital Alcoholic Unit. The results in this larger series confirm essentially the above findings. Similarly, blood pyruvate tests in a total of 380 patients and cocarboxylase tests in about 250 patients bear out the conclusions derived from the smaller initial sample. The overall impression gained from these investigations, and from the results of tests for urobilinogen and bilirubin in urine, is that of a frequent disturbance of blood and urine chemistry related to liver function and vitamin B_1 blood level. This is despite the absence of clinical evidence of abnormalities, and of a rapid improvement in a considerable proportion of patients after a relatively short period of abstinence from alcohol and a vitamin-supplemented full diet. All these observations once more bear out the necessity of the diagnosis and treatment of alcoholism at an earlier stage, before the development of clinical evidence of physical complications.

Acknowledgments

We acknowledge gratefully the technical co-operation of Mr. L. G. Coates, Warlingham Park Hospital laboratory, and the staff of the Mental Hospitals' Group Laboratory.

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https://doi.org/10.1192/bjp.105.440.748 Published online by Cambridge University Press