ACUTE ALCOHOLIC HEPATITIS WITHOUT JAUNDICE

BY

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Acute alcoholic hepatitis with frank jaundice and typical histological changes in the liver is a severe and sometimes fatal illness which follows intensified drinking of alcohol by the chronic alcoholic (Beckett *et al.*, 1961). A similar less severe illness with the characteristic histological changes may occur without jaundice. This subicteric disorder, like the jaundice one, produces anorexia, nausea and vomiting, upper abdominal pain, and fever. Alcoholism may remain unsuspected or even be denied initially by the patient. Recovery occurs spontaneously without specific treatment, as the symptoms temporarily prevent further drinking of alcohol.

Five examples of this milder subicteric illness have been recognized recently. Their details are summarized in Tables I and II, and a typical case history is given.

Several other patients have been suspected of having this condition, although histological proof is lacking. Some of the cases described here had previously had similar illnesses, which were given, probably erroneously, such diagnoses as cholecystitis, dyspepsia, or "P.U.O." This suggests that the condition may not be uncommon, and, like the jaundiced illness, be frequently misdiagnosed.

Illustrative Case History

A sailor aged 59 (Case 1) had been a heavy drinker for 30 years. At the age of 31 he had had an attack of jaundice of undetermined aetiology, although it had followed a debauch and was accompanied by upper abdominal pain. After protracted celebrations over Christmas, he was admitted to the Royal Free Hospital at the end of January, 1960, with a four-weeks history of intermittent right upper abdominal pain, nausea, vomiting, and general malaise. Nothing to suggest jaundice had been noticed. Positive physical findings were limited to palmar erythema, a non-tender liver enlarged 4 cm. below the costal margin, and a low-grade fever lasting nine days.

TABLE I.—Main Presenting Features

Case No.	Age and Sex	Duration of illness before admission (days)	Main presenting symptoms	Known duration of fever in hospital (days)	Liver enlargement below Rt. costal margin	Splenomegaly	Upper Abdominal Tenderness	Prothrombin Concentration (%)	S.G.O.T. (on admission)
1	59 M	28	R upper abdominal pain. Anorexia. Vomiting. Malaise	9	4 cm.	Nil	None	100	60
2	35 F	35	R upper abdominal pain. Anorexia. Nausea. Vomiting. Diarrhoea.	7	4 cm.	Nil	None	43	78
3	54 M	5	R upper abdominal pain. Anorexia. Oedema of legs	6	4 cm.	Nil	None	100	—
4	65 M	28	Anorexia. Lower central chest pain. Loss of weight. Diarrhoea	6	Nil	Nil	None	100	42
5	59 M	7	R upper abdominal pain. Anorexia. Nausea. Vomiting	2	Nil	Nil	None	100	(5th day after admission) 35

Investigations.—Hb, 16.9 g./100 ml.; W.B.C., 9,850/c.mm.; E.S.R. 39 mm. in 1 hour (Westergren). Serum glutamic oxaloacetic-transaminase (S.G.O.T.), 60 units. Serum total proteins, 7.3 g./100 ml. (albumin 4.6 g., globulin 2.7 g.). Total serum bilirubin, 0.9 mg./100 ml.; serum alkaline phosphatase 10 units/100 ml.; thymol turbidity, 1 unit; thymol flocculation negative; colloidal gold, 0; zinc sulphate turbidity, 2. Prothrombin concentration, 100%. Pyruvate tolerance test within normal limits. Liver biopsy (third day after admission): marked fatty change with cellular degeneration and necrosis and with inflammatory activity; stellate scarring; moderate amount of iron pigment intracellularly in the Kupffer cells and in the portal triads.

Progress.—On a low-fat diet he rapidly became symptom-free and regained his appetite, being discharged after 13 days in hospital.

TABLE II.—Summary of Histological Findings

Case No.	Type of Specimen	Days after Admission	Cirrhosis	Portal Scarring	Fat	Mallory's Hyaline	Cellular Degeneration and Necrosis	Bile Stasis	Acute Inflammation	Bile Duct Hyperplasia	Stellate Scarring
1	Biopsy	9	0	0	++	0	+	0	+	0	+
2	"	6	++	++	++	++	0	0	+	0	+
3	"	41	++	++	++	++	0	0	+	0	+
4	"	18	0	+	++	0	+	0	+	+	+
5	"	10	0	+	++	+	+	0	+	+	+
5	"	4	0	+	+	+	+	0	+	+	+

+ = Marked change. ++ = Moderate change. ± = Scanty change.
0 = Absent.

Histology

The histological appearances, details of which are given in Table II, are similar, though in lesser degree, to those found in jaundiced alcoholics (Beckett *et al.*, 1961). Naturally the changes present in any one section will depend on the size of the biopsy, and more particularly on the stage of the illness when it was taken. The features common to all five biopsies were cellular degeneration and necrosis, with an acute inflammatory reaction, and stellate scarring. Fat was present in significant amounts in four biopsies out of five. Mallory's hyaline was present in two biopsies. Only one patient showed the changes of established cirrhosis.

Clinical Commentary

The prominent clinical features of these cases were upper abdominal pain, predominantly right-sided and persisting for varying periods of time, anorexia, pyrexia, nausea, and even vomiting following the imbibing of

excessive quantities of alcohol. A history of alcoholism was not readily forthcoming in two patients. The prospect of surgical intervention in such cases is considerable, though a fruitless operation would be less harmful than in those with jaundice or ascites.

Three patients had themselves correlated upper abdominal pain with excessive drinking on several previous occasions. Two of them had been told elsewhere that the gall-bladder was the source of their pain; one had had a cholecystectomy for symptoms which persisted unchanged, as did his habits thereafter, while the other, notably reticent about being an alcoholic, had evaded this operation only by failure to accept admission for it on two occasions. Surprisingly none of the patients described had tenderness of the liver.

With the exception of a slightly raised serum bilirubin initially in Case 3 and a low serum albumin with reduced prothrombin concentration in Case 2, the standard tests of liver function were within normal limits in all cases. The S.G.O.T. was raised in three of the four cases in which it was estimated (in one only marginally so).

In contrast to jaundiced cases, no abnormality in the total or differential white-cell count and no anaemia was encountered (although one was known to have had a macrocytic anaemia during a previous similar episode elsewhere).

Some conclusive diagnostic biochemical test in addition to the serum transaminases would be of great value, but clinical awareness of the illness is essential if these and needle biopsy of the liver, at present the only certain method of diagnosis, are to be undertaken.

The important differential diagnosis from acute alcoholic hepatitis without jaundice is probably pancreatitis, acute recurrent or chronic, to which alcoholics appear to have an increased susceptibility (Shallenberger and Kapp, 1958; Bartholomew and Cain, 1961; Howard and Ehrlich, 1961), although this is denied by others. Pancreatitis, not thought to have produced the symptoms in the present series, is probably a more severe illness, at least in the earlier attacks, affecting particularly alcoholics below the age of 40, and has a poor prognosis (Howard and Ehrlich, 1961). Later the symptoms become less severe and in about a third of patients pancreatic exocrine or endocrine deficiency develops, causing such conditions as mild diabetes, steatorrhoea, and pancreatic calcification (Case 2 of the present series had this trio, together with a non-functioning gall-bladder, on cholecystography).

In some patients (possibly in the one referred to) hepatitis and pancreatitis may occur at the same time. In future studies, therefore, it might be desirable for pancreatic function studies, unfortunately notoriously difficult to carry out, to be done in addition to those on the liver. Howard and Ehrlich made no reference to liver biopsies or serum transaminases in their patients with pancreatitis.

Peptic ulceration and alcoholic gastritis are the other conditions in which alcoholic excess and upper abdominal pain are likely to be associated. In none of the present cases was there any clinical or radiological evidence of these.

Discussion

There is nothing new in the notion that a carousal may be followed by a disorder of the liver, without jaundice being present. This was described by French (1912), who regarded habitual intemperance as the major

factor, but also suggested that lack of exercise, over-eating, and tropical diseases might play a part. Hurst (1941) made almost identical observations, again specifying the European in tropical climates as being prone to alcoholism and suggesting the other possible factors mentioned above. He thought clinical recovery was the rule provided teetotalism was practised thereafter, and he recognized that the patient with established cirrhosis came into a different category, but admitted that no histological proof existed for his beliefs.

As Hurst's patients either recovered or much later appeared as cases of established portal cirrhosis, no further progress in the understanding of their illnesses, histologically or otherwise, could be made at that time. Now that needle biopsy of the liver is a safe procedure in skilled hands, it is possible to establish the presence and nature of the structural changes. Indeed, as no test of liver function, other than the recently introduced serum enzyme tests such as the transaminases, constantly indicates liver cell damage, biopsy is the only way of making an accurate diagnosis.

The histological abnormalities in this acute illness are liver-cell degeneration and necrosis surrounded by acute inflammatory cells, together with inflammatory changes in the portal tracts. Mallory's alcoholic hyaline, probably the result of liver-cell degeneration, may be seen. Fatty change is almost universal, as is some degree of stellate scarring of the portal tracts in the more prolonged cases. In addition to these changes, there will also be evidence of any pre-existing disease. It must be stressed that established cirrhosis is not an essential part of this illness, and indeed was seen only once in the present series.

The illness discussed here does not appear to have been described adequately before, although Neame and Joubert (1961), in a study of hypoglycaemia following alcoholic bouts in non-jaundiced Africans and Indians, suggested that the hypoglycaemia was caused by an acute toxic hepatitis due to alcohol. The report of their liver biopsies made no reference to cellular degeneration and necrosis or to acute inflammatory changes; 14 of the 17 had a normal architectural pattern. Nevertheless, the serum transaminases were constantly raised, indicative of liver-cell necrosis. These authors were inclined to associate the hypoglycaemia with poor nutrition, but neither of these was observed in our patients.

The precise effect of alcohol on the liver of the chronic alcoholic has been debated for years. Some workers believe that it has no direct effect, and the work of Summerskill *et al.* (1957) apparently confirmed this; on careful observation of liver-function tests and biopsies they found no evidence of deterioration after the administration of alcohol. They did not, however, study changes in serum transaminases. Bang *et al.* (1958) observed elevation of S.G.O.T. activity following the drinking of alcohol by chronic alcoholic patients, and concluded that such changes were sensitive indices of liver damage; they failed to show any such rise in healthy volunteers. Hed (1959) confirmed these findings. Neame and Joubert (1961) observed rises in serum transaminase activity following the administration of alcohol to one of their patients after initial recovery.

The role of malnutrition is also not fully defined. Alcoholics clearly neglect their food, often for long periods. In consequence some authorities believe that malnutrition is as important as alcohol itself, if not more so. Madsen *et al.* (1959) stressed the role of prolonged

and inadequate dietary intake in the production of abnormal S.G.O.T. activity after acute alcoholic intoxication. Likewise all the patients of Neame and Joubert (1961) were in a state of poor nutrition. In contrast, our patients showed no signs of malnutrition, although a considerable proportion of their total calorie intake was supplied by the alcohol. In a study of the dietary habits of alcoholics in France, Pequignot (1960) found no difference in nutrition between those with cirrhosis and those without, but those with cirrhosis had taken on average two and a half times as much alcohol as those without. Measurements of nutrition, however, are seldom defined, nor do they usually extend much further than a clinical estimate.

Some patients with alcoholic hepatitis (acute or sub-acute icteric or subicteric) give a previous history of hepatitis said to be of viral origin. Sometimes such jaundice occurred after the patient became an alcoholic, but in others it preceded this.

The ability of the liver to withstand the damaging effects of alcohol may be dependent on the quantity of intracellular enzymes capable of breaking down alcohol—that is, the concentration of alcoholic dehydrogenases. This concentration may be basically determined by constitutional and hereditary factors but subsequently reduced by such events as prolonged malnutrition or liver-cell damage and increased by adaptation to gradually rising intake of alcohol. On this theory, therefore, the rate at which alcohol reaches the liver appears to be the most important factor, but the critical one, above which liver damage occurs, may vary from individual to individual according to the enzyme content of their cells.

It is evident from the cases described that any chronic alcoholic in recurrent alcoholic bouts may be subject to repeated attacks of acute hepatitis, icteric or subicteric, and that these attacks may easily pass unobserved or undiagnosed. A parallel exists in viral hepatitis. Many patients with subicteric hepatitis have been found in epidemics by needle liver biopsies, and, more recently, by serum transaminase estimations. Are these repeated episodes of hepatitis, recognized or unrecognized, steps in the evolution of cirrhosis in the alcoholic? This theory has much to commend it, and is supported by Bang *et al.* (1958) among others. As only a relatively small proportion of lifelong alcoholics ultimately develop cirrhosis, some factor other than alcohol must operate—perhaps, as suggested above, the individual sensitivity of the liver cells and its enzymes to alcohol. The evidence presented strongly favours a direct toxic action of alcohol on certain livers vulnerable to it in some way as yet unexplained.

Summary

Acute alcoholic hepatitis without jaundice may follow intensified drinking by the chronic alcoholic, who develops anorexia, nausea and vomiting, upper abdominal pain, and fever. A liver biopsy shows evidence of foci of liver-cell degeneration and necrosis surrounded by acute inflammatory changes, also present in the portal tracts, together with the changes of any underlying pre-existing disease. This illness may occur in the absence of cirrhosis. Raised concentrations of the serum transaminases are usually the only biochemical abnormalities indicative of liver-cell damage. Five typical cases are summarized.

Although misdiagnoses are apparently common, recovery usually occurs spontaneously. The role of this

condition, often recurrent, in the evolution of alcoholic cirrhosis is briefly discussed.

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CAREER CHOICE IN MEDICINE

BY

A GROUP OF FIFTH-YEAR MEDICAL STUDENTS

AND

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The wide variety of careers now open to new graduates, the probable shortage of doctors, and the long duration of medical education all make it imperative that individual choice of career should be sound and also that planners should have some idea of the intentions of medical students. Partly to explore this field and partly as an educational exercise in survey techniques, we have carried out a local pilot study of three main questions: (1) What branches of medicine do Aberdeen students intend to enter? (2) At what stage are decisions made or preferences developed? (3) What factors influence choice of career?

Methods

As time was limited, information was collected by questionnaire. The response rate varied by class as follows:

Year of Study	Proportion Returning a Usable Questionnaire
1	57 out of 85 (67%)
2	80 89 (90%)
3	54 73 (74%)
4	49 69 (71%)
5	40 44 (93%)
6	18 67 (27%)

The relatively low return in the first year may have been due to a feeling that the survey scarcely applied at that point in the course. The very poor response from the final year seemed, on the other hand, to be due to a more sophisticated attitude, coupled, perhaps,

*The members of the Study Group were: Robin C. Fraser (chairman), Stanley Cruickshank, Wm. G. H. Diack, Christabel Fraser, George B. Fraser, Derek W. G. Gray, Marion H. Hall, Ove J. Hjort, Hans M. Hoyeraal, Calvin H. R. Inalsingh, and Arnt Jakobsen.