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The Role of Thiamine Deficiency in the Aetiology of the Hallucinatory States Complicating Alcoholism

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Excessive alcohol consumption over a prolonged period of time may result in a variety of neuropsychiatric complications (Victor and Adams, 1953). The most frequent of these is alcoholic tremulousness which may be complicated in 25 per cent of cases by perceptual disturbances ranging from transitory misinterpretations of familiar objects to visual and auditory hallucinations (Victor and Adams, 1953). Closely related to this condition are delirium tremens (Victor and Adams, 1953; Lundquist, 1961; Nielsen, 1965), and acute or chronic auditory hallucinosis (Benedetti, 1952; Victor and Hope, 1958). In clinical practice intermediate or atypical forms of these syndromes are seen (Sabot, Gross and Halpert, 1968).

The aetiology of these tremulous-hallucinatory states remains controversial. The view that sudden abstinence after a long period of alcohol consumption could result in delirium tremens was first proposed by Blake in 1825. Some recent clinical and experimental evidence has supported this withdrawal theory. In a detailed clinical study of 266 alcoholics, Victor and Adams (1953) delineated a clearly defined withdrawal syndrome. According to these authors, the mildest degree of this syndrome, alcoholic tremulousness, may occur after a few hours abstinence with a relatively short preceding period of heavy drinking, whilst the most severe form, delirium tremens, occurs about 72 hours after withdrawal but only with a prolonged preceding period of excessive drinking. The experimental production of tremulousness, fits, hallucinosis and delirium (Isbell *et al.*, 1955; Mendelson and La Dou, 1964) provides additional support for an alcoholic abstinence syndrome.

Other authors (Bleuler, 1911; Lundquist, 1961; Nielsen, 1965) have not accepted the withdrawal theory, citing cases of delirium tremens occurring in patients who were continuing to drink. They emphasized the aetiological role of factors such as nutritional deficiencies, concurrent infections, injuries or other somatic disorders.

The possible role of nutritional deficiencies in the aetiology of these tremulous-hallucinatory states was first put forward by Kraepelin (1904) and later by Goodhart (1957). It is well known that alcoholics may neglect their diet. There is considerable evidence that deficiencies of nutriments, particularly vitamins, may cause other neuropsychiatric complications in alcoholism, such as Wernicke's encephalopathy and polyneuropathy. It is relevant that in a large series of patients with Wernicke's encephalopathy (Victor and Adams, 1953), nearly one quarter had concomitant delirium tremens.

Kershaw (1967) and Morgan (1968) have focussed attention on the role of thiamine deficiency in alcoholic hallucinatory states. Using a microbiological technique, Kershaw demonstrated abnormally low blood thiamine levels in seven out of nine patients with delirium tremens. Morgan used the pyruvate tolerance test (Joiner, McArdle and Thompson, 1950), to estimate thiamine deficiency in 17 alcoholics, of whom 8 had hallucinatory states. He suggested that thiamine deficiency might lead to those hallucinatory states which occur in habituated individuals while they are continuing to drink, but that abstinence alone could precipitate delirium tremens.

In recent years doubt has been thrown on the specificity of the pyruvate tolerance test as a measure of thiamine deficiency (Victor, Adams and Collins, 1971). The measurement of red cell transketolase activity has been reported useful

for detecting marginal thiamine deficiency (Dreyfus, 1962), and has been shown to correlate well with direct measurement of blood thiamine (Fennelly *et al.*, 1964a).

The aim of the present study was to use this assay in examining the role of thiamine deficiency in the aetiology of the hallucinatory states complicating alcoholism.

Case Material and Method

Two groups of patients were selected from those admitted to general medical or psychiatric units in the Oxford area for conditions related to excessive alcohol consumption. Group A consisted of patients who had experienced visual or auditory hallucinations, with or without confusion, in the week before or after admission. These symptoms appeared to be related to the consumption of alcohol and not of other drugs. Group B consisted of non-hallucinated patients who showed one or more of the following indices of alcohol dependence; loss of control or inability to abstain from alcohol, early morning relief drinking, alcoholic amnesias, or an abnormal pattern or frequency of drinking. In fact at least three of these features were present in all patients in both groups. Patients were included only if they reported drinking heavily for at least 10 days before alcohol withdrawal. The latter had taken place either in the 2–3 days before admission, or on admission.

Psychiatric and physical examination was carried out when the patient came into hospital, and a daily clinical reassessment was made for as long as tremulous or hallucinatory symptoms persisted. As soon as the patient was well enough, a detailed history was taken using a semi-structured interview schedule. Particular attention was paid to drinking and dietary habits during the months preceding admission.

Thiamine nutrition. Two tests to assess possible thiamine deficiency were made on each patient; the estimation of the transketolase activity of haemolysed packed red cells, before and after the addition of thiamine—the difference in the two levels of activity being the 'thiamine effect' (Racker *et al.*, 1953) and the pyruvate tolerance test after an oral loading dose of 50 g. glucose (Gloster and Harris, 1962). Blood sugar and lactate were also estimated at the same times. The usual precautions were observed for the pyruvate tolerance tests, i.e. complete bed rest, and the avoidance of hand clenching during venepuncture. The tests were carried out on each patient as soon as possible after admission and during the period of tremulous symptoms. The average delay in performing the tests was: Group A 50 hours, and Group B 53 hours, after admission.

The 'thiamine effect' in the transketolase test was considered to be abnormal if more than 25 mi.u./ml. and the pyruvate tolerance test abnormal if the pyruvate level rose above 1·2 mg./100 ml. or failed to return to 1·0 mg. 120 minutes after the loading dose.

Liver function. Tests were carried out on each patient not only to assess liver function but also because low blood transketolase activity, unrelated to thiamine deficiency, is found in some patients with hepatic cirrhosis (Fennelly *et al.*, 1964b).

Tests used to assess liver function included the bromsulphthalein retention test (Mateer *et al.*, 1942), the estimation of the plasma bilirubin (Malloy and Evelyn, 1937) plasma proteins (method of Weichselbaum, modified 1946), plasma alanine-transaminase (Wroblewski and La Due, 1956), γ-glutamyl-transpeptidase (Szasz, 1969) and plasma zinc turbidity flocculation test (Kunkel, 1947).

Results were considered to be abnormal when the bromsulphthalein retention was more than 9 per cent at 45 minutes after dye injection; plasma bilirubin more than 1·2 mg./100 ml.; plasma proteins—total, less than 6·5 or more than 8 g./100 ml., albumin, less than 3·5 g./100 ml.; plasma alanine-transaminase more than 35 units; plasma γ-glutamyl-transpeptidase more than 33 mi.u./ml. and zinc turbidity test more than 7 units.

Results

The series consisted of 30 patients, 27 males and 3 females. There were 15 patients with hallucinations and 15 without. The average age was 43 years.

The main psychiatric and biochemical findings are summarized in Table I. The hallucinatory group comprised seven patients with both visual and auditory hallucinations, four patients with visual hallucinations alone, one patient with visual misperceptions, and three patients with auditory hallucinations alone. The average duration of limb tremor was relatively short, 2·7 days for Group A and 3·4 days for Group B. This was probably because most Group A patients, and all Group B patients, were sedated with tranquillizers (such as diazepam, chlordiazepoxide or chlorpromazine). The exceptions were three patients in Group A (Nos. 3, 14 and 20).

On physical examination two patients in Group A and three in Group B had hepatic enlargement; one patient in each group had signs of polyneuropathy. Full haematological examination showed that no patients were anaemic.

Recent drinking history

The average duration of the drinking episode preceding admission was 8·3 months for Group A and 25 months for Group B. Seventy-three per cent of patients in Group A were predominantly spirit drinkers as against 46 per cent in Group B. One patient (No. 24) in Group A and two patients in Group B (Nos. 4 and 11) had been drinking methylated spirits before admission.

TABLE I

Summary of clinical and biochemical findings

GROUP A HALLUCINATED Patient no.	Hallucinations (preceding and subsequent to admission)	Duration of recent drinking episode (regular drinking)	Dietary neglect	Pyruvate tolerance test	Red cell transketolase estimation	Liver function tests
2	Saw butterflies and horrible animals. Also heard critical voices	6 months	+	Normal	Normal	Normal
3	Heard voices. Transitory tactile misperceptions	4 months	++	Normal	Normal	Normal
8	Disorientation in time. Saw strange figures in room. Heard voices and music. Tactile misperceptions	3 months	++	Normal	Normal	Abnormal
9	Saw threatening figure of man shouting at him	12 months	++	Normal	Normal	Minimal abnormality
10	Saw butterflies and people with knives. Heard voices, mutterings and music	7 months	++	Abnormal	Normal	Abnormal
12	Heard music and whisperings	1 month	+++	Abnormal	Abnormal	Abnormal
14	* Disorientation for time and place. Saw rats climbing walls	3 weeks	Uncertain	Normal	Normal	Normal
17	Saw strange figures in room and springs hanging from coat	1 month	Uncertain	Normal	Abnormal	Normal
18	* Saw horrible faces, an octopus and monkeys. Attacked by imaginary assailants. Heard spirits talking to him. Disorientated for time and place	3–6 months	++	Abnormal	Just normal	Abnormal
20	Heard buzzing sounds	10 days	+	Normal	Normal	Abnormal
23	Objects appeared distorted. Walls closed in on him	5 years	−	Abnormal	Normal	Minimal abnormality
24	Saw bizarre animals and human faces	12 months	++	Normal	Normal	Normal
26	Saw bizarre animals, e.g. sea-horses in room. Heard strange screaming noises	3 months	++	Abnormal	Normal	Abnormal
27	* Saw small men climbing walls. Disorientated for time and place	Uncertain	Uncertain	Abnormal	Minimal abnormality	Normal
28	Saw faces and horrible animals. Heard them scream and shout at him	4 months	++	Normal	Normal	Normal

* Delirium tremens.

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TABLE I—*continued*

GROUP B. NON-HALLUCINATED Patient no.	Duration of recent drinking episode (regular drinking)	Dietary neglect	Pyruvate tolerance test	Red cell transketolase estimation	Liver function tests
1	5 years	++	Abnormal	Normal	Abnormal
4	6 months	++	Abnormal	Normal	Normal
5	2 years	+	Normal	Normal	Minimal abnormality
6	3–6 months	+	Normal	Normal	Abnormal
7	1–3 months	+	Normal	Normal	Minimal abnormality
11	5 weeks	+	Normal	Normal	Normal
13	18 months	+	Abnormal	Normal	Normal
15	6 weeks	+	Normal	Normal	Abnormal
16	5 years	+	Abnormal	Abnormal	Normal
19	3 years	+++	Normal	Normal	Abnormal
21	3 years	+++	Normal	Normal	Minimal abnormality
22	3 months	++	Abnormal	Normal	Abnormal
25	4 years	+	Normal	Normal	Normal
29	6 weeks	+	Normal	Normal	Abnormal
30	3 years	+	Normal	Normal	Abnormal

\+ During month preceding admission one cooked meal daily. Snacks only at most other mealtimes.
++ During month preceding admission no cooked meals on most days.
+++ During month preceding admission no cooked meals on most days with loss of weight exceeding 6 kilograms.

Dietary findings

An attempt was made to assess the patient's dietary habits in the month preceding admission and to grade the severity of dietary neglect as indicated in Table I. There was a tendency for patients in Group A to show greater dietary neglect. However, only one patient who reported severe dietary neglect and weight loss greater than 6 kg. before admission had biochemical evidence of thiamine deficiency. It is of interest that patient No. 2 who experienced visual and auditory hallucinations while continuing to drink, had taken 'Multivite' tablets daily in the months preceding admission.

Biochemical findings

A summary of the biochemical results is given in Table I. It will be seen from this table that a single patient in each group (Nos. 12 and 16) had abnormalities of both the pyruvate test and the red cell transketolase activity. One patient in Group A (No. 17) had abnormal red cell transketolase activity, but a pyruvate tolerance which was normal; another patient in Group A

(No. 27) had an abnormal pyruvate tolerance and a borderline red cell transketolase result. Eleven pyruvate tolerance tests, six in Group A and five in Group B, were abnormal. Five of these patients also had abnormalities in the blood sugar and lactate curves, suggesting that some abnormality, other than thiamine deficiency might be present.*

Eighteen of the patients gave one or more abnormal results to the liver function tests, and four had borderline results. Eleven patients had abnormal bromsulphthalein retention tests, two abnormal alanine-transaminase levels, twelve had abnormal transpeptidase levels and half the patients had slightly low plasma globulin levels. These results appeared to be equally divided between the two groups.

No patient had an abnormal plasma bilirubin level.

* Detailed values of the pyruvate tolerance tests, red cell transketolase activity, blood sugar and lactate levels are available on application to the first named author.

Relationship of hallucinations to alcohol withdrawal

The relationship of withdrawal to the onset of hallucinations was determined for all patients in Group A. The findings are summarized in Table II. In five patients, there was a clear relationship between the cessation of drinking and the onset of the hallucinatory state; two of these had delirium tremens. By contrast there were nine patients who experienced hallucinations while continuing to drink of whom seven had hallucinations at night only and four reported that their hallucinations ceased on further drinking.

TABLE II
Relationship of hallucinations to alcohol withdrawal

Patient no.	Type of hallucinatory experience	Duration of hallucinatory experience	Relationship of alcohol withdrawal to psychiatric symptoms
2	Visual and auditory	Intermittent over 4 weeks	Still drinking
3	Auditory	24 hours	After withdrawal
8	Visual, auditory, tactile	4 days	After withdrawal
9	Visual	Intermittent over 1 week	Still drinking
10	Visual and auditory	Intermittent over 2 weeks	Still drinking
12	Auditory	Intermittent over 2 weeks	Still drinking
14	Visual	24 hours	After withdrawal
17	Visual	Intermittent over 1 week	Still drinking
18	Visual and auditory	48 hours	After withdrawal
20	Auditory	24 hours	After withdrawal
23	Visual misperceptions	Intermittent over 4 weeks	Still drinking
24	Visual	Intermittent over 8 weeks	? After withdrawal
26	Visual and auditory	Intermittent over 4 weeks	Still drinking
27	Visual and auditory	Intermittent over 1 week	Still drinking
28	Visual and auditory	Intermittent over 1 week	Still drinking

Discussion

The salient findings in this study were that abnormalities of the red cell transketolase activity were found in two of 15 alcoholic patients who reported recent hallucinatory experiences, and in one of 15 alcoholic patients with no such hallucinatory experiences. Abnormalities of the pyruvate tolerance test were found in six patients in Group A and five patients in Group B. Thus, no significant difference was found between the two groups in two investigations said to indicate thiamine deficiency. This distribution of abnormality in the pyruvate tolerance test differs from that of Morgan (1968) who found a preponderance of abnormalities in his hallucinatory group.

A suggestive finding in our study was the lack of correspondence between abnormalities in the red cell transketolase and in the pyruvate tolerance tests. This may be because the pyruvate tolerance test is not specific for thiamine deficiency or has a different sensitivity. As early as 1950 Joiner, McArdle and Thompson reported that the test may be abnormal in thyrotoxicosis, congestive heart failure, pregnancy, arsenical poisoning, and a group of peripheral neuropathies not caused by thiamine deficiency. Earl and his co-workers (1953) found abnormally high levels of blood pyruvate following glucose administration in patients with pernicious anaemia. Similar findings were reported by Henneman *et al.* (1954) in patients with schizophrenia, manic-depressive psychosis and multiple sclerosis. In a recent review Victor, Adams and Collins (1971) have also cast considerable doubt on the specificity of this test.

The red cell transketolase test including the 'thiamine effect' may prove to be a better test of thiamine deficiency, but it has not been so extensively studied as the pyruvate tolerance test and may also be subject to influences not related to thiamine deficiency.

In a series of eight alcoholic patients with hallucinations, Morgan (1968) drew attention to three who experienced hallucinations while continuing to drink. He suggested that thiamine deficiency, as determined by the pyruvate tolerance test, may play a particular role in the aetiology of hallucinations in this sub-group. Amongst our 15 patients with hallucinations, 9 had hallucinations while continuing to drink; within this sub-group, abnormalities were found in the red cell transketolase test alone in one patient, in the pyruvate tolerance test alone in four patients, and in both tests in one patient. In the remaining six hallucinated patients, there was a minimally abnormal transketolase test and only one abnormal pyruvate tolerance test. This difference in the distribution of abnormalities of the pyruvate tolerance test within the hallucinatory group is not statistically significant and does not support Morgan's findings.

In evaluating these findings it should be borne in mind that the exact nature of the various hallucinatory phenomena in alcoholics is difficult to determine. Perceptual misinterpretations of varying degrees of complexity may be intermingled with true hallucinations. It is particularly difficult to differentiate these perceptual disorders in patients who are continuing to drink. In the present study no attempt at differentiation was made.

Overall our findings do not indicate that thiamine deficiency can be definitely implicated as a major factor in the aetiology of alcoholic hallucinatory states. On the other hand some support for the withdrawal theory is provided by five patients in whom either delirium tremens or a tremulous-hallucinatory state clearly followed sudden abstinence. Isbell *et al.* (1955) emphasized the importance of relative as opposed to absolute withdrawal. This concept could be invoked to account for the hallucinations which occurred in the sub-group who were continuing to drink,. It is relevant here that seven of the nine patients in this sub-group—reported that the hallucinations occurred only at night and in four ceased on further drinking. Moreover, it is arguable that in some members of the non-hallucinated group the onset of hallucinations was forestalled by the prophylactic use of tranquillizers.

Recent observations on the physiology of sleep may be relevant here (Greenberg and Pearlman, 1967). In some patients with delirium tremens following alcohol withdrawal, these authors found that sleep was characterized almost entirely by REM activity. It was suggested that in these patients the hallucinations of the

waking state were closely related to this increased REM activity. A similar physiological disturbance may accompany relative withdrawal. Further light may be thrown on this subject by experiments concerned with the effects on REM sleep of the various tranquillizing drugs used in treating alcohol withdrawal states.

Summary

Biochemical tests of thiamine deficiency were carried out in 15 alcoholic patients with recent hallucinatory experiences and 15 alcoholic patients without hallucinations. The red cell transketolase activity was abnormal in two hallucinated and one non-hallucinated patients. The pyruvate tolerance test was abnormal in six hallucinated and five non-hallucinated patients. Abnormal liver function tests were found in several patients in each group. The role of alcohol withdrawal in the aetiology of tremulous and hallucinatory states is discussed.

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