THE NATURE AND TREATMENT OF DELIRIUM TREMENS AND ALLIED CONDITIONS

By

R. W. ARMSTRONG, M.A., M.D., D.P.M.

Physician Superintendent, Littlemore Hospital;
Clinical Lecturer in Psychiatry, University of Oxford

and

JONATHAN GOULD, B.Sc., M.B., B.S., M.R.C.P., D.P.M.

Consulting Psychiatrist, Broadmoor Institution;
Associate Chief Assistant
Department of Psychological Medicine, St. Bartholomew's Hospital

INTRODUCTION

DELIRIUM tremens and toxi-infective delirium are not now common diseases, but are still encountered often enough for their treatment to present problems. Delirium tremens is a medical emergency and intercurrent pneumonia is a serious complication, more likely to occur if the patient's over-activity persists. Toxi-infective delirium is less frequently accompanied by crude over-activity, but this may be a source of significant added strain in the severely ill patient, in whom it is more likely to occur. The standard treatment for delirium tremens is by sedation, and the giving of fluids and glucose. Paraldehyde seems to be the drug of choice. Opinion is divided on whether it is advisable to continue to give moderate amounts of alcohol. Sedation is the standard treatment in toxi-infective delirium, and here barbiturates tend to be used.

The role of intensive vitamin treatment in some toxi-organic states has been recently reported (1) and in a preliminary communication on the treatment of drug-induced mental disorder (1a), it was indicated that the technique of using massive doses of vitamins was first developed in connection with the treatment of delirium tremens. We treated our first case of this disorder by this means in 1944 and also at that time, arguing independently by the analogy between Korsakow's disease and pre-senile dementia mentioned by Strauss in 1946 (16), treated similarly a case of Alzheimer's disease. This latter case responded for three months with moderate improvement to 100 mg. aneurin hydrochloride intramuscularly daily combined with large doses of the crude B complex and ascorbic acid by mouth. Owing to various circumstantial factors at the time, treatment lapsed and the patient, a woman of 58, deteriorated. The response was not such as impressed us with the advisability of further experiment in the same dosage range, but, on the basis of later experience, we would now suggest more intensive parenteral treatment under in-patient conditions in the first instance.

The fourteen cases forming the material in which this paper is based comprise:

Alcoholic Deliria	5 cases
Deliria associated with alcohol and infection ..	2 cases
Deliria associated with infection	2 cases

https://doi.org/10.1192/bjp.101.422.70 Published online by Cambridge University Press

Deliria associated with infection and sedation ..	2 cases
Non-delirious Alcoholic Psychoses	2 cases
Coma due to alcohol and barbiturates	1 case

They thus form a continuum with the cases of deliria, psychosis and coma due to drugs reported earlier (1).

The use of high potency vitamin mixtures was extended from delirium tremens to include deliria due to drugs, and toxi-infective delirium as well as certain other disorders of brain function on the grounds of—(1) the basic similarity of these toxi-organic reactions, (2) the probably similar biochemical aetiology, namely interference with brain carbohydrate respiration. The argument and the technique has been further extended to cover the milder mental reactions associated with and commonly accepted as part of the clinical syndrome of acute infections, and has been indicated elsewhere (1).

The premises from which this work started were simple: Delirium tremens was considered to be essentially an avitaminosis B_1 equivalent, but accepting the view that single avitaminosis did not typically occur clinically, we gave very large amounts of several vitamins. The decision with regard to oral and parenteral routes was at first in part determined by the availability of injectable preparations and the size of the dose by the acuteness of the clinical condition. Reference at that time to a small sample of the literature indicated the difference between our use of mixed vitamins and the usual method of giving one vitamin in high concentration and the technique has since been developed independently. The literature will be reviewed later, and a rationale for the method and an aetiological hypothesis for delirium tremens will be offered.

Case Reports

Case 1.—Male, aged 55, publican. On admission he was a case of typical delirium tremens with marked tremor and restlessness. He picked at the bedclothes and clutched at the air but was not violent. He was confused, incoherent, thick in speech and consciousness was moderately clouded. One day later he was more obviously hallucinated and talked of animals which he could see but of which he was not afraid. He was able to state his age, his residence and that he had always been nervous and in the habit of drinking four to five pints of beer daily.

Treatment was then begun, with a slow intravenous injection of 120 mgm. of aneurin hydrochloride and 600 mg. nicotinic acid. During the injection the patient's restlessness and confusion noticeably diminished and he was obviously quieter and more relaxed by the time the injection was completed, hallucinations and jactitations having disappeared. Tremor was also greatly reduced and he was able to sleep for an hour without sedation although previously paraldehyde had been quite ineffective as an hypnotic. In about four hours he commenced to deteriorate. Intravenous injection of 60 mg. B_1 and 600 mg. nicotinic acid was given three times daily for three days accompanied by 1,250 mg. ascorbic acid and large amounts of thiamin and nicotinic acid by mouth (see chart). Glucose was also included and on one occasion 3 gm. of sulphapyridine was injected as a precaution against the development of broncho-pneumonia. (Penicillin was not available at that time.)

On the following day he was still restless and confused. Tremor of the hands, a furred tongue and sluggish pupils were present but he was obviously better than on admission. Four days from the start of treatment he was mentally clear and much improved physically. Neurological signs had disappeared, he was no longer restless, and was sleeping well. Vitamins B and C continued to be given by mouth in large doses for a further three days. His discharge from hospital was held up by an irrelevant physical disability (hernia) for which he required surgical treatment.

Case 2.—Male, aged 19, seaman. Admitted "collapsed"—apparently in alcoholic stupor. On recovery of consciousness, he was apprehensive, restless, complaining and suspicious. Within a few hours it was clear that he experienced illusions and hallucinations—of men with green beards who were about to abduct him. (The theatre orderlies visiting the wards wore green gowns.) Within 24 hours he became difficult to manage, needed sedation, and attempted repeatedly to leave his bed to escape his imaginary tormentors. The past history included poor family relationships, repeated changes of job, sea-faring as an evasion of a difficult home situation, and heavy drinking when in port. The most recent bout of very mixed drinking had lasted ten days and for several days he had eaten little.

Examination revealed coarse tremor of hands, exaggerated knee jerks, relatively reduced ankle jerks, and tenderness on pressure of calf muscles. He was accessible for short periods though a poor witness and prone to wander from the point, as his attention rapidly reverted to his delirious experiences. He was given:

Vitamin B_1	400 mg. I.V.		
Vitamin C	300 mg.	per os	four hourly
Vitamin B_2	9 mg.		
Nicotinamide	50 mg.		
Multivite caps.	3		

During the first injection of aneurin he noticed no change, but within thirty minutes he found that the beards of the men had gone, and he could recognize them as ward orderlies. He remained tense and apprehensive but to a lesser degree. He slept for some time. After the second injection he became quite quiet, co-operative and well. A third injection was given. He was discharged 48 hours after the first injection.

Case. 3—Male, aged 64 years, publican. He had been a heavy drinker for many years and had a previous attack of delirium tremens some four months before admission. His condition on admission was typically one of delirium tremens, with visual hallucinations of a terrifying character and delusions that a gang of men had been raiding his house at night. He had been restless and sleepless for several days and showed some confusion and clouding of consciousness with gross recent amnesia. Physically he showed coarse tremor of the hands and face, the pupils were sluggish and there was arteriosclerosis. There were no signs of peripheral neuritis.

On the day of admission he was given thiamin 100 mg. I.M. and orally, 600 mg. nicotinic acid, together with 60 mg. each of thiamin, riboflavin and pyridoxin.

This was continued for three days after which the intramuscular thiamin was omitted. Ascorbic acid was not given. There was marked improvement within 24 hours of admission. He slept well after his first injection and his confusion and memory defect rapidly improved. Six days after admission he was cheerful and rational and this improvement was maintained, so that eight days after admission he was deemed to have recovered completely. He was, therefore, discharged at the end of seventeen days, when it was considered that he had reverted to his customary condition of chronic alcoholism with some facility and slight intellectual impairment.

Case 4.—Male, aged 42, bartender. The patient gave a history of dyspepsia and consistent heavy drinking (with no bouts of delirium), extending over the past ten years. In 1950 he uneventfully underwent gastrectomy for peptic ulcer after a month of preliminary medical treatment which included vitamin supplements to the hospital diet. No alcohol was given during his stay in hospital. In 1951, a year after operation, he was re-admitted on account of gross melaena due to anastomotic ulcer (Hb. 48 per cent.). During the interval his consumption of alcohol had remained steady. Four days after admission he commenced to be restless, getting out of bed, staring apprehensively at the wall, trembling, muttering to himself and approaching his food with suspicion. On questioning he admitted to visual hallucinations, involving queer animals and people hurrying to and fro, both on the wall and about the ward. In the succeeding twenty four hours he deteriorated. He was then given, intravenously:

Vitamin C	..	1,000 mg.
Vitamin B_1	..	1,000 mg.
Vitamin B_2	..	20 mg.
Nicotinamide	..	100 mg.

together with incidental sedation. Recovery was complete by the end of twenty four hours as far as psychotic experience and behaviour were concerned, although the patient remained emotionally labile for a further day.

This case shows some interesting features, namely that withdrawal of alcohol during the phase of medical treatment, when a nutritious diet and vitamin supplements were given, was not attended by any mental disturbance in spite of the history of consistent heavy drinking and dyspepsia. Similarly a high level gastrectomy was not followed by mental disturbance, and this may be correlated with the preceding month of medical treatment. (The stomach was shown to be the site of atrophic gastritis. At this time his haemoglobin was satisfactory.) Some ten months after operation, however, his general practitioner considered the patient to be developing an anxiety state and referred him for psychiatric opinion. His emergency admission in fact occurred two weeks before the arranged date of psychiatric interview. This was a year after operation and markedly reduced appetite had been present for a short time before the gross melaena occurred. Drinking had not apparently increased. On admission his haemoglobin was 48 per cent. and he was given two and a half pints of blood uneventfully. Some forty hours or so after this the psychosis became declared. In other words it would appear that the absence of even a poorly functioning stomach might have contributed to a biochemical disturbance of brain function presumably related to the reduced absorbtion of vitamins from food.

Case 5.—Male, aged 33, accustomed for many years to drinking five pints of beer a day had come to this country three months earlier on business. During his voyage of six weeks he had drunk more heavily and had come "near to delirium tremens" during the course of an infection at sea. For three weeks he had drunk excessively and eaten little. There was a history of depressive moods commencing during his preparation for the journey and becoming more marked as the months went by, from which he sought relief in alcohol.

When seen he presented a clinical picture of depression and of acute alcoholism. He was overflowing with shallow remorse and self-reproach. He beat his breast and cried out "No, no, don't!" particularly when he felt his moods of depression approach. He was tremulous, unsteady in gait, staccato in speech, staring in gaze, suspicious of his medical attendants, and while he did not admit to hallucinations, repeatedly glanced apprehensively over his shoulder. Confusion as such was absent, but he was unable to maintain a coherent conversation. Physical examination revealed discrepancies in the tendon jerks, which were uneven and unequal; mild lesions of the mouth, a smoothed tongue, faint cracks in the angles of the lips, and tenderness of the calf muscles to pressure. He was considered to be an acute alcoholic psychosis—illustrating incipient delirium tremens. He was given daily, intravenously:

Vitamin C	..	500 mg.
Vitamin B_1	..	500 mg.
Vitamin B_6	..	150 mg.
Nicotinamide	..	150 mg.
Pantothenic Acid		50 mg.

After the first injection his consumption of alcohol dropped. After two injections he was more composed. In a week he was well, but for some memory impairment and persisting depression. The depression responded to E.C.T. and he was sent home.

Case 6.—Male, aged 72. A long standing hypertensive (190/110) with arteriosclerosis, auricular fibrillation, emphysema, enlargement of the liver and pneumonitis, was admitted in a state of delirium. There was a past history of gross alcoholism and of an attack of delirium lasting eight days occurring thirty years earlier, during the course of a pneumonia. Evidence of recent increase in the amount of alcohol taken, and of secret drinking was available.

On examination there was tremor of the face muscles and the arms. He was restless, picking at the sheets and at the air for the butterflies he hallucinated. Disorientation was marked and he wrongly identified those around him on occasion. He repeatedly attempted to get out of bed and imagined that he was still engaged in his normal pursuits. When medication was offered, by mouth or by injection, he became annoyed and resistive. Auditory hallucinations were also present. He was given intravenously:

Vitamin C	..	400 mg.
Vitamin B_1	..	300 mg.
Vitamin B_2	..	20 mg.
Vitamin B_6	..	100 mg.
Nicotinamide	..	100 mg.
Dextrose ..	..	3 g.

During the administration he became steadily calmer and more lucid and by the end of the injection (some fifteen minutes) he was pleasantly co-operative, though the confusion had not cleared. The five assistants necessary at the start of the injection were no longer required to restrain him. The blood pressure dropped from 190/110 to 134/85 during the injection.

At intervals of eight hours he was given:

Vitamin C	..	200 mg.
Vitamin B_1	..	50 mg.
Vitamin B_2	..	5 mg.
Vitamin B_6	..	50 mg.
Nicotinamide	..	50 mg.
Dextrose ..	..	1·5 g.

The improvement however was not maintained and in fact he deteriorated to his original condition during the next thirty-six hours. He was then given the original dose, and this was repeated after a night's sleep. He at once fell asleep again and on waking sixteen hours later was quite well. There can be but little doubt that one of the factors in this patient's psychosis was the poor vascular supply to the brain. This case demonstrates the desirability of maintaining the high concentration of vitamins in order to obtain the best therapeutic result.

Indeed it is quite possible that his progress would have been more rapid had he been given the sort of dosage used in Cases 2, 4, 7, 10, but this was not done on account of his heart condition, as a reduction of blood pressure had occasionally been noticed in other patients receiving large amounts of vitamins intravenously. The delirium in this case commenced within the first thirty-six hours of the infection, about eighteen hours before admission and there is no reason to believe that his intake of alcohol had been altered before the infection supervened.

Case 7.—Female, aged 42, was admitted on account of a compound fracture of the right tibia and fibula. She walked on her fractured leg to the hospital accompanied by her husband, both in a drunken state. Evidence indicated a long standing heavy consumption of spirits.

The fracture was set and plastered under thiopentone, nitrous oxide, oxygen and ether, the patient having become sober. Pyrexia 99°–100° F. was present and persisted, as did the raised pulse and respiration rates (X-ray five days later showed bilateral pneumonitis), and did not respond to penicillin 2,000,000 units daily for two days, followed by 600,000 units daily. Two days after admission she suddenly became acutely hallucinated, restless and voluble. She imagined men to be walking outside her window and rapidly became hostile, fearful and accused the house-surgeon of murdering and dismembering her husband, even though a few minutes later she would carry on a conversation with her spouse whom she declared to be under the bed or in the corridor. Her restlessness and noisiness increased steadily and she became quite unco-operative. Sedatives had little or no effect. On the third day of the delirium she was given, intravenously:

Vitamin C	..	1,500 mg.
Vitamin B_1	..	1,000 mg.
Vitamin B_6	..	200 mg.
Nicotinamide	..	200 mg.
Dextrose ..	..	3·5 g.

with considerable improvement for several hours. Instructions for repeated doses of half the above amounts at 4–8 hourly intervals miscarried and only one injection of the halved quantities was given in the next twenty hours. She remained, however, less disturbed.

A further half dose was given with little apparent immediate benefit but after a sleep the patient was quite normal and remained so. This case shows, as does Case 6, the desirability of maintaining a high concentration of vitamins. It would appear, however, that much larger doses seem to be required when both infective and pharmacological factors (alcohol or drugs) are associated with the delirium than when the infective state alone appears responsible for the mental disturbance (1).

Case 8.—Female, aged 32, jilted by her lover two days earlier, and much distressed thereby, presented with pain in the right chest and mild mental confusion of some ten to twelve hours' duration, but increasing in intensity. When seen in bed three hours later, she was passively resistant to nursing attention and medical examination. She lay on her right side, moaning, inattentive to surroundings, and when induced to answer questions, her replies though relevant, lacked normal courtesy. Disorientation was absent but she could not sustain a train of thought or give consistent attention. Physical examination revealed no localizing signs at this stage but the degree of "toxaemia" was so pronounced that fulminating influenza was considered the most likely diagnosis. T. 103° F, P. 128, R. 28.

The past history included concussion nine months earlier and glandular fever (treated with streptomycin) four to five months before the present illness. The patient had a labile low blood pressure. She was given intravenously:

Vitamin C	..	400 mg.
Vitamin B_1	..	300 mg.
Vitamin B_6	..	50 mg.
Nicotinamide	..	100 mg.

One hour later she was mentally clear and co-operative. The following morning pain in the right shoulder was present and the right lower lobe was solid. Penicillin 1,000,000 units was given. The patient remained clear-headed, cheerful and experienced no sense of illness. T. 101° F., P. 90, R. 30. Further doses of intravenous vitamins were given daily for ten successive days:

Vitamin C	..	300 mg.
Vitamin B_1	..	50 mg.
Vitamin B_6	..	50 mg.
Nicotinamide	..	50 mg.
Pantothenic Acid		25 mg.

Penicillin being continued at 600,000 units in the day. Recovery was uneventful and she set herself to put her emotional affairs in order.

This case demonstrates the response of the mental obfuscation which here was not sufficiently marked to be called confusional psychosis, to intravenous vitamins while the disease process continues (1). This case (lacking a history of alcoholism) could well be contrasted with Case 7 where the persisting infection and the past history of gross alcoholism was associated with a psychotic behaviour more resistant to vitamin therapy. The smaller doses were used in this case as it had been found that these are more suitable to the milder toxic features accompanying acute infections (1).

Case 9.—Male, aged 69 years with no occupation, was admitted under certificate. Five and thirteen years earlier he had experienced depressive episodes for which he had been admitted to hospital and from which he recovered well.

On this occasion his mental state was one of toxic confusional psychosis associated with pneumonia. He was confused and showed clouding of consciousness. Disorientation in time was present. He had vague paranoidal ideas that he was being poisoned and he was restless

noisy and frequently violent. Physically he was regarded as dangerously ill on admission, owing to his chest condition which included areas of consolidation in both lungs and many moist sounds at both apices.

On the day after admission he was given intramuscular injections of aneurin hydrochloride 75 mg. plus nicotinic acid 100 mg. q.t.d. plus ascorbic acid 300 mg. orally t.i.d. This regime was continued for forty-eight hours. Sulphonamides were also given. By the following day he was significantly better, and a week later he had greatly improved mentally and physically: although still feeble, he was by then regarded as out of danger.

Treatment was continued by benzedrine and sedation and improvement was steady until he left hospital, recovered nine weeks after admission.

Case 10.—A female, aged 22, a nurse, suffered from severe pain in the lower limb associated with a small localized undirected mass in the deep tissues of the posterior part of the thigh. A low grade pyrexia was present, T. 99–99·6° F. For the pain she received pethidine 200 mg. or more daily. After several weeks, during which no adequate diagnosis could be established, it was noticed that her composure was becoming undermined and her behaviour more emotional and over-reactive. She was then transferred to another hospital on admission to which she was noticed to exhibit "choreiform" movements, particularly of the upper limbs. For the control of these she was given, in forty-eight hours, the following—Phenobarbitone 19 gr., Pethidine 400 mg., Sodium Amytal 6 gr. When seen by one of us she was accessible only momentarily. She lay in bed repeatedly throwing herself about and contorting her body, moaning, clamouring for relief of pain, she was childish at times, and slurred in speech. Occasionally she bewailed her removal from the care of the doctor who previously attended her, bleating "He doesn't want me any more" and at these times would beat her head violently against the pillows. Some of her infrequent responses to remarks suggested a Ganser syndrome. For instance when it was suggested that she should switch off the light which offended her eyes, she searched everywhere in a clumsy manner but succeeded in avoiding the switch which was obvious, handy, and whose position in the side room she must have known very well indeed from her work on the ward.

She was given intravenously:

Vitamin C	..	1,500 mg.
Vitamin B_1	..	1,000 mg.
Vitamin B_2	..	10 mg.
Vitamin B_6	..	100 mg.
Nicotinamide	..	200 mg.
Pantothenic Acid		25 mg.

This served to make her far less restless and in the next twenty-four hours she needed only 200 mg. of pethidine for the pain and no sedation at all. Twenty-four hours later the same amount was repeated. She slept and was quite recovered, psychiatrically, when she woke in the morning. The pain, swelling and pyrexia continued.

This case is regarded as illustrating a combination of drug-induced and toxi-infective psychosis. In the absence of pyrexia one would have expected the patient to be fairly deeply narcotized in view of the intensity of the sedation.

Case 11.—A woman of 33, a markedly neurotic subject, received E.C.T. with anaesthesia and muscle relaxants for a depression of some three years' standing after failing to respond to acetylcholine therapy. The course of electroplexy was attended by increasing disinhibition of behaviour and the emergence of some early mild hypomanic reactions. The last (10th) treatment was given at a time when the patient had been pyrexial for two days. Pyrexia lasted another thirty-six hours and at one point reached 102° F. (influenzal coryza was diagnosed). Anorexia had been marked for some months and there had been a loss of one stone in weight. A day after the last electrical treatment she became acutely psychotic and was first seen by one of us in this state a day later. The clinical picture was mixed. Psychomotor over-activity with rapid change of mental content involving several themes and emotional lability (the mood changing from tearfulness to elation and irritability) were presenting features. Clouding of mind was present with poor accessibility to rational conversation. She was acutely fearful of being taken away from home and much pre-occupied with emotionally significant themes such as her own integrity and her husband's (? imagined) infidelity. The tongue was dirty and raw, the calves tender and the tendon jerks uneven. She was given intravenously:

Vitamin C	..	750 mg.
Vitamin B_1	..	500 mg.
Vitamin B_2	..	20 mg.
Vitamin B_6	..	100 mg.
Nicotinamide	..	200 mg.
Pantothenic Acid		10 mg.

in the day for five days with the result that a much more manageable simple hypomania was left after three days treatment.

Case 12.—A man, aged 73, was seen on account of increasing confusion of recent onset. The history showed that for many years he had drunk one and a half bottles of whisky per day, with no overt ill effects, but that in the last eighteen months this had been reduced to about one bottle per day. Sixteen months earlier he had been given colchicine for a rash encircling the neck and soon after this he had developed a slight coronary infarct, from which he had recovered uneventfully. Nine days before being seen he had vomited and commenced to talk gibberish. His secretary noticed that one side of his face was immobile. For the next week he was treated by rest in hospital, the condition being regarded as a mild stroke, but he did not improve and was then permitted to return home. The night before being seen he had a temperature of 102° F.

On examination he looked ill, T. 99·4° F., P. 98, R. 24. He was obese, emphysematous and there were signs of early pneumonia at the lung bases. Psychiatrically, he was completely confused with gross impairment of memory, even over a two-minute period. The right angle of the mouth drooped and the right knee jerk was absent. No other neurological signs were elicitable. The impression was gained that the absent right knee jerk was a long standing sign, unconnected with the present condition. The blood pressure was 110/70. Signs of vitamin insufficiency (1) included: smoothing of several areas of the tongue, minor lesions of the inner surface of the lower lip, dryness and scaling of the limbs, marked tenderness of the calf muscles on pressure.

He was given intravenously:

Vitamin C	..	500 mg.
Vitamin B_1	..	200 mg.
Vitamin B_2	..	10 mg.
Vitamin B_6	..	200 mg.
Nicotinamide	..	200 mg.
Pantothenic Acid		12½ mg.
Dextrose ..	..	1 g.

at 2 p.m. By 4 p.m. he was considerably more alert though bouts of confusion persisted. By 11 p.m. he had deteriorated and the injection was repeated. Overnight he slept fitfully until 2 a.m. and was then given sodium amytal 3 gr. which was followed by slumber. On waking further mental improvement was apparent, but the signs of consolidation at the bases had progressed, and he remained pyrexial. The same dose of vitamins was given once in the next day and penicillin commenced at night. By evening his confused state was very considerably reduced, occurring only for a few minutes at a time. Parenteral vitamins were continued for several more days, the psychiatric syndrome resolving rapidly.

It is a matter of speculation whether the initial mental disturbance might have been a variant of Wernicke's encephalopathy, as opposed to a slight thrombosis or haemorrhage.

Case 13.—A 48 year old male was prone to bouts of excessive drinking which would last up to nine days. At these times he ate little and would drink one to two bottles of whisky per day. In two of these bouts he was treated with vitamins parenterally. On the first occasion he had been drinking for six days and was given:

Thiamin ..	..	200 mg.	I.M. q.t.d.
Ascorbic Acid	..	300 mg.	orally q.t.d.
Riboflavin	..	6 mg.	
Nicotinamide	..	50 mg.	

After one day he left the nursing home against advice to resume his drinking but returned two days later when he was given:

Ascorbic Acid	..	1·5 g.	intravenously.
Thiamin ..	..	1·0 g.	
Riboflavin	..	10 mg.	
Pyridoxin ..	..	100 mg.	
Nicotinamide	..	200 mg.	
Glucose ..	..	1·0 g.	

Two hours later he was composed and co-operative. Half the above dose was given at half-day intervals on three occasions and the patient was discharged. On the second occasion he presented after drinking for seven days. He was given the larger dose mentioned above, but for the fact that instead of including B_6, 100 mg. in the mixture, Pyridoxin 400 mg. was injected twenty-five minutes before the rest (in view of Wordsworth's interesting observations on the relief in three minutes of simple drunkenness by 100 mg. of vitamin B_6 intravenously (40)) but without apparent effect. His composure was restored forty-five minutes after the injection of the mixed vitamins was completed. Three further injections at half day intervals were given.

The failure of pyridoxin alone to influence the clinical picture in this case is not surprising, as simple drunkenness and alcoholic psychoses very probably differ greatly in their biochemical nature. The clinical picture presented by this patient before treatment with parenteral vitamins included tremor of face and hands, slurring of speech, unsteadiness of stance, retardation, truculence and suspiciousness to the point of near-delusion (he feared his food might be tampered with and could not be persuaded to eat it until a while after he had received the injection).

This case illustrates the advantage of the large dose and the parenteral route, particularly when quick results are necessary.

Case 14.—Barbiturates and Alcohol.—The synergistic effects of barbiturates and alcohol have a topical significance and the following case is described as it connects the material of this paper with some other aspects of the use of parenteral high potency vitamin mixtures described elsewhere (1, 1a).

Miss G.B., aged 29, lived alone in a small flat. She lacked appetite and slept badly. Depressive mood swings, lasting up to three weeks, had occurred frequently since adolescence. For some months she had been more severely and persistently depressed following an emotional upset. For forty-eight hours she neither slept nor ate. She then consumed 2/3 of a bottle of whisky and 21 gr. of Sodium Amytal. A friend chanced to call at this point and hurried the patient to a nearby doctor, on whose surgery floor she went into coma. She was at once transferred to a nursing home, receiving 6 mg. picrotoxin en route. On arrival she was given:

Vitamin C	..	1,500 mg.	intravenously.
Vitamin B_1	..	1,000 mg.	
Vitamin B_6	..	100 mg.	
Nicotinamide	..	200 mg.	
Dextrose ..	..	2 gm.	

Three hours later she was awake, oriented and rational, though tense. Within four hours she was eating poached eggs on toast.

Comment on Dosage

In Table I the doses used in the various cases are shown. It will be noticed that the doses vary from case to case. The really rapid improvements or recoveries tend to be associated with the dosage pattern—Ascorbic acid 1,500 mg., aneurin hydrochloride 1,000 mg., nicotinamide 100–200 mg. The fairly frequent inclusion of pyridoxin, riboflavin and pantothenic acid has not so far led to obvious differences in response of the cases who receive them —although there is evidence that pantothenic acid may offset the hypotensive response sometimes associated with large doses of aneurin hydrochloride (1). Case 8 is an exception to the rule that strikingly rapid improvement is associated only with the massive doses. In this patient, however, there was no evidence that alcohol or drugs were implicated in the toxi-confusional mental state, and her response to the lower dosage is in keeping with findings in other conditions dependent upon infection, and not associated with clinical psychosis which will be published elsewhere.

In attempting to evaluate the technique of intensive mixed parenteral vitamin treatment of deliria associated with alcohol and toxi-infective states certain limitations must be kept in mind:

(1) The amount of alcohol consumed is usually unknown except in roughest measure. The onset of delirium tremens and/or psychosis may however be regarded as indicating a critical level of physiological disturbance and hence providing a common base line.

(2) The dosage pattern and its results:

(*a*) The pattern was empirical.

(*b*) Physiological considerations led us to include B_1, B_6 and pantothenic acid, but so far no striking evidence as to their short term importance has been obtained (e.g. in Case 13, the clinical result was the same whether 100 mg. or 400 mg. of B_6 was used).

(*c*) The dosage pattern has varied, even in its two most significant factors —vitamins C and B_1—though nicotinamide when used has varied less, between 100–200 mg.

(*d*) All the rapid responses have been associated with vitamin C 900 mg.–1,500 mg., B_1 1,000–1,200 mg., nicotinamide 100–200 mg. with the exception of Case 8 where the psychosis was in no way associated with drugs or alcohol, but only with infection (1).

Case	Age/Sex	Diagnosis	Duration before Vitamins	Past History of Alcoholism	Days of Vitamin Therapy	Dextrose	Ascorbic Acid C.	Aneurin HCL. B_1	Nicotinic Acid	Nicotinamide	Pyridoxin B_6	Riboflavin B_2	Pantothenic Acid	
(1)	55/M	D.T.s	2 days	++++	3		1,250 mg. oral	180 mg. I.V. 75 mg. oral +(60 mg. B_1 in 1st injection)	1,800 mg. I.V. 600 mg. oral					I.V. given in 3 aliquots per day. Immediate improvement.
(2)	19/M	D.T.s	1 day	++	1		900 mg. oral	1,200 mg. I.V.		150 mg. oral	Multivite caps. three, 4 hourly	27 mg. oral		Symptom free in 18 hours. B_1 given in 3 aliquots at 4 hourly intervals
(3)	64/M	D.T.s	several days	++++	7		0	60 mg. oral 100 mg. I.M.	600 mg. oral	200 mg. oral	60 mg. oral	60 mg. oral		Improvement in 24 hours. Symptom free in 6 days.
(4)	42/M	D.T.s	1 day	++++	1		1,000 mg. I.V.	1,000 mg. I.V.		100 mg. I.V.		20 mg. I.V.		Recovery within 24 hours. Improvement ++ in few hours.
(5)	33/M	D.T.s incipient	several weeks	+++	5		500 mg. I.V.	500 mg. I.V.		150 mg. I.V.			50 mg. I.V.	Improvement in a few hours. Recovery within a week.
(6)	72/M	Alcoholic Delirium with infection	1 day	++++	2	3 g.	400 mg. I.V.	300 mg. I.V.		100 mg. I.V.	100 mg. I.V.	20 mg. I.V.		Repeated (after intermediate smaller dosage) after 36 hours and again 8 hours later—Recovery.
(7)	42/F	Alcoholic Delirium with infection	3 days	++++	1	3 g.	1,500 mg. I.V.	1,000 mg. I.V.		200 mg. I.V.	200 mg. I.V.			Two half doses given in the following 24 hours. Recovery in 36 hours.
(8)	32/F	Delirium with infection	15 hours	Bouts of social drinking	10	1 g.	400 mg. I.V.	300 mg. I.V.		100 mg. I.V.	50 mg. I.V.			Mental symptoms clear in one hour.
(9)	69/M	Delirium with infection	several days	—	2	—	900 mg. oral	300 mg. I.M.	600 mg. I.M.					Mentally improved in 3 days, clear in one week.
(10)	22/F	Delirium with infection and sedation	2 days	—	1	3 g.	1,500 mg. I.V.	1,000 mg. I.V.		200 mg. I.V.	100 mg. I.V.	10 mg. I.V.	25 mg. I.V.	Repeat once (24 hours later). Mentally clear 12 hours after 2nd injection (i.e. in 36 hours).
(11)	33/F	Delirium with infection and sedation	2 days	—	5	—	750 mg. I.V.	500 mg. I.V.		200 mg. I.V.	100 mg. I.V.	10 mg. I.V.	10 mg. I.V.	In two aliquots given daily confusional aspects clear in three days.
(12)	73/M	Non-delirious alcoholic psychosis	9 days	++++	5	2 g.	1,000 mg. I.V.	400 mg. I.V.		400 mg. I.V.	400 mg. I.V.	20 mg. I.V.	25 mg. I.V.	In two aliquots at 8 hourly intervals, initial transient improvement in 2 hours, considerable improvement in 36 hours.
(13)	48/M	Non-delirious alcoholic psychosis	7 days	++++ in bouts	2	2 g.	1,500 mg. I.V.	1,000 mg. I.V.		200 mg. I.V.	100 mg. I.V.	10 mg. I.V.		Half doses repeated b.d.—3 injections. Recovery in an hour.
(14)	29/F	Alcoholic and barbiturate coma	1 hour	Social drinking	1 injection	2 g.	1,500 mg. I.V.	1,000 mg. I.V.		200 mg. I.V.	100 mg. I.V.			Awake in 3 hours. Eating in 4 hours.

(3) In order adequately to establish the most satisfactory pattern of dosage, it would be necessary to have a much larger series of cases, and to work with the theory of limiting factors. Of all the vitamins to be used, only one should be in less than saturation concentration. Thus the clinical effects of varying the dose of one factor could be assessed. In order to apply this method and have sufficient results for statistical analysis, series as large as those published by Rosenbaum, Petrie and Lederer (10) are probably necessary, but instead of supplying, as did those authors, a single vitamin in the context of almost certain relative insufficiency of the others (and thus inviting further biochemical imbalance), it would be necessary to saturate with all factors except the one under observation. Even so the results are not likely to be simple and easy for analytical purposes, because it is known, for instance in the case of pantothenic acid and riboflavin, that the administration of one causes a rise in the blood level of both (41).

Literature

During the period 1937–43 a good deal was written concerning the value of different vitamins, usually thiamin or nicotinic acid, in various psychiatric conditions, particularly delirium tremens. Both thiamin (2, 5, 6), and nicotinic acid (3, 4, 7), had advocates and critics as specific "cures" in delirium tremens while it was also claimed that the administration of either was ineffective (10, 11). Other workers (8a, b, 9a, b) reaffirmed the good results of treatment without the specific use of vitamins although much ascorbic acid was apparently included in their regime. The administration of vitamins as prophylaxis against the central and peripheral neural sequelae of alcoholic psychoses was advocated by some (18a, b, c) who opposed their use in the treatment of the acute condition. These workers also cited instances where recovery from delirium tremens did not occur until large injections of vitamins and/or liver were given, and they admit freely that the early differentiation of cases needing vitamins from those who would recover without their aid was not possible.

Thiamin given parenterally was reported as of value in the treatment of Korsakow's psychosis and alcoholic psychoses other than delirium tremens (13, 14, 15) and also in presenile dementia (16). Some workers stressed the fact that the mode of action was obscure, as Avitaminosis B_1 could not be demonstrated in Korsakow's disease (15, 12a).

The value of nicotinic acid in certain psychoses was also established in this period. Alcoholic pellagra was identified with true pellagra (17, 30) and later acute nicotinic acid deficiency encephalopathy was described, initially in alcoholics (18, 19). This syndrome includes stupor, cogwheel rigidities and grasping and sucking reflexes. The case often showed signs of mixed vitamin lack as well as organic disease. Meanwhile the value of nicotinic acid in the pellagrous psychoses had been shown (20a) and was then extended to cases of stupor with evidence of nicotinic acid lack short of typical pellagra. Later nicotinic acid was demonstrated to be effective in some instances of clouded consciousness, not showing signs of pellagra, but conforming to the picture of toxi-exhaustive psychosis (20b, c).

This material demonstrates a nexus comprising vitamins, alcoholic psychoses and their sequelae, pellagrous psychoses and certain "organic" psychoses not usually considered as avitaminotic in nature. Concepts of avitaminosis and deficiency diseases influenced clinical thinking and gave rise to therapeutic attempts centred on the discovery of a single vitamin which would cure all

instances of the same clinical syndrome. In 1943 Sydenstricker (20c) observed that Wernicke's encephalopathy, which was known to respond very well indeed to thiamin, responded even better to six intravenous injections per day of 50 mg. nicotinamide and 5 mg. each of thiamin, riboflavin, pyridoxin and calcium pantothenate. This dosage is of interest in that the mixture and the amounts are unusual for the time, and but for the absence of vitamin C the daily totals approach those we have used, although it was not until recently that Sydenstricker's paper came to hand.

The general trend in this earlier literature was to give thiamin, commonly by injection, in daily doses of 10–20 mg. occasionally 50 mg. and rarely 100 mg. nicotinic acid was given, usually orally, in amounts up to 2,000 mg. in the day in the treatment of acute nicotinic acid deficiency encephalopathy. Nicotinamide was given in 1/3 the amounts of the acid. Those vitamins not given specifically were supplied in generous dietary amounts. Some of the case reports (3, 18, 20a) reveal that another vitamin had been given in specific fashion before the one claimed as the cure, but that the possibility of integration of effects was overlooked. Mainzer and Kraus (3) gave 550 mg. of thiamin in two days to a patient who, from their account exhibited evidence of mixed vitamin lack while suffering from delirium tremens. His condition worsened, but responded when 100 mg. and 500 mg. of nicotinic acid was administered in the subsequent two days. Mainzer and Kraus consider that nicotinic acid was the specific therapeutic agent. Rosenbaum, Piker and Lederer (10) analysing the results of the use of thiamin and of nicotinic acid in a large number of cases of delirium tremens, and comparing these cases with others treated by conventional methods point out that there is no marked difference in duration of psychosis although those patients receiving thiamin (50 mg. daily) required much less sedative than any other group. Those receiving nicotinic acid required, according to the figures given, more sedatives than any other group, but this feature is not commented upon by the authors. Sydenstricker *et al.* (20a) present nine case histories to illustrate the value of nicotinic acid, and in no less than five of these significant amounts of liver and/or thiamin were also given parenterally.

More recent work in these fields exploits high intravenous dosage of vitamins. Sydenstricker (20b) had reported a case of acute psychosis in a pellagrin controlled by 600 mg. nicotinic acid and other vitamins orally daily for a month. The psychosis responded in fifteen minutes to the intravenous injection of 150 mg. sodium nicotinate. Seliger (21) recorded the use of 500–600 mg. Thiamin given intravenously in a glucose drip, together with general sedation, as a method of treating delirium tremens with symptomatic recovery in ten hours, and Fischbach (22) claimed 25 mg. of A.C.T.H. to be specific in delirium tremens although he failed to consider the influence of the three litres of glucose solution containing 1,000 mg. of ascorbic acid which were also given. Toxi-confusional psychoses associated with laboratory findings indicative of liver failure were treated successfully with nicotinamide 300 mg. intravenously daily and later 100 mg. orally daily, provided perseverance up to four months was shown (23). A high vitamin diet was part of the regime.

Apart from Sydenstricker's (20c) remarks about Wernicke's encephalopathy, the work reviewed shows the tendency to exhibit one vitamin in high concentration in acute psychoses, and to assume that dietary measures will suffice for the rest. It was accepted that spontaneously occurring vitamin lack rarely, if ever, involves only one factor, and it was known that the administration of a single vitamin in high concentration may precipitate signs of deficiency of

other vitamins, particularly among the inter-related members of the B group (24).

Such mechanisms may indeed account for the occasional report of evidence (3, 10) that large amounts of a given vitamin have been followed by deterioration of the clinical condition.

Some confusion of thought appears to have developed in the literature on vitamins and psychosis. The clinical search has been for the single effective cause of the given clinical syndrome analogous to the role of the pneumococcus in pneumonia. This is an example of the mechanical causality recently examined critically by Strauss (25), Bomford (26) and Sir Russell Brain (27) and of the undue extension of concepts beyond their context discussed by Pirie (28). The idea of the single effective cause in this field contradicts the known inter-relationship of the B vitamins and this was partially reconciled by the method of dietary supplementation. Finally the view of vitamins as simple catalysts in tissue metabolism, daily requirements of which are small, was at variance with the use of the larger therapeutic doses. Nicotinic acid requirements may be an exception here for these are not strictly determined. These latter considerations led to speculation on the drug-like actions of the vitamins when given in large amounts (29a), particularly with regard to nicotinic acid and vasodilation, but this view has been met by the evidence that the amide is as effective, even though lacking the vasodilatory activity of the acid (29b).

So far, the use of vitamins in certain major psychoses and their organic sequelae have been described, and two methods are discernible.

(1) The specific exhibition of a single vitamin—the value of this technique being much challenged especially with regard to delirium tremens.

(2) The use of moderate amounts of mixed vitamins in the treatment of certain organic conditions. Here while the therapeutic value was more readily admitted, the aetiological justification was much doubted, as avitaminosis was deemed absent in these states.

Let us now turn to certain clinical and physiological considerations, which are considered to have a bearing on the nature and treatment of delirium tremens and certain toxic confusional psychoses.

Clinico-Physiological Considerations

Delirium tremens is always associated with alcohol, but may persist in the absence of alcohol from the C.S.F. (35). The onset is often preceded by three days or so of over-activity associated with abstention from alcohol as well as food. Delirium tremens, however, does not occur if adequate food intake and dietary excess of vitamins is ensured (36). This evidence may be held to show that delirium tremens is not simply caused by the presence of excessive amounts of alcohol in the tissues. Drunkenness, narcosis or anaesthesia occur in such conditions. Factors precipitating delirium tremens include pyrexia, infection, anaesthetics, operation, injury, exposure and vigorous exercise. These situations of stress like the prodromal over-activity make heavy demands on the vitamin B and C supplies of the body (37, 31, 32).

Pathological indulgence in alcohol is associated with impaired intake and absorbtion of carbohydrates and vitamins, and lack of ascorbic and nicotinic acids and of thiamin has been demonstrated (12a, b, c). (The implications of vitamin insufficiency for the stability of brain carbohydrate respiration, and the crucial role of vitamins in the structure of the brain

enzymes has been discussed elsewhere (1, 1a).) Thus the carbohydrate respiration of brain tissue, in which vitamins are essential, is put under stress. Alcohol can spare carbohydrate and protein in general metabolism, but only to a limited extent. In brain respiration, alcohol produces an alteration of the metabolic pattern as shown by the reduction both of the oxygen uptake and the R.Q. (38a, b, 33a, b). Two concurrent processes may thus be postulated in the development of delirium tremens:

(1) A progressive imperilling of the basic carbohydrate respiration of the brain due to increasing insufficiency of vitamins. The mild but increasing hyperglycaemia in delirium tremens is consistent with this suggestion (39a, b, c).

(2) A deviant pattern of metabolism due to the forcing of alcohol as an alternative oxidizable substratum.

Anorexia, a prodromal feature of delirium tremens occurs also as a result of thiamin lack. Whatever the origin, the abstention from food may be considered to precipitate or aggravate matters, for supplies of carbohydrates and vitamins as well as alcohol are cut off. The prodromal over-activity, itself a product of the deteriorating cerebral metabolic state makes further demands on the inadequate vitamin stores.

The psychosis may be deemed to declare itself when the chain of reversible oxidization-reduction reactions characteristic of intracellular brain carbohydrate metabolism (34) is sufficiently impaired. Perhaps the special clinical features of delirium tremens are in part determined by the deviant pattern of metabolism due to the alcohol. The basic structure of the delirium, however, is similar to other pharmacologically determined disorders (1) where alcohol is not implicated, and favours the opinion that the essential disturbance is one of disordered brain carbohydrate respiration and acute vitamin insufficiency.

If this interpretation of delirium tremens be accepted (imperilling of carbohydrate respiration due to vitamin lack and forcing of alcohol as an alternative substratum with consequent alteration of metabolic pattern), then it follows that in different cases, different factors may predominate. This reconciles the earlier conflicting evidence on the therapeutic value of glucose, fluid, thiamin and nicotinic acid and suggests that treatment should provide all relevant factors. Vitamins should be given in amounts not only large enough to cover the likelihood of therapeutically induced imbalance, or daily dietary needs, but large enough to rectify the disturbed metabolic pattern of the brain, were this to be due to lack of one or several components of the therapeutic barrage.

The patterns of dosage employed in our cases is in keeping with this general theme and, although the number of cases is small, suggests that the more rapid results are obtained with the higher total daily doses of vitamins. We would suggest that further clinical trial is called for and that in a typical delirium tremens or toxi-infective delirium—the following dosage regime be used:

Ascorbic acid 1,500 mg., aneurin hydrochloride 1,000 mg., nicotinamide 100–400 mg., pyridoxin 200 mg.; repeat in 4–8 hours s.o.s., followed by half doses at 4–8 hourly intervals as indicated clinically.

Elsewhere (1) it has been pointed out that the bodily reserves of ascorbic acid, thiamin and nicotinamide are relatively meagre if sudden demands have to be met, and that the bodily requirements of these vitamins are raised by infection, increase of metabolism, and increase of temperature. It has also been shown that barbiturates exert their action in the central nervous system by

interfering with the respiratory enzymes of the brain (33a, b) and thus the combination of barbiturates and enzymes may be clinically reversed by the administration of vitamins, or the formation of new enzymes may be thus facilitated. This it is suggested is the way in which the vitamins act in the drug induced psychosis (1). That toxic-delirium is probably due to vitamin insufficiency has also been discussed (1). That the synergistic effect of alcohol and barbiturates impinges on the enzyme systems of the brain is consistent with the dramatic results obtained in Case 14.

Summary

Fourteen cases of delirium and allied psychotic states associated with alcohol, infection and at times drugs, have been treated with high potency vitamin mixtures given parenterally.

The response obtained is sufficiently good to warrant more extended trial, and a pattern of dosage for this is suggested. The technique, which was developed empirically, can be shown to be supported by physiological considerations.

Delirium tremens may be considered as resulting from the imperilling of the basic carbohydrate respiration of the brain (due to vitamin insufficiency) coupled with the forcing of alcohol as an alternative oxidizable substrate, resulting in deviant patterns of brain metabolism which become manifest as the psychosis.

Acknowledgments

We acknowledge with pleasure our indebtedness to Dr. B. S. Cooper, for the clinical history given as Case 8.

References

1. Gould, *Proc. Roy. Soc. Med.*, 1954. March.
1a. *Idem*, *Lancet*, 1953, p. 570. 21 March.
2. Kloster, *Nervenartzt*, 1938, **11**, 413.
3. Mainzer and Kraus, *Brit. med. J.*, 1939, p. 331. 12 August.
4. May, *Med. Record*, 1939, **150**, 124 and 162.
5. Sciclounoff and Flagg, *Revue Méd. de la Suisse Romande*, 1940, p. 715.
6. Kiene *et al.*, *J.A.M.A.*, 1940, **114**, 22, 2191.
7. Sydenstricker, *Amer. Psychiat. Assoc. Cincinnati, Ohio*, 1940.
8a. Bowman *et al.*, *J. Nerv. Ment. Dis.*, 1939, **90**, 569.
8b. *Idem*, *J.A.M.A.*, 1939, **112**, 1217.
9a. Wortis *et al.*, *Amer. J. Psychiat.*, 1938, **94**, 891.
9b. *Idem*, *Arch. Neurol. and Psychiat.*, 1939, **41**, 655.
10. Rosenbaum *et al.*, *Amer. J. Med. Sci.*, 1940, **200**, 677.
11. Wortis, *Quart. J. Study Alcohol*, 1940.
12a. *Idem*, *New York State J. Med.*, 1939, **39**, 1178.
12b. Wortis *et al.*, *Amer. J. Psychiat.*, 1941, **98**, 340.
12c. *Idem*, *New York State J. Med.*, 1941, **41**, 14, 1461.
13. Brodsky, *J. Connecticut Med. Soc.*, 1938, **2**, 228.
14. Roch and Sciclounoff, *Schweiz. Med. Wochenschr.*, 1938, **50**, 1343.
15. Bowman, Goodhart and Jolliffe, *J. Nerv. Ment. Dis.*, 1939, **90**, 5, 569.
16. Brain and Strauss, *Recent Advances in Neurology and Neuropsychiatry*, 1946. 5th edition, p. 152. London: Churchill.
17. Spies and de Wolf, *Amer. J. Med. Sci.*, 1953, **186**, 521. October.
18. Cleckley *et al.*, *J.A.M.A.*, 1939, **112**, 2107.
19. Jolliffe *et al.*, *J.A.M.A.*, 1940, **114**, 307.
20a. Sydenstricker, *South. Med. J.*, 1938, **31**, 11, 1155.
20b. *Idem*, *Amer. J. Psychiat.*, 1941, **98**, 83.
20c. *Idem*, *Proc. Roy. Soc. Med.*, 1943, **36**, 169.
21. Seliger, *Amer. J. Psychiat.*, 1948, 1052, 129.
22. Fischbach, *J.A.M.A.*, 1952, **149**, 10, 927.
23. Foster, *J. Nerv. and Ment. Dis.*, 1949, **110**, 1, p. 1. July.
24. Spies *et al.*, *J.A.M.A.*, 1939, **113**, 931. 16 September.
25. Strauss, *Reason and Unreason in Psychological Medicine*, 1953. London: Lewis.
26. Bomford, *Brit. med. J.*, 1953, 4811, p. 633. 21 March.
27. Brain, *Lancet*, 1953, *i*, p. 959. 16 May.
28. Pirie, N. W., *Brit. J. Phil. Sci.*, 1952, **2**, 8, 269.
29a. Airing, *Amer. J. Psychiat.*, 1941, **98**, 83.
29b. *Idem et al.*, *Arch. Neurol. and Psychiat.*, 1941, **46**, 649.
30a. Spies *et al.*, *Amer. J. Med. Sci.*, 1938, **196**, 461.
30b. *Idem*, *ibid.*, 1939, **199**, 268.

31. URBACH, *Exp. Med. and Surg.*, 1952, **10,** 1, p. 7.
32. MILLS, *J.A.M.A.*, 1941, **117,** 18, p. 1500. November.
33a. QUASTEL, *Physiol. Rev.*, **19,** No. 2, p. 135.
33b. *Idem*, *Brit. Med. Bull.*, 1953, **9,** 2, 142.
34. BOWMAN, *Physiol. Rev.*, 1939, **19,** 2, 184.
35. DEMOLLE, quoted by Kinnier Wilson in *Neurology*, 1947, **1,** 696. London: Arnold.
36. SPIES, *J.A.M.A.*, 1940, **115,** 523.
37. COWGILL, *The Vitamin B_1 Requirements of Man*, 1934. Yale Univ. Press.
38a. HIMWICH *et al.*, *Proc. Soc. Exp. Biol. Med.*, 1933, **30,** 904.
38b. *Idem*, *J.A.M.A.*, 1933, **100,** 651.
39a. TOULASE *et al.*, *Annales Médico-Psychologiques*, 1931, **89,** 1, 124.
39b. *Idem*, *ibid.*, 1933, **91,** 1, 1.
39c. ENZIÈRE, *Arch. de la Soc. des Science Méd. de Montpellier*, 1932, **13,** 581.
40. WORDSWORTH, *Brit. med. J.*, 1953, **1,** 935.
41. SPIES *et al.*, *J.A.M.A.*, 1940, **115,** 523. 17 August.