involuntional depression. Thus, one authority speaks of five varieties: constitutional depression, prolonged neurasthenic malaise, true simple melancholia, depressive delusion with intense fear, and catatonic melancholia (but the last two are, of course, usually involuntional, and the first covers Reiss's group of 1910, now swallowed up in the reactive group). It is true that some features common in involuntional melancholia are rare in other forms of depression, but since these probably depend on the patient's age and on degenerative cerebral disease (often of the vessels), or on schizophrenic admixture, it does not seem necessary for classification to stress them as such, but rather to use the patient's age as the sole reason for calling the depression "involuntional," and to seek for further data which will illuminate the prognosis and treatment.

The necessity for making sure that a depression is not due to G.P.I., pernicious anaemia, or other organic disease is present to everyone's mind. But it is less often remembered that the discovery of hysterical, obsessional, or other psychopathic trends in the patient may be important too. A very depressed young woman may be troubled by the thought that she has injured her child through leaving pins about which he could swallow; the obsessional component in this needs examination. A depression in a patient aged 50 may be accompanied by many hysterical symptoms; if the patient has most of his life shown nothing hysterical in his behaviour the possibility of a cerebral arteriosclerosis must then be reckoned with. Or a depression may be found to have developed in a person of schizoid personality, and to be ushering in a schizophrenia. Depression is a very ready psychic response; hence it cannot be evaluated and pigeon-holed without a survey of the patient's life. It was not for lack of instances to support their view that the psychiatrists of the last century believed that most mental diseases began with a stage of depression.

Conclusion

The classification, or avoidance of classification, which I would propose is: first, to determine whether the depression is severe or mild—melancholia or neurasthenia, descriptively speaking; and, of course, there are many grades. Next, does it depend on physical disease, and, if so, how completely? What happened in any previous attacks? On what discoverable influences does it depend: age; constitutional morbid trends; lifelong environmental factors, recent more acutely disturbing ones? What, in sum, is the presumptive balance of environmental forces responsible for the illness as against inherited ones; and what is the balance between environmental influences that may be modified for the better and those that are irremediable? Has the morbid condition been going on long enough to have, so to speak, established an autonomy, set up bodily and mental habits that are inveterate? Have the patient's character and surroundings worked to his advantage or disadvantage during the illness? These are points to weigh rather than points on which to classify; matters of clinical judgment, not solely of observation. A classification can, however, be built upon them. It is because we have no sure means of distinguishing exactly the numerous causes in each case, and their effects, that we must deny ourselves the ease of a simple classification: I think it is a deceptive ease and a deceptive simplicity. No doubt increasing knowledge will bring an improved, eventually even a stable, classification based on aetiology, and pointing, it may be hoped, to treatment: whether it comes by way of genetics, psychology, or somatic pathology, it will be welcome so long as it is useful and valid.

THE CLINICAL SIGNIFICANCE AND ESTIMATION OF BLOOD VITAMIN B₁

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Vitamin B₁ has been used therapeutically in many diseases, but only in beriberi is there overwhelming evidence of its importance. Therapeutic successes, however, have been claimed in nearly all forms of neuritis; thus, Russell (1936) and others have reported dramatic improvement in patients with subacute combined degeneration of the spinal cord following parenteral administration of vitamin B₁ concentrates. We, however, have failed to obtain such striking responses in a series of patients suffering from the disease in varying degrees of severity, although partial relief was noted in a few; a similar series of patients treated in the usual way with liver extracts or preparations of hog's stomach showed much more satisfactory improvement.

Writers on nutrition differ noticeably in their views of the incidence of vitamin B₁ deficiency; thus, whereas Hutchison and Mottram (1936) state that "it is in the perversity of things that food faddists have raised more to-do about vitamin B₁, which few, if any of us, lack," Vorhaus (1937) and McCarrison (1936) have remarked on the relative frequency of this deficiency, McCarrison writing that "the insufficient ingestion of vitamin B₁ is a common food fault."

Our disappointing results in subacute combined degeneration of the cord, the difficulty of assessing the value of vitamin B₁ in this disease, and the many statements that these patients are deficient in vitamin B₁ led us to investigate the possibility of estimating satisfactorily the state of vitamin B₁ nutrition in a series of normal subjects and in patients. The vitamin B₁ content of a diet is not easily estimated from a list of its constituents, and Williams (1938) considers that it is impossible to do so from the available data with an error of less than 50 per cent. Biological assay and the chemical methods so far employed are not sensitive enough to measure the minute quantities present in blood. Roscoe (1936) attempted to estimate the urinary excretion of the vitamin, using for a test the cure of neuritis in rats, but concluded that the method was of little value, while Harris and Leong (1936) have used the rat bradycardia technique.

Test for Vitamin B₁ in Blood

It appeared possible that a satisfactory test for vitamin B₁ in blood might be based upon Schopfer's discovery (1935) that the growth of the mould *Phycomyces blakesleeanus* was proportional within certain limits to the amount of vitamin B₁ present in the medium. By plotting the weight of mycelium obtained against the quantity of vitamin B₁ added, a smooth curve could be produced, and Schopfer used this as a quantitative test for vitamin B₁ in foodstuffs and animal tissues. We have employed Schopfer's technique and applied it to the

estimation of the vitamin B₁ content of human blood; our method is very similar to that since described by Meiklejohn (1937), details of which were kindly made available to us by Professor R. A. Peters. The test we used was as follows:

Technique of the Method Used

Two series of flasks are set up: (1) *The standard range*, containing medium to which known amounts of vitamin B₁ up to 0.5 μ g. per flask have been added; and (2) a similar range of flasks into which are placed duplicated quantities of 1, 2, and 3 c.cm. respectively of the blood under investigation.

The medium for the standard range of flasks is dextrose (0.556 M), asparagine (0.030 M), magnesium sulphate (0.002 M), potassium dihydrogen phosphate (0.011 M); but only half the amount of asparagine is put into the blood-containing flasks. Oxalated blood is used, and the blood-containing flasks are allowed to stand for several hours to allow the corpuscles to form a firm cake at the bottom. The contents of all the flasks are adjusted to pH 6.5 to 6.7 by adding N/10 NaOH and then sterilized by autoclaving. After inoculation with 0.2 c.cm. of a spore suspension of *Phycomyces blakesleeanus* (containing not less than 1,000,000 spores per c.cm.) they are set aside in the dark at a temperature of 20° C. for ten days, when the mycelia are removed, washed, and dried at 110° C. for two hours. The weights of mould in the standard range are plotted against the amounts of vitamin B₁ added and a smooth curve is drawn through the points on the graph. The vitamin B₁ content of the blood can then be read off on this graph from the weight of mycelium obtained similarly with the blood samples. It is unfortunately necessary to construct a fresh graph for the standard range with each series of estimations. Thus, in Case 11 the standard range was as in Fig. 1.

FIG. 1.—Specimen curve showing weight of phycomyces obtained with known amounts of vitamin B₁.

The weights of mycelia, using 1, 2, and 3 c.cm. of this patient's blood, were 22, 44, and 65 mg. respectively, which from this graph give 7, 7.1, and 7.3 μ g. per 100 c.cm.

Evidence in Support of the Method

In spite of the fact that this method may not estimate the vitamin in its natural state in the blood but possibly only its hydrolytic disintegration products, it appears to give a good estimate of the vitamin B₁ content of the blood. There is much experimental evidence in support of this view: (1) The only factor other than vitamin B₁ that has been shown to affect the mould growth is the concentration of nitrogen in the medium; allowance can be made for this. (2) The addition to the medium of a mixture of the two fission products of vitamin B₁—namely, 4-amino-5-aminomethyl-2-methylpyrimidine and 4-methyl-5-oxethylthiazol (kindly supplied by Professor A. R. Todd)—permits the mould to grow as effectively as with the vitamin B₁ itself. (3) The addition of vitamin B₁ to blood, at least in small amounts, usually increases the growth of mycelium to the same extent as would be produced by the same quantity of vitamin B₁ in the absence of blood. (4) The growth-promoting factor in blood resembles vitamin B₁ in that it is completely destroyed by heat at pH 9. (5) The growths obtained using 1, 2, and 3 c.cm. respectively of blood give values for the vitamin B₁ content per 100 c.cm. that agree within the limits of experimental error for the test. (6) Meiklejohn has shown that blood from pigeons fed on vitamin-B₁-deficient diets gives much less growth than that from normal pigeons. (7) We have found that blood withdrawn after intramuscular injection of pure vitamin B₁ into a non-deficient subject produces a greater growth of the mould, the increase starting about ten minutes after the injection and falling to normal within approximately one hour.

It is not yet possible entirely to exclude the presence of other limiting factors in blood, but the values given by duplicate estimations correspond reasonably, and the error for the test is apparently less than 10 per cent.

Normal Controls

Having established the fact that this phycomyces test gives a fairly reliable method of estimating vitamin B₁, we determined the standard range for normal blood, taken from healthy members of the departmental staff, who gave figures ranging between 6.5 μ g. and 16.5 μ g. per 100 c.cm. of blood. Meiklejohn obtained a range of 6.5 to 14 μ g. in a series of six estimations on human blood. We have therefore considered the normal range to be 6.5 to 16.5 μ g. per 100 c.cm. of whole blood (Table I).

TABLE I.—Estimations carried out on Normal Subjects

Initials	Sex	Age	Vitamin B ₁ in μ g. per 100 c.cm. blood*
A. N.	M	40	7.5
E. P.	F	26	9.5
L. E.	M	29	16.5
B. P.	M	25	7.5
T. J.	M	31	7.0
W. B.	M	17	8.2
S. C.	M	33	6.7
E. B.	F	24	6.5
			7.0

* Each figure is the average of duplicate estimations on 1, 2, and 3 c.cm. of blood respectively.

Vitamin B₁ in Disease

Estimations have also been carried out on a series of patients suffering from a variety of diseases, including those in which a deficiency of vitamin B₁ has been said to be an important aetiological factor (Fig. 2; Table II).

FIG. 2.—Blood vitamin B₁ in normal controls and patients.

Black columns = Deficient patients (vitamin B₁ present in deficient amount). Shaded columns = Intermediate group. Unshaded columns = Normal (vitamin B₁ present in normal amount).

I. Vitamin B₁ and the Nervous System

The study of beriberi and experimental investigations in animals have established beyond doubt an intimate and fundamental relation between vitamin B₁ and the nervous system; it is therefore natural that the vitamin has proved of most value in neurological conditions, particularly neuritis and polyneuritis. It has been claimed that the histological changes in the central nervous system in human beriberi are indistinguishable from those of toxic, especially alcoholic, polyneuritis, but recent work by Davison and Stone (1937) indicates that the pathological changes in the nervous system of rats suffering from inanition are essentially the same as those in animals deprived of vitamin B₁ or vitamins B₁ and B₂; these changes are the same whether the animals are starved with or without the administration of vitamins B₁ and B₂.

ALCOHOLIC NEURITIS

The most striking therapeutic results have been obtained in cases of alcoholic neuritis, and there are now many claims for its efficacy in this condition (Vorhaus, 1937; Jolliffe and Colbert, 1936). Although most of the clinical observations were not adequately controlled, the recent careful investigation by Goodhart and Jolliffe (1938) has confirmed the good results. Moreover, the patients can be cured in spite of continuing the intake of alcohol.

There is considerable evidence supporting the view that this condition is attributable to lack of vitamin B₁ rather than to a specific toxic action of the alcohol on nervous tissue. For example: (a) Alcohol does not hasten the onset of beriberi and actually delays the onset of symptoms of polyneuritis in rats. (b) The clinical and pathological manifestations of alcoholic polyneuritis are strictly comparable to those of beriberi (Minot *et al.*, 1933); transitional cases occur in which more definite symptoms of beriberi develop (Weiss and Wilkins, 1936). (c) There is evidence of dietary neglect in those alcoholics who develop nervous symptoms (Jolliffe *et al.*, 1936; Minot *et al.*, 1933; Alsted and Lunn, 1938). (d) There is evidence of defective assimilation in alcoholics. (e) Storage in the liver is probably defective in alcoholics,

and it has been claimed that the irritant effect of alcohol on the stomach and liver causes vitamin deficiency. (f) There is evidence of increased tissue demand for the vitamin in alcoholics.

TABLE II.—Estimations carried out on Patients with Various Diseases

Case No.	Sex	Age	Disease	Vitamin B ₁ in µg. per 100 c.cm. blood
1	F	50	Alcoholic neuritis before treatment	4.0
			After treatment	8.0
2	M	47	Polyneuritis (toxic)	9.4
3	M	61	" (infective)	7.0
4	F	52	" (toxic)	7.0
5	F	48	Subacute combined degeneration of the cord, untreated	9.8
6	M	62	"	8.8
7	M	51	"	8.6
8	M	65	"	7.8
9	F	53	Subacute combined degeneration of the cord, treated	++
10	M	55	"	8.0
11	M	47	"	7.2
12	M	16	Diabetic neuritis	6.1
13	F	61	"	6.0
14	M	52	" .. (coma)	4.5
15	F	45	Nutritional neuritis	3.5
16	F	48	"	4.5
17	M	62	Malnutrition	4.7
18	M	69	Scurvy	5.5
19	M	62	"	4.8
20	F	46	Simple achlorhydric anaemia ..	6.0
21	F	55	"	5.7
22	F	48	"	5.3
23	F	38	Secondary microcytic hypochromic anaemia	11.6
24	F	42	"	9.2
25	F	58	"	8.0
26	F	48	Pernicious anaemia	9.8
27	M	55	"	9.7
28	M	58	"	9.2
29	M	62	"	8.8
30	F	63	"	8.5
31	M	38	"	7.5
32	F	61	Pernicious anaemia + diabetic neuritis	6.0
33	M	59	Pernicious anaemia + carcinoma	5.3
34	M	59	Pernicious anaemia + furunculosis	5.2
35	F	58	Peptic ulcer	8.0
36	M	31	"	6.0
37	F	24	Thyrotoxicosis	7.1
38	F	39	"	5.4
39	F	34	"	5.0
40	F	35	Addison's disease	11.0
41	M	19	Eunuchoid infantilism	5.4
42	M	16	Diabetes mellitus	6.1
43	F	61	"	6.0
44	M	52	" .. (coma)	4.5
45	M	64	Arteriosclerosis	7.4
46	F	67	Hyperpiesis	6.8
47	F	40	" and malnutrition ..	5.5
48	M	23	Heart failure	7.5

Alcoholic neuritis appears to be more intimately associated with vitamin B₁ deficiency than any other form of neuritis apart from beriberi; it is relatively very uncommon in this country, and is rarely seen in hospital patients.

One female patient (seen through the courtesy of Dr. F. R. Ferguson), who was known to have taken two bottles of whisky daily for many years, suffered from polyneuritis and Korsakoff's psychosis. Several estimations of the blood vitamin B₁ gave values of only 4 µg. per 100 c.cm. That the patient's symptoms could be attributed to the deficiency of vitamin B₁ was supported by the marked improvement in both her neurological and her mental condition after the institution of a course of injections of crystalline vitamin B₁ (4 mg.) thrice weekly. She now has a normal vitamin B₁ value of 8 µg. per 100 c.cm.

NON-ALCOHOLIC POLYNEURITIS

In recent publications it has been suggested that vitamin B₁ acts specifically in cases of neuritis of the most divergent aetiology: Vorhaus (1937) claimed complete disappearance of all symptoms in 90 per cent. of 250 cases, and in 70 per cent. of cases of localized neuritis improvement occurred in spite of the presence of septic foci. He concluded that "the action of vitamin B₁ in neuritis bears a close analogy to that of iron in anaemia." Russell (1936) recorded dramatic improvement in an old-standing case of chronic progressive polyneuritis; similar results have been claimed by many other workers.

We examined three cases of non-alcoholic toxic or infective polyneuritis and found blood vitamin B₁ values of 7, 7, and 9.4 µg. per 100 c.cm. respectively, which are well above lowest normal values. Treatment, however, with vitamin B₁ failed to produce any improvement.

SUBACUTE COMBINED DEGENERATION

As already mentioned, vitamin B₁ has been claimed to produce very good results, even complete remission, in these cases. We have been unable to confirm this, and poor therapeutic responses in this disease after vitamin B₁ have also been reported by other workers (Sciclounoff and Broccard, 1936; Fouts *et al.*, 1932, *etc.*). We found that in seven patients the blood vitamin B₁ was normal, ranging between 7.2 and 9.8 µg. per 100 c.cm.

DIABETIC NEURITIS

Two patients with diabetic neuritis were not significantly deficient (6 and 6.1 µg.), but a third one had a definitely low blood vitamin B₁ value (4.5 µg.); this latter patient was in a state of mild diabetic coma.

NUTRITIONAL NEURITIS

Two patients with neuritis due to a definite nutritional deficiency were examined; they showed complete recovery after suitable treatment with normal diet and added vitamin B₁.

The first patient, a woman aged 45, had suffered from neuritis and hyperpiesis for two years; she had complained of flatulent dyspepsia, vomiting, constipation, and anorexia, and had greatly restricted her food intake; in attempts to control the vomiting she never ate eggs, fruit, or vegetables of any kind, and had actually been taking little else but tea and biscuits. There was no evidence of organic disease other than a severe hypochromic microcytic anaemia, achlorhydria, and a subnormal blood vitamin C value (0.16 mg. per 100 c.cm.); her blood vitamin B₁ was the lowest obtained in this series, being only 3.5 µg. per 100 c.cm. of whole blood. Another woman, aged 48, had complained of paraesthesiae and ataxia for some nine months; she had suffered from long-standing anorexia and was obviously undernourished. There was no evidence of organic disease, but she had a moderate hypochromic microcytic anaemia and hypochlorhydria. Examination showed absence of all deep

reflexes and disturbances of sensation in the lower limbs. Her blood vitamin B₁ was only 4.5 µg. per 100 c.cm.

II. Vitamin B₁ and Anaemias

In view of the fact that many types of anaemia are essentially nutritional deficiency diseases, and of the probable coincident deficiency of vitamin B₁, the importance of improving the general nutrition of the patient cannot be emphasized too strongly. Nevertheless Davidson (1931), using yeast in a series of different types of anaemia, obtained good results in only one case, while yeast preparations are only in exceptional cases effective in pernicious anaemia, as we also have noted. Wills (1931) found marmite effective for tropical macrocytic anaemia, but as its efficiency is not destroyed by previous autoclaving it cannot be due to the vitamin B₁. Elsom (1937) reported eight cases of macrocytic anaemia in pregnant women who responded to brewers' yeast orally and to liver parenterally; the clinical disturbances appeared when calculations based upon Cowgill's (1934) formula indicated a deficiency of vitamin B₁.

We examined the blood from six untreated cases of pernicious anaemia without spinal cord involvement. They formed a representative group of patients with typical uncomplicated pernicious anaemia taken from a series of over 1,000 cases; the blood vitamin B₁ values (7.5 to 9.8 µg. per 100 c.cm.) were all within the normal range. On the other hand, the blood from three cases of pernicious anaemia with complications gave much lower values, which clearly depend on the complicating disease.

The first patient, a woman aged 61, had a diabetic neuritis (blood vitamin B₁, 6.0 µg.); the second, a man aged 59 who had been under adequate control and treatment with hog's stomach for three years, had a normal blood count and was suffering from severe furunculosis; his blood vitamin B₁ value was only 5.2 µg. The third patient, also a man aged 59, had been under treatment for eight years, and although his blood count was normal he complained of a recent and sudden onset of difficulty in breathing with hoarseness and loss of weight: examination showed an inoperable carcinoma of the larynx. His blood vitamin B₁ value was 5.3 µg. per 100 c.cm.

Three female patients with nutritional iron deficiency (achlorhydric) microcytic anaemia had the typical symptoms and signs associated with achlorhydria; their haemoglobin percentages and colour indices were low and they responded completely to intensive iron therapy; the blood vitamin B₁ values were 6, 5.7, and 5.3 µg. per 100 c.cm. of blood respectively—definitely below the accepted minimum of the normal range. It is well known that this type of patient often shows other concurrent dietetic deficiencies, so that low values for the blood vitamins B₁ and C (Portnoy and Wilkinson, 1938) are commonly found.

Microcytic hypochromic anaemia secondary to other diseases, however, gave normal values, as might be expected in the absence of any nutritional deficiency. Thus three patients, in whom the anaemia directly followed (1) haematemesis from duodenal ulcer, (2) peptic ulceration, (3) severe menorrhagia, had blood vitamin B₁ values of 8, 9.2, and 11.6 µg. per 100 c.cm. of blood respectively.

Three patients with malnutrition had definitely low values for vitamin B₁ in the blood.

Two of these patients were indigent males (aged 62 and 69 years respectively) suffering from very severe scurvy; they were grossly undernourished and neither had taken fresh food of any kind for many months, having eaten only poor quality bread, margarine, tea, and very occasional small portions of meat. They both had most extensive ecchymoses and widespread purpura, particularly of the legs, arms, and face, and haemorrhages from the mucous membranes. Plasma ascorbic

acid determinations showed gross deficiencies (Portnoy and Wilkinson, 1938), in one instance (Case 18) the plasma vitamin C content being less than 0.1 mg. per 100 c.cm. The vitamin B₁ contents of the blood in these two cases were 4.8 and 5.5 μ g. respectively. Both patients responded dramatically to treatment with intravenous administration of ascorbic acid and full normal diets. The third patient (Case 17) in this group had taken a poor diet for many years and was obviously much undernourished, but he did not show any evidence of scurvy; the vitamin B₁ content of his blood was only 4.7 μ g. per 100 c.cm.

III. Vitamin B₁ and Cardiovascular and Kidney Disease

Cardiovascular disorders are common and often important features in beriberi, and there is evidence that the heart returns to a normal condition when adequate amounts of vitamin B₁ are given. Weiss and Wilkins (1936) have reported a series of alcoholic patients displaying severe cardiac failure, which they attribute to an unbalanced food intake, particularly lacking in vitamin B₁; they claim that minor degrees of circulatory disturbance due to vitamin B₁ deficiency are often seen.

During the course of this investigation we did not encounter any patients whose heart disease could reasonably be attributed to a deficiency of vitamin B₁, and our impression is that such cases are distinctly uncommon.

In a woman, aged 67, suffering from essential hypertension, with a normal blood urea and electrocardiogram, we found the blood vitamin B₁ was normal: 6.8 μ g. per 100 c.cm. A second poorly nourished patient, with hyperpiesis, albuminuria, an enlarged liver, and oedema of the legs, but a normal blood urea, and who had had two previous attacks of eclampsia, had a blood vitamin B₁ of only 5.5 μ g. per 100 c.cm.

A man aged 64 with arteriosclerosis and nephritis had a blood pressure of 135/80, albuminuria, a normal blood urea, impaired renal function, anaemia (red blood cells 3,872,000 per c.mm., haemoglobin 62 per cent., colour index 0.8, white blood cells 8,800 per c.mm.), and a blood vitamin B₁ within the normal range—7.4 μ g. per 100 c.cm. A young man aged 23 suffering from extreme heart failure of obscure aetiology, whose heart was very much enlarged, was found to have a blood vitamin B₁ of 7.5 μ g. per 100 c.cm. After a serious prolonged illness he eventually recovered.

Endocrine Diseases

A few preliminary observations were made on a miscellaneous group of patients with endocrine disturbances, but the numbers are as yet too few to permit deductions to be made. Any changes in vitamin B₁ metabolism are probably secondary to other metabolic disturbances. It has been shown that the need for vitamin B₁ is increased in states of increased metabolism in animals (Cowgill, 1934). Clinical hyperthyroidism, however, is usually associated with increased appetite and the consumption of a well-balanced diet, and only rare instances are accompanied by anorexia. Moreover, the reports of the clinical trial of vitamin B₁ in various metabolic disturbances are conflicting. There is, however, a close relation between vitamin B₁ and carbohydrate metabolism, and changes in the blood vitamin B₁ content in these conditions may be determined by associated disturbances of the carbohydrate metabolism. The following were the observations made:

1. In three of our patients with thyrotoxicosis two had basal metabolic rates of +80 per cent. and +68 per cent. respectively; their blood vitamin B₁ values were subnormal, being 5.4 μ g. and 5 μ g. per 100 c.cm. respectively. The third patient (a woman aged 24) had had five operations on the thyroid gland and still presented the typical symptoms of toxic hyperthyroidism with a basal metabolic rate of +48 per cent., achlorhydria, and a hypochromic microcytic anaemia; her blood vitamin B₁ was 7.1 μ g. per 100 c.cm.

2. A youth aged 19 with eunuchoid infantilism presented the typical appearance of hypogonadism and dwarfism, had a mild hypochromic microcytic anaemia, a basal metabolic rate of -40 per cent., and a normal glucose tolerance; his blood vitamin B₁ was subnormal, being only 5.4 μ g. per 100 c.cm.

3. A woman with very severe Addison's disease who responded dramatically to treatment with large doses of cortin had a blood vitamin B₁ value of 11 μ g. per 100 c.cm. at a time when her blood pressure was 65/55.

Vitamin B₁ Tolerance Tests

The possibility of using tolerance tests for determining vitamin B₁ deficiency has been under investigation, and the conclusions will be published separately. The results so far obtained resemble those of Portnoy and Wilkinson (1938) using vitamin C—that is to say, there is a rapid rise in the blood vitamin B₁ level within the first fifteen

FIG. 3.—Vitamin B₁ tolerance curves.

to twenty minutes after administration of vitamin B₁, followed by a quick fall to normal levels. The pure vitamin B₁ (aneurin) is given by parenteral injection, intramuscularly for preference, and samples of blood are withdrawn at frequent intervals, the vitamin B₁ being estimated by the method described herein. A disadvantage of these tolerance tests is that relatively large samples of blood must be withdrawn by venous puncture at short intervals—every five minutes for the first twenty to thirty minutes, and then half-hourly.

In Fig. 3 are shown specimen normal curves following the intramuscular injection of 4 mg. pure vitamin B₁ (aneurin). It will be seen that the maximum blood vitamin B₁ peak occurs about fifteen to eighteen minutes later, and is followed by a rapid fall to normal levels within an hour.

DISCUSSION

Our investigations seem to show that gross vitamin B₁ deficiency is rare in this country. This is not unexpected, since the daily requirement for the normal individual is about 500 international units (1 mg. pure vitamin B₁): vitamin B₁ has a very wide distribution in foodstuffs, and it is therefore almost impossible for the intake to be inadequate with a reasonable diet. This is in marked contrast to the position with vitamin C, the distribution of which is restricted to certain types of food such as fresh fruits and green vegetables: further, vitamin C is required in much larger daily amounts, and is present in the blood in much greater quantities.

Nevertheless, vitamin B₁ deficiency may arise from (1) an inadequate supply, (2) inadequate absorption,

(3) inadequate utilization, or (4) through its destruction in the alimentary tract.

1. *Inadequate Supply.*—It is known that the storage of vitamin B₁ in the body is limited, and therefore a minimal intake is essential to meet the normal requirements; thus the deficiency observed in patients with alcoholic neuritis, severe malnutrition, and scurvy is undoubtedly due to a defective intake of vitamin B₁, and this is probably also a factor in incipient diabetic coma. Excessive vomiting as in hyperemesis gravidarum may lead to loss from the stomach of vitamin B₁ taken in food and the development of a deficiency; this may be the mechanism by which polyneuritis of pregnancy is produced. A normal intake of vitamin B₁ may be inadequate in certain conditions of hypermetabolism such as pregnancy, lactation, and hyperthyroidism, in which increased supplies of vitamin B₁ may be required. Thus the low values in our hyperthyroid patients may be attributed to a failure to meet an increased demand; it is interesting that the patient who gave a normal figure did not show the typical emaciation associated with thyrotoxicosis.

2. *Inadequate Absorption.*—The vitamin B₁ deficiency observed in cases of simple achlorhydric microcytic anaemia may be an impairment of vitamin B₁ absorption, but the part played by the achylia gastrica in this respect is not known, and it may be concerned with some further intermediate chemical mechanism. Many difficulties arise, since in pernicious anaemia and subacute combined degeneration of the cord achlorhydria is almost invariably present, but the blood vitamin B₁ values are normal in the absence of complications, so that there must obviously be other factors of importance.

3. *Inadequate Utilization.*—This is associated with hypometabolism (as shown by some cases of hypochromic anaemia which fail to respond unless thyroid is given with the iron), toxæmias as from chronic nephritis, and infection; the low figure given by the patient with carcinoma of the larynx may come into this category. It is interesting to note that Schopfer and Jung (1937) found less vitamin B₁ in cancerous tissues than in normal tissues. An unbalanced diet, especially an excessive intake of carbohydrate, has long been known to affect the utilization of vitamin B₁.

4. *Destruction of Vitamin B₁.*—The destruction of vitamin B₁ in the alimentary tract could also lead to an insufficient supply of vitamin B₁ being available for absorption, but the conditions under which this might arise are not clear.

It is evident that a vicious circle arises: in many of these deficiencies an inadequate dietetic intake leads to anatomical or physiological changes within the intestine and then to diminished absorption, which in turn leads to further disorder of the intestinal function. Moreover, some balance between the specific nutritional elements, such as iron and vitamin B₁, may be necessary.

THERAPEUTIC VALUE OF VITAMIN B₁

The only conditions in which a gross deficiency of vitamin B₁ was found were: alcoholic neuritis, nutritional neuritis, scurvy, and malnutrition, and in these cases marked improvement followed the administration of vitamin B₁ (and vitamin C in the scorbutic patient). A partial deficiency was observed in simple achlorhydric anaemia.

The cases of subacute combined degeneration of the spinal cord gave normal figures, so the poor therapeutic results following the administration of vitamin B₁ obtained by us and other workers are not surprising. Similarly,

in spite of a few sporadic claims for its efficacy, the vitamin has not proved of much value in polyneuritis other than the alcoholic, gestational, and nutritional forms, and this finding corresponds with the values for blood vitamin B₁ found in this series. It appears, therefore, that the changes in the nervous system in these conditions, though clinically similar to those reported in beriberi, are of different aetiology and not associated with vitamin B₁ deficiency. There is no clinical evidence that vitamin B₁ is concerned in haemopoiesis, and this is corroborated by the normal figures given by this test in the uncomplicated primary anaemias.

Summary

1. The Schopfer phycomyces test has been applied to the estimation of vitamin B₁ in the blood.

2. The modified method described can be adapted as a reasonable test for vitamin B₁ nutrition, and appears to be the best method at present available for dealing with the small quantities of vitamin B₁ in the blood, but it is too laborious and exacting in technique to serve as an ordinary routine laboratory method.

3. The range for the vitamin B₁ content of blood in eight normal subjects was 6.5 to 16.5 µg. per 100 c.cm.

4. From our experiments vitamin B₁ was found to be present in normal amounts in the blood of patients with subacute combined degeneration of the spinal cord, polyneuritis (excluding that due to alcohol and malnutrition), pernicious anaemia without neurological involvement before and after treatment, and secondary microcytic anaemia.

5. Gross deficiencies were present in alcoholic neuritis (4 µg. per 100 c.cm.), nutritional neuritis (3.5 and 4.5 µg. per 100 c.cm.), scurvy (4.8 and 5.5 µg. per 100 c.cm.), and malnutrition (4.7 µg. per 100 c.cm.); partial deficiencies were noted in simple achlorhydric anaemia (5.3 µg. to 6 µg. per 100 c.cm.).

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REFERENCES

- Alsted, G., and Lunn, V. (1938). *Acta med. scand.*, **94**, 601.
 Cowgill, G. R. (1934). *The Vitamin B Requirement of Man*, Yale University Press, New Haven; H. Milford, Oxford University Press, London.
 Davidson, S. (1931). *Lancet*, **2**, 1395.
 Davison, C., and Stone, L. (1937). *Arch. Pathol.*, **23**, 207.
 Elsom, K. O. (1937). *J. clin. Invest.*, **16**, 463.
 Fouts, P. J., Kempf, G. F., Greene, J. A., and Zervas, L. G. (1932). *J. Indiana med. Ass.*, **25**, 448.
 Goodhart, R., and Jolliffe, N. (1938). *J. Amer. med. Ass.*, **110**, 414.
 Harris, L. J., and Leong, P. C. (1936). *Lancet*, **1**, 886.
 Hutchison, R., and Mottram, V. H. (1936). *Food and the Principles of Dietetics*, Arnold, London.
 Jolliffe, N., and Colbert, C. N. (1936). *J. Amer. med. Ass.*, **107**, 642.
 ——— and Joffe, P. M. (1936). *Amer. J. med. Sci.*, **191**, 515.
 McCarrison, Sir R. (1936). *Cantor Lectures: Nutrition and National Health*, p. 31.
 Meiklejohn, A. P. (1937). *Biochem. J.*, **31**, 1441.
 Minot, G. R., Strauss, M. B., and Cobb, S. (1933). *New Engl. J. Med.*, **208**, 1244.
 Portnoy, B., and Wilkinson, J. F. (1938). *British Medical Journal*, **1**, 554.
 Roscoe, M. H. (1936). *Biochem. J.*, **30**, 1053.
 Russell, W. R. (1936). *Edinb. med. J.*, **43**, 315.
 Schopfer, W. H. (1935). *Z. Vitaminforsch.*, **4**, 67.
 ——— and Jung, A. (1937). *Ve Congrès Int. Tech. et Chim. des Indust. Agric., Scheveningue*.
 Sciclounoff, F., and Broccard, R. (1936). *Schweiz. med. Wschr.*, **66**, 985.
 Vorhaus, M. G. (1937). *Amer. J. digest. Dis. Nutrit.*, **3**, 915.
 Weiss, S., and Wilkins, R. W. (1936). *Trans. Ass. Amer. Phys.*, **51**, 341.
 Williams, R. R. (1938). *Ergebn. Vitamin und Hormonforsch.*, **1**, 214.
 Wills, L. (1931). *British Medical Journal*, **1**, 1059.