

swelling is almost always associated with bright red discoloration or exaggeration of the normal color. It is remarkable how little of coating there may be, even though the patient eats poorly. As the process extends, more and more of the tongue is involved and there is an increase in the intensity of the red discoloration and in the swelling. If treatment is not given, ulcers may appear along the sides and tip, rarely on top (fig. 2).

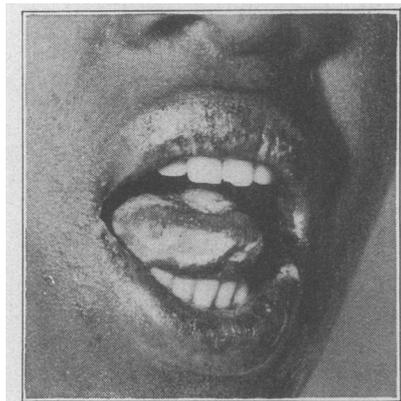


Fig. 2.—Early ulceration of the tongue.

tender (fig. 3). If left untreated, the process extends and often involves large areas, and here and there may appear ulceration of a mild form. The diffuse redness of buccal membranes and soft palate suggests that seen at the onset of influenza, except that there may be no conjunctivitis and no rhinitis. The gums are quite like any form of severe "pyorrhoea" and the Vincent's organism is easily demonstrated. A publication by one of us (T. D. S.) describing the relation of vitamin deficiency to Vincent's infection is soon to appear.

These lesions respond almost immediately to adequate specific therapy if such treatment is started early in the course of the disease. The methods of treatment which we found to be most efficacious in the treatment of pellagra have likewise proved to be beneficial in treating the glossitis and stomatitis complicating chronic alcoholism. These methods consist in the administration of a well balanced, highly nutritious diet of at least 4,000 calories a day supplemented by 25 Gm. of yeast or liver extract three times a day. Wheat germ, administered in amounts of 50 Gm. four times a day as a supplement to the diet, is also very beneficial. Response to such methods of treatment is dramatic; marked improvement occurs in from twenty-four to thirty-six hours, and within a few days the tongue and mucous membranes have changed from dark red to grayish pink and have returned to their normal size.

Whether or not the glossitis and stomatitis observed in the chronic alcoholic addict and characterized by reddening, swelling and ulcerations of the tongue, gums

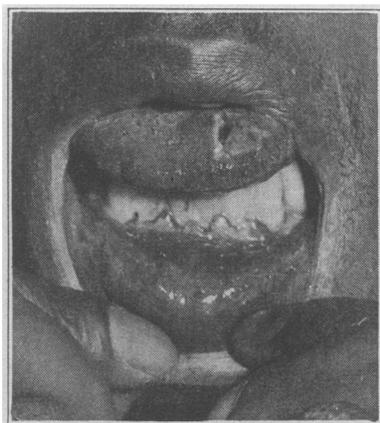


Fig. 3.—Ulceration on dorsum of tongue and marked gingivitis.

Often the tongue becomes semianesthetic, though occasionally it is hypersensitive. There is not so much complaint of sore tongue in the delirium tremens group as among the outspoken pellagrins.

Stomatitis follows a course similar to that of glossitis. The gums and mucous membranes become deeply reddened, swollen and

and oral mucous membranes would eventually develop into a condition recognizable as true pellagra is not pertinent to the welfare of the patient. The important thing is that the physician be constantly on the watch for such oral changes so that proper treatment may be administered in time to prevent the development of more serious conditions.

#### SUMMARY

In a series of over 200 patients suffering from chronic alcoholism and pellagra, approximately 60 per cent were found to have specific lesions of the mouth and tongue. Early treatment consisting of a nutritious diet of 4,000 calories and 75 Gm. of yeast or liver extract daily caused the lesions to disappear. Such lesions frequently precede alcoholic pellagra and are considered to be manifestations of a serious deficiency state.

### THE ETIOLOGY OF POLYNEURITIS IN THE ALCOHOL ADDICT

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That vitamin deficiency may be an etiologic factor in the development of polyneuritis in the alcohol addict was first mentioned on theoretical grounds by Shattuck<sup>1</sup> in 1928 and Minot<sup>2</sup> in 1929. The work of Wechsler,<sup>3</sup> Minot, Strauss and Cobb,<sup>4</sup> and Meyer<sup>5</sup> indicates that the alcohol addict with polyneuritis has, as a rule, a qualitatively inadequate intake of food and vitamins, and that the clinical manifestations and pathologic observations of beriberi and "alcoholic" polyneuritis are similar. These authors suggested, therefore, that vitamin B deficiency may be the decisive factor in producing polyneuritis in alcohol addicts. Strauss<sup>6</sup> and Blankenhorn and Spies<sup>7</sup> showed that patients having "alcoholic" polyneuritis improved if treated with a diet rich in all vitamins, supplemented by oral and parenteral administration of preparations rich in vitamin B, even while they were given from a pint to a quart of blended whisky daily. Strauss concluded that ingestion of whisky has no demonstrable toxic effect on the peripheral nerves.

Cowgill<sup>8</sup> has shown that the vitamin B ( $B_1$ ) requirement of man can be estimated by the formula

$$\frac{\text{Vitamin B mg. equivalent}}{\text{Calories}} = 0.0000284 \text{ weight in grams.}$$

This formula indicates that the vitamin B requirement of man is proportional to both caloric intake and body weight. From the nature of the equation, the expression  $\frac{\text{Vitamin B mg. equivalent}}{\text{Calories}}$  (hereafter referred to as the

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1. Shattuck, G. C.: Relation of Beriberi to Polyneuritis from Other Causes, *Am. J. Trop. Med.* **8**: 539-543 (Nov.) 1928.

2. Minot, G. R.: Some Fundamental Clinical Aspects of Deficiencies, *Ann. Int. Med.* **3**: 216-229 (Sept.) 1929.

3. Wechsler, I. S.: Unrecognized Cases of Deficiency Polyneuritis (Avitaminosis?), *M. J. & Rec.* **131**: 441-444 (May 7) 1930; *Etiology of Polyneuritis*, *Arch. Neurol. & Psychiat.* **29**: 813-827 (April) 1933.

4. Minot, G. R.; Strauss, M. B., and Cobb, Stanley: "Alcoholic" Polyneuritis: Dietary Deficiency as a Factor in Its Production, *New England J. Med.* **208**: 1244-1249 (June 15) 1933.

5. Meyer, August: Ueber das Vorkommen von B-Avitaminose unter den hiesigen Lebensbedingungen, *Schweiz. med. Wchnschr.* **62**: 1243 (Dec. 31) 1932.

6. Strauss, M. B.: The Etiology of "Alcoholic" Polyneuritis, *Am. J. M. Sc.* **139**: 378-382 (March) 1935.

7. Blankenhorn, M. A., and Spies, T. D.: Prevention, Treatment, and Possible Nature of the Peripheral Neuritis Associated with Pellagra and Chronic Alcoholism, *Tr. A. Am. Phys.* **50**: 164, 1935.

8. Cowgill, G. R.: The Vitamin B Requirement of Man, New Haven, Yale University Press, 1935.

vitamin/calory ratio) may be used as a quantitative expression, by reference to Cowgill's prediction chart,<sup>8</sup> of the adequacy or inadequacy of the vitamin B content of the diet of an individual of known weight. Using this method in a recent study, we<sup>9</sup> estimated the vitamin/calory content of the diets of forty-two alcohol addicts who gave reliable histories. By including in the estimation of the vitamin/calory ratio the first 1,600 calories derived from alcohol we demonstrated (1) that the diets of alcohol addicts with polyneuritis failed over an effective period of time to contain adequate quantities of vitamin B as compared with the predicted requirement of each patient; (2) that the diets of alcohol addicts without polyneuritis, though the addiction was of long duration, contained adequate quantities of vitamin B as compared with the predicted requirement; (3) that certain subjects without polyneuritis consumed enough alcohol over an adequate period of time to cause peripheral nerve involvement if alcohol per se was its cause. We present in this study additional evidence, in the form of therapeutic results, that vitamin B deficiency is the cause of polyneuritis in the alcohol addict. In presenting this evidence we are aware of the hazard of interpreting therapeutic results without a definite objective yardstick. Moreover, peripheral neuritis is a chronic disease, subject to wide variations in the degree of involvement, in which therapy effects complete cure only after a long period of time, with an occasional complete failure.<sup>10</sup> These subjects frequently have a multiple rather than a single deficiency, and in some the pathologic changes may be so far advanced as to be irreversible. Even in experimental animals, maintained with a diet deficient only in vitamin B, therapy which is usually curative may fail completely.<sup>8</sup> However, by the alternate case method of study we have obtained three groups of subjects of about equal severity of peripheral nerve involvement in whom we believe the therapeutic results may be compared.

#### METHODS OF STUDY

The alcohol addicts selected for this study had polyneuritis, as evidenced by symmetrical sensory changes in the peripheral nerve distribution of the lower extremities and, as a rule, by changes in the deep tendon reflexes. Patients having complications likely to increase the vitamin B requirement, or likely to prevent absorption from the gastro-intestinal tract or utilization of vitamins (pneumonia, tuberculosis, hyperthyroidism, delirium, vomiting, diarrhea, pellagra, clinical icterus, ascites), were excluded from this study. A palpable liver, dependent edema, low grade fever, achlorhydria, anemia, anorexia or a psychosis not associated with delirium did not cause exclusion. The selected patients were placed in rotation into groups A, B and C until twenty-three subjects were studied; then five successive patients were placed in group C, making a total of twenty-eight subjects. Certain subjects in groups A and C, following observation in their respective groups, received treatment designed to test a therapeutic agent. All subjects were given physical therapy, and symptomatic treatment was given as occasion required. Observations on changes in the neurologic status were made by the same observer at weekly inter-

vals, and in certain subjects daily. Because of variations in interpreting hyperactivity or sluggishness of tendon reflexes, they are reported only as being present or absent. For similar reasons, changes in skin sensitivity are reported as to extent but not degree. Changes in vibratory sense are reported as to extent of complete loss.

Group A: The seven patients in this group were given a basal diet<sup>11</sup> estimated to contain 2,190 calories and 3,680 mg. equivalent (736 Sherman units) of vitamin B. The vitamin/calory ratio of this diet is 1.7, which is of borderline adequacy for subjects weighing from 58 to 63 Kg. Subject 5 weighed 56 Kg., and the remaining subjects weighed 58 Kg. or more. Subjects 3, 4 and 6 received daily 18 Gm. of vegex<sup>12</sup> which had been autoclaved on two successive days for four hours at 20 pounds pressure. This treatment, as shown by growth tests on rats, destroys the antineuritic vitamin B.

Group B: The eight patients in this group received the same basal diet as those in group A, but in addition they were given 18 Gm. of unheated vegex daily. The vegex contains about 225 mg. equivalent (45 Sherman units) of vitamin B per gram. This added 4,050 mg. equivalent of vitamin B to the basal diet, making the vitamin/calory ratio 3.6, which is double the vitamin B requirement of a subject weighing 64 Kg.

Group C: The thirteen patients in this group received a vitamin rich diet estimated to contain 3,100 calories and 17,250 mg. equivalent of vitamin B, resulting in a vitamin/calory ratio of 5.5. To this diet was added 18 Gm. of vegex daily, bringing the vitamin/calory ratio up to 6.8. This ratio is almost twice that received by subjects in group B, and four times that received by subjects in group A.

#### RESULTS

Observations on the objective neurologic signs of peripheral nerve involvement in the seven patients in group A, and the results of maintaining them with a diet containing a vitamin/calory ratio of 1.7, are summarized in table 1. No patient showed objective signs of motor or sensory improvement. Subject 6, who weighed 90 Kg., developed a bilateral foot drop after twenty-nine days. Subjects 2, 3 and 4 showed advancement in the sensory abnormalities at the end of twenty-eight, thirty-three and twenty-seven days respectively of observation. Subjects 3, 4 and 6 received autoclaved vegex in addition to the basal diet, but, like the subjects who did not receive this supplement, they failed to improve.

Observations on the eight subjects in group B, maintained with the identical diet as the subjects in group A but with a supplement of 18 Gm. of (unheated) vegex daily, are summarized in table 2. No subject became worse. Subject 9 failed to show either motor or sensory improvement after forty-four days. In three subjects (8, 11 and 15) sensory improvement was observed by the twenty-first day; in the remaining four sensory improvement was observed later. Six of the eight subjects in this group showed motor involvement by our criteria. Improvement in the motor phase was observed in three of these by the twenty-first day. In two (subjects 8 and 15) the motor improvement consisted of a return of knee jerks, and in the third (subject 11) the bilateral foot drop disappeared. In no subject were

9. Jolliffe, Norman; Colbert, C. N., and Joffe, P. M.: Observations on the Etiologic Relationship of Vitamin B (B<sub>1</sub>) to Polyneuritis in the Alcohol Addict, *Am. J. M. Sc.* **191**: 515-526 (April) 1936. Jolliffe, Norman, and Joffe, P. M.: Relation of Vitamin B (B<sub>1</sub>) Intake to Neurological Changes in the Alcohol Addict, *Proc. Soc. Exper. Biol. & Med.* **32**: 1161-1162 (April) 1935.

10. Vorhaus, M. G.; Williams, R. R., and Williams, R. E.: Studies on Crystalline Vitamin B<sub>1</sub>: Experimental and Clinical Observations, *J. A. M. A.* **105**: 1580-1584 (Nov. 16) 1935.

11. The basal diet consisted of oatmeal, 40 Gm.; white bread, 240 Gm.; macaroni, 30 Gm.; milk, 90 cc.; meat (beef, mutton or chicken), 150 Gm.; white potatoes, 130 Gm.; vegetables (beets, carrots, onions), 100 Gm.; stewed fruit (apples, apricots), 150 Gm.; butter, 45 Gm.; sugar, 30 Gm.

12. Courtesy of Vegex, Inc., New York.

absent ankle jerks noted to return within twenty-one days.

Observations on the thirteen subjects in Group C, maintained with a vitamin rich diet containing a vitamin/calory ratio of 5.5 supplemented by 18 Gm. of vegex daily, giving a total vitamin/calory ratio of

TABLE 1.—Changes in Objective Neurologic Signs of Peripheral Nerve Involvement in Seven Subjects Maintained with a Diet Containing a Vitamin/Calory Ratio of 1.7

Case	Age	Sex	Motor				Sensory				Results					
			Deep Tendon Reflexes				Foot Drop	Wrist Drop	Vibratory	Position	Calf Tender-ness	Skin Sensi-tivity	Days of Treatment	Motor	Sensory	
			Ankle	Knee	Biceps	Triceps										
1	28	♂	0	0	0	0	+	N	N	N	N	+	K	0	U	U
2	30	♂	+	+	+	+	N	N	N	N	N	+	ML	0	U	W
3	59	♂	0	+	+	+	N	N	N	N	N	+	P	0	U	W
4	43	♀	0	0	+	+	N	N	N	N	A	+	ML	0	U	W
5	44	♀	0	0	0	0	+	N	N	Pel. A	+	+	P	0	U	U
6	54	♂	0	0	0	0	N	+	N	Pel. T	+	+	ML	0	W	U
7	35	♀	0	0	+	+	+	N	N	K	N	+	K	0	U	U

In this and the following tables: 0 = absent, + = present, N = normal, T = absent in toes, A = absent or abnormal in ankles and below, ML = absent or abnormal below midleg, K = absent or abnormal below knees, MTh = absent or abnormal below midthigh, Ped. = absent or abnormal below pelvis, P = abnormal on plantar surface, G = abnormal in all extremities; I = improved, U = unimproved, W = worse.

6.8, are summarized in table 3. No subject became worse. All the subjects in this group showed improvement in the sensory status, eleven of them within twenty-one days, while objective motor improvement was noted in ten subjects, all within twenty-one days. At the beginning of treatment the knee jerks were absent in ten subjects; they appeared in seven within twenty-one days. At the beginning of treatment ankle jerks were absent in all thirteen subjects; they appeared in five within twenty-one days. In the three subjects who showed no motor improvement the ankle jerks remained absent after thirty-eight, forty-eight and thirty-three days, and the knee jerks after thirty-eight and thirty-three days of treatment.

Observations on the five subjects originally treated in group A or C but who later received different therapy are summarized in table 4. Subject 6, who grew worse after twenty-nine days in group A on the basal diet supplemented by 18 Gm. of autoclaved vegex, was then placed in group C. No improvement was noted by the twenty-first day, but by the thirty-fourth day the foot drop and wrist drop had disappeared and biceps jerks returned, and sensory improvement was noted.

Subject 5 was treated for thirty-nine days in group A on the basal diet without motor or sensory improvement occurring. She was then given for seventy-two days 10,000 mg. equivalent daily of a vitamin B concentrate<sup>13</sup> by mouth. This supplement brought the vitamin/calory ratio up to 6.5. No objective motor or sensory improvement was observed during this time. A preparation of vitamin B for parenteral administration was not then available.

Subject 7 was treated for seventy-four days in group A on the basal diet without improvement occur-

ring. At this time there were absent ankle jerks, a bilateral foot drop, and extreme skin hyperesthesia in the lower extremities. The patient was given by intravenous injection for five consecutive days 10 mg. daily of crystalline vitamin B<sub>1</sub>.<sup>14</sup> Within forty-eight hours, after 20 mg. of crystalline vitamin B<sub>1</sub>, the knee jerks had returned, the foot drop disappeared, and the sensory status was strikingly improved. By the sixth day, after 50 mg. of crystalline vitamin B<sub>1</sub>, the patient was able to get out of bed for the first time in eighty days. On the ninth day the diet was changed to the vitamin rich diet of those in group C supplemented by 18 Gm. of vegex, but within a week (sixteenth day) the knee jerks had disappeared, the foot drop returned, and the sensory abnormalities had recurred, though by no means as severely as previously. Continuing the vitamin rich diet and vegex, 10 mg. of crystalline vitamin B<sub>1</sub> was given daily by intravenous injection for two days beginning on the seventeenth day. Dramatic improvement was again noted within forty-eight hours. The patient remained in the hospital seven days more, during which time the improvement was maintained; it has been maintained since then for eight months.

Subject 4 was observed for twenty-seven days in group A with the basal diet and a supplement of 18 Gm. of autoclaved vegex. During this time, sensory abnormalities became worse. The patient was then given by intravenous injection for fourteen consecutive days 10 mg. daily of crystalline vitamin B<sub>1</sub>. Sensory improvement was noted on the third day. The knee jerks returned on the fourteenth day, and further sensory improvement was noted. The patient was placed on the vitamin rich diet used in group C, and there has been no regression up to the time of this writing, twenty days later.

TABLE 2.—Changes in Objective Neurologic Signs of Peripheral Nerve Involvement in Eight Subjects Maintained with a Diet Containing a Vitamin/Calory Ratio of 1.7 plus 18 Gm. of Vegex

Case	Age	Sex	Motor				Sensory				Results					
			Deep Tendon Reflexes				Foot Drop	Wrist Drop	Vibratory	Position	Calf Tender-ness	Skin Sensi-tivity	Days of Treatment	Motor	Sensory	
			Ankle	Knee	Biceps	Triceps										
8	42	♂	0	0	+	+	N	N	N	N	N	+	P	0	I	I
9	47	♀	0	0	0	0	N	N	N	N	N	+	P	0	U	U
10	39	♂	0	0	0	0	+	+	N	N	A	+	P	0	U	I
11	44	♀	0	0	+	+	+	N	N	N	N	+	P	0	I	I
12	47	♂	0	0	0	0	N	N	N	N	A	+	P	0	U	I
13	35	♂	+	+	+	+	N	N	N	N	A	+	K	0	-	I
14	45	♂	+	+	+	+	N	N	N	N	N	+	ML	0	-	I
15	38	♀	0	0	+	+	N	N	N	N	N	+	A	0	I	I

Subject 24 was treated in group C for eighty-five days, with good motor and sensory improvement. The sensory status at this time was normal, but the knee and ankle jerks remained absent and the gait was on a widened base. She was then treated as an outpatient for 127 days, taking an unweighed but vitamin rich diet supplemented by three level teaspoonfuls of vegex (about 18 Gm.) daily. The knee and ankle jerks

13. Courtesy of Eli Lilly & Co., Indianapolis.

14. Courtesy of Merck & Co., Inc., Rahway, N. J.

remained absent and the gait abnormal. The patient was then given 10 mg. daily of crystalline vitamin B<sub>1</sub> by intravenous injection for nine consecutive days. During this time no change in reflexes was noted, but the patient experienced severe paresthesias of the toes.

TABLE 3.—Changes in Objective Neurologic Signs of Peripheral Nerve Involvement in Thirteen Subjects Maintained with a Diet Containing a Vitamin/Calory Ratio of 5.5 plus 18 Gm. of Vegex

Case	Age	Sex	Motor				Sensory				Results				
			Deep Tendon Reflexes				Foot Drop	Wrist Drop	Vibratory	Position	Calf Tender-ness	Skin Sensi-tivity	Days of Treatment	Motor	Sensory
			Ankle	Knee	Biceps	Triceps									
16	45	♀	0	0	+	+	N	N	N	N	N	0	I	I	
17	29	♂	0	0	+	+	N	N	N	N	N	0	I	I	
18	42	♂	0	0	+	+	N	N	N	N	N	0	I	I	
19	48	♂	0	0	+	+	N	N	N	N	N	0	I	I	
20	48	♂	0	0	+	+	N	N	N	N	N	0	I	I	
21	35	♀	0	0	+	+	N	N	N	N	N	0	U	I	
22	37	♀	0	0	+	+	N	N	N	N	N	0	I	I	
23	40	♂	0	0	+	+	N	N	N	N	N	0	I	I	
24	34	♀	0	0	+	+	N	N	N	N	N	0	I	I	
25	52	♂	0	0	+	+	N	N	N	N	N	0	I	I	
26	39	♂	0	0	+	+	N	N	N	N	N	0	I	I	
27	40	♀	0	0	+	+	N	N	N	N	N	0	U	I	
28	45	♀	0	0	+	+	N	N	N	N	N	0	I	I	

On the tenth day, however, the knee jerks were obtained, and they were still present thirty days later at the time of this writing.

COMMENT

The etiology of polyneuritis in the alcohol addict is further clarified by the response of the subjects in this study to diets containing various quantities of vitamin B. The subjects in group A who received a diet of borderline adequacy in vitamin B or slightly less than their predicted requirement, depending on their weight, failed to show improvement. In some there was advancement in objective neurologic signs of peripheral nerve involvement. If alcohol per se were the cause of peripheral neuritis, the removal of alcohol from the daily regimen should have resulted in some of the subjects showing improvement during the period of observation, which varied from twenty-seven to seventy-four days. Their failure to improve when alcohol was withdrawn, together with the observation of Strauss<sup>6</sup> and of Blankenhorn and Spies<sup>7</sup> that "alcoholic" polyneuritis will improve while patients consume from a pint to a quart of whisky daily if the diet is rich in vitamin B; and together with the evidence of Jolliffe, Colbert and Joffe<sup>9</sup> that alcohol addicts who maintain an adequate vitamin/calory ratio do not develop polyneuritis even though they consume large amounts of whisky over many years, leads us to believe that alcohol

per se is not the direct cause of a symmetrical peripheral neuritis.

In table 5 we have summarized the changes occurring within twenty-one days in the three groups of cases. The subjects in group A, given a basal diet containing a vitamin/calory ratio of 1.7, failed in every instance to show either motor or sensory improvement. The subjects in group B, given the same diet plus a supplement of vegex by mouth sufficient to increase the vitamin/calory ratio to 3.6, showed as a group definite but moderate improvement. The subjects in group C, who received a vitamin rich diet which, supplemented by vegex, contained a vitamin/calory ratio of 6.8, showed more rapid and decided improvement than the subjects in group B. The vitamin B adequacy of the three groups may be stated as follows: group A, borderline; group B, approximately twice the predicted requirement; group C, approximately four times the predicted requirement. The degree of improvement was therefore roughly proportional to the vitamin B intake. The contention that the amount of vitamin B intake decisively governs the degree of improvement is valid in groups A and B. The only difference in the

TABLE 4.—Changes in Objective Neurologic Signs of Peripheral Nerve Involvement in Five Subjects on Various Forms of Therapy

Case	Treatment	Day	Motor				Sensory				Results			
			Deep Tendon Reflexes				Foot Drop	Wrist Drop	Vibratory	Position	Calf Tender-ness	Skin Sensi-tivity	Motor	Sensory
			Ankle	Knee	Biceps	Triceps								
6	V/C 5.5 plus vegex	0	0	0	0	0	N	N	N	N	N	0	I	I
5	V/C 1.7 plus B <sub>1</sub> concentrate	0	0	0	0	0	N	N	N	N	N	0	U	U
7	V/C 1.7 plus 50 mg. B <sub>1</sub>	0	0	0	0	0	N	N	N	N	N	0	I	I
	V/C 5.5 plus vegex	9	0	0	0	0	N	N	N	N	N	0	U	U
	V/C 5.5 plus vegex plus 20 mg. B <sub>1</sub>	19	0	+	+	+	N	N	N	N	N	0	I	I
	V/C 5.5 plus vegex	26	0	+	+	+	N	N	N	N	N	0	U	U
4	V/C 1.7 plus auto-claved vegex plus 140 mg. B <sub>1</sub>	0	0	0	0	0	N	N	N	N	N	0	U	U
24	High vitamin diet plus vegex	50	0	0	0	0	N	N	N	N	N	0	U	U
	High vitamin diet plus vegex plus 90 mg. B <sub>1</sub>	137	0	+	+	+	N	N	N	N	N	0	I	I
	High vitamin diet plus vegex	167	0	+	+	+	N	N	N	N	N	0	U	U

B<sub>1</sub> concentrate (Eli Lilly & Co.) 10,000 mg. equivalent daily. Mg. B<sub>1</sub> refers to crystalline B<sub>1</sub> (Merck & Co., Inc.). Vegex always used in 18 Gm. amounts daily.

regimen of these two groups was that subjects in group B were given 18 Gm. of vegex daily, while subjects in group A received either autoclaved vegex or no vitamin B supplement. Vegex is a complex preparation of autolyzed brewers' yeast containing, in addition to vitamin B, vitamin G, which now is thought<sup>15</sup> to

15. Birch, T. W.; György, Paul, and Harris, L. J., The Vitamin B<sub>2</sub> Complex: Differentiation of the Antiblacktongue and the "P.-P." Factors from Lactoflavin and Vitamin B<sub>6</sub> (So-Called "Rat Pellagra" Factor), Parts I-VI, Biochem. J. 19: 2830-2850 (Dec.) 1935.

consist of several fractions such as the pellagra preventive factor, the anti-black tongue factor, lactoflavin, and vitamin B<sub>6</sub>. In autoclaving this product we may have destroyed or impaired another fraction in addition to vitamin B. It may be suspected that the failure of patients in group A, who received autoclaved vegex, to improve was due to the destruction of this other factor, and that the response of the subjects in group B was due to its presence in the unheated vegex. That this is not the true explanation is shown by the course of subjects 4 and 7, who responded with improvement when the basal diet, or the basal diet plus autoclaved vegex, was supplemented by crystalline vitamin B<sub>1</sub>. If the improvement of patients in group B were due to another fraction than vitamin B, it would not have occurred in subjects 4 and 7. The failure of subject 7 (table 4) to maintain the improvement that occurred after 50 mg. of crystalline vitamin B<sub>1</sub> was given with the basal diet, and her maintaining the improvement that occurred after 20 mg. of crystalline vitamin B<sub>1</sub> was given with the vitamin rich diet supplemented by vegex, and the permanent improvement of subject 4 after 140 mg. of crystalline vitamin B<sub>1</sub> was administered with the basal diet supplemented by autoclaved vegex suggests that some factor may be present in both autoclaved and unheated vegex which in itself is not curative but which, when present with adequate

TABLE 5.—Summary of Changes in Objective Neurologic Signs of Peripheral Nerve Involvement in Groups A, B, and C Within Twenty-One Days

	No. of Cases	Vitamin/Calory Ratio of Diet	Worse		Unimproved		Improved	
			Motor	Sensory	Motor	Sensory	Motor	Sensory
Group A	7	1.7	1	3	6	4	0	0
Group B	8	3.6	0	0	3	1	3	7
Group C	13	6.8	0	0	3	2	10	11

amounts of vitamin B, augments the curative properties of the latter.

Patients in group C, whose vitamin B intake was approximately four times their requirement, showed more decided improvement than those in group B, who received only two times their vitamin B requirement. For example, in patients in group B, absent ankle jerks were not observed to return within twenty-one days, while in patients in group C, absent ankle jerks returned within twenty-one days in five of the thirteen subjects.

While we are justified in attributing the better response of patients in group B than those in group A to vitamin B, the still better response of the patients in group C cannot with certainty be attributed solely to the increase in vitamin B. The diet in group C contained 50 per cent more calories and an equal increase in protein. Vitamins A, D and C were also present in larger amounts than in the diet of groups A and B. When we increased the vitamin B content from around 3,000 mg. equivalent in the diet of groups A and B to 17,000 mg. equivalent in the diet of group C, we also increased other fractions of the vitamin B complex. In this connection the observation of Elsom<sup>16</sup> is significant: ". . . vitamin fractions contained in yeast were necessary in addition to preparations of vitamin B<sub>1</sub> and B<sub>2</sub> for complete relief from the changes which accompanied deficiency" in the vitamin B complex. This clinical observation is confirmed by deficiency

experiments. When separate fractions of the vitamin B complex are added to a diet lacking in the entire vitamin B complex, there occurs a temporary increment in weight which is not maintained until all necessary factors are included in the diet.

It is difficult to account for the failure of subject 7 to maintain the improvement produced by 50 mg. of crystalline vitamin B<sub>1</sub> administered by parenteral injection. Before and during this therapy the patient received the basal diet. From the day following the last administration of crystalline vitamin B<sub>1</sub> she was given the vitamin rich diet supplemented by vegex. In spite of this, regression occurred within a week. To the vitamin rich diet plus vegex we then added within two days 20 mg. of crystalline vitamin B<sub>1</sub>. The prompt improvement which followed this time has been maintained over a period of eight months of observation. Our previous suggestion that some factor may be present in both autoclaved and unheated vegex which, while not curative in itself, augments the curative action of vitamin B may be the correct explanation of the relapse. On the other hand, the explanation may be a temporary failure of this patient to absorb the vitamin B given by mouth during the week between the end of the first and the beginning of the second period of crystalline vitamin B<sub>1</sub> therapy.

The failure of subject 5 to respond by improvement after seventy-two days of treatment with the basal diet supplemented by the oral administration of 10,000 mg. equivalent of a vitamin B concentrate does not mean that this preparation is without value. We have treated two subjects<sup>17</sup> having gestational polyneuritis, also due to vitamin B deficiency,<sup>18</sup> with this preparation, with excellent results. Furthermore, subject 5 had a very severe polyneuritis and may represent a group of subjects in whom the pathologic changes have advanced so far as to be irreversible. Another explanation may be that her polyneuritis was on a different etiologic basis, a possibility to which we have referred in a previous study.<sup>9</sup>

Failure of the tendon reflexes to return after a few weeks or months of vitamin B therapy by mouth does not necessarily indicate that they will be permanently absent. The knee jerks in subject 24, after 221 days of known absence, returned when the vitamin rich diet was supplemented for nine successive days by the daily intravenous administration of 10 mg. of crystalline vitamin B<sub>1</sub>.

#### SUMMARY

We have observed twenty-eight alcohol addicts having uncomplicated polyneuritis who were given diets containing slightly inadequate or barely adequate quantities of vitamin B, or diets containing either approximately two times or four times the estimated vitamin B requirement. Those receiving borderline amounts of vitamin B showed no improvement in the objective signs of peripheral neuritis over a period of a month. Two of these subjects were then given crystalline vitamin B<sub>1</sub> by intravenous injection, with dramatic response in one and a good response in the other. Subjects treated with a vitamin B intake approximately twice their predicted requirement showed improvement, but not as rapidly or in equal degree as those receiving four times their vitamin B requirement. We have discussed the relation of alcohol to the etiology of polyneuritis, and the possibility of a fraction in the vitamin

17. Unpublished observations.

18. Strauss, M. B., and McDonald, W. J.: Polyneuritis of Pregnancy: A Dietary Disorder, *J. A. M. A.* **100**: 1320-1323 (April 29) 1933.

16. Elsom, K. O.: Experimental Study of Clinical Vitamin B Deficiency, *J. Clin. Investigation* **15**: 40-51 (Jan.) 1935.

B complex other than vitamin B itself augmenting the action of vitamin B on polyneuritis in the alcohol addict. We conclude that

1. Alcohol per se is not the cause of polyneuritis in the alcohol addict.
2. Vitamin B deficiency is a cause of polyneuritis in the alcohol addict.

#### ABSTRACT OF DISCUSSION

ON PAPERS OF DRs. BLANKENHORN AND SPIES AND  
DRs. JOLLIFFE AND COLBERT

DR. H. B. MULHOLLAND, University, Va.: Until recently the etiology of polyneuritis in chronic alcoholism was thought to be due to the effect of the alcohol on the nervous tissues. The work of Strauss and others demonstrated an improvement in the symptoms and signs of nervous lesions occurring in alcoholic addicts in spite of the continuance of an average alcohol intake, when the patients were put on adequate diets. This is further amplified by these authors, who in a new and ingenious method of attack have apparently shown that vitamin B is quantitatively concerned in the etiology and cure of this condition. I am interested in the fact that in order to obtain satisfactory results it is often necessary to give patients many times the average requirement of vitamin B. This fact has been shown to be true in other deficiency syndromes. It is therefore possible that the factors of absorption and storage may play an important part in the development of deficiency states. An example is the case which responded to the intravenous administration of crystalline vitamin B<sub>1</sub> after not having shown any improvement on a very high intake by mouth. A case of chronic alcoholism recently observed in our hospital presented the picture of macrocytic anemia and symptoms of peripheral neuritis. The reflex changes were of a minor degree, and the lesions cleared up so promptly on the administration of liver and adequate diet that I believe this is another evidence of a deficiency neuritis complicating pernicious anemia in a chronic alcoholic patient. I wonder whether the authors have observed any such cases with macrocytic anemias in their series. The whole question of peripheral neuritis should be reopened and resurveyed in the light of recent work; for instance, peripheral neuritis complicating diabetes and other diseases. The importance of mouth lesions occurring in deficiency diseases, particularly those associated with the vitamin B complex, has just recently been recognized. Indeed, in pellagra these lesions may be used as a guide to the efficacy of therapy. The authors have called attention to a common condition occurring in chronic alcoholic patients which, if treated by adequate dietary measures, may preclude the advent of more serious deficiency states. The lesions described are certainly rather typical of pellagra as seen in the nonalcoholic patient. These two papers seem to carry important therapeutic implications in the treatment of chronic alcoholism.

DR. TOM SPIES, Cincinnati: I cannot agree with Drs. Jolliffe and Colbert that their conclusions concerning vitamin B have been established. The present status can be approached best from a historical standpoint. Lettsom in 1787 first described alcoholic polyneuritis and attributed it to a neurotoxic effect of the alcohol. This belief was not seriously questioned until 1928. The first controlled information occurred by accident when Dr. De Wolf and I were studying the relationship between chronic alcoholism and the development of alcoholic pellagra. We observed that the neuritis did not progress in patients taking large quantities of whisky if they ate large amounts of food. Dr. Strauss, using the same method, showed subsequently that alcoholic neuritis unaccompanied by pellagra responded in a similar manner. Later, Dr. Blankenhorn and I treated fifty cases of alcohol polyneuritis, some with and some without pellagra. Their cure was reported in May 1935. At that time we stressed the therapeutic value of a high caloric, well balanced diet supplemented by large amounts of the vitamin B complex in the form of yeast, liver extract or wheat germ. Drs. Jolliffe and Colbert added the next step by attempting to establish a quantitative relationship between the number of calories and the amount of the vitamin B complex in the diets of these people. Such a relationship

had already been established in animals by Dr. Cowgill. In my opinion, Drs. Jolliffe and Colbert have not proved their point. First, their method of calculating the dietary intake is open to criticism. They failed to consider that the alcoholic addict is interested only in drink and will lie and throw food away to avoid eating. Second, they take alcohol away from people who are accustomed to large amounts. Third, they give these patients physical therapy, which in itself sometimes aids in the treatment of polyneuritis. Fourth, the studies are sufficiently long to allow a possible deficiency of certain other portions of the diet to arise. I believe that vitamin B<sub>1</sub> has something to do with alcoholic polyneuritis, but I also feel that it is not the only factor involved. From my studies it seems that the more restricted diets require larger supplements of the vitamin. The contribution of Drs. Jolliffe and Colbert is significant and I am sure that they will soon put the study on a more scientific basis.

DR. NORMAN JOLLIFFE, New York: In answer to Dr. Mulholland's question concerning macrocytic anemias in these patients, we found in 100 consecutive cases of polyneuritis that about one third showed a macrocytic anemia. As to the points made by Dr. Spies: We are aware that alcohol addicts as a group give unreliable histories, that they are liars, and that they frequently have memory impairment. For this reason I wish to reemphasize our method of judging the accuracy of histories. We chose patients that seemed to us likely to give a reliable history; and then only about one in ten would give us the same history on several successive days. If the history of those who did this could be confirmed by relatives or friends, we would accept that history as true. If our error in estimating the diet was as great as 50 per cent, in only one subject would the vitamin B intake be changed sufficiently to be an exception to our conclusions. As to physical therapy, all three groups received it, and this factor, if it played a curative rôle, was constant. The diet may be restricted, as Dr. Spies has brought out, so much that even crystalline vitamin B<sub>1</sub> will not cause a response. That was shown in one of our patients (case 7). This patient for seventy-four days was given the basal diet. Fifty milligrams of crystalline vitamin B<sub>1</sub> caused only a temporary though dramatic improvement. But 20 mg. of crystalline vitamin B<sub>1</sub> given to the same patient while on a vitamin rich diet was followed by permanent improvement. Another subject (case 4) who received the basal diet plus autoclaved vegex responded permanently following crystalline B<sub>1</sub>. This leads us to believe, as Dr. Spies suggested, that other factors present in the B complex influence the curative response to crystalline B<sub>1</sub>. This phenomenon occurs in the experimental animal that is deprived of the entire vitamin B complex. When separate fractions of the B complex are added, only a temporary response occurs. Add a second fraction, and again a temporary response follows. A permanent response is not established until all fractions of the vitamin B complex are added to the diet. I believe this is the explanation for the failure of crystalline vitamin B<sub>1</sub> to maintain a permanent response in subject 7 on the incomplete diet.

DR. M. A. BLANKENHORN, Cincinnati: I can construe Dr. Mulholland's discussion as a question directed to our paper about macrocytic anemia and answer it with practically the same answer that Dr. Jolliffe does; that is to say, among our patients that were reported as having pellagra, a large number were found to have macrocytic anemia. I am grateful to Dr. Mulholland for making the statement that these mouth lesions in the condition we have described here greatly resemble the pellagra of the South. In presenting this question of sore mouth in chronic alcoholism, we have avoided almost too carefully the word "pellagra" because of the psychology of medical minds. When we describe the condition as pellagra, the doctors of the North will say "Pellagra is a disease of the South and we do not have it in this community and there is no use looking for it." When we speak of this disease in the South, the doctors say "That is alcoholism, and it is quite different from the pellagra we have in the South." We welcome the opinion, therefore, that the two conditions are identical. I will close by reiterating the point emphasized yesterday by Dr. Carlson, that the early recognition of deficiency states is not scientific and is still in the realm of the practicing physician who sees and looks for minutiae.