ABSTRACT OF DISCUSSION

DR. ISAAC R. PELS, Baltimore: This contribution by Dr. Macht is noteworthy from the standpoint that it illustrates the evaluation of various drugs that penetrate the skin through a method that has not been universally used. The fact that he stressed the penetration of animal fats is, of course, important. We all know that; but I wish he had said something, and he probably does in his paper, regarding the use of vanishing creams and their pharmacologic action. A discussion of the scientific details of this paper obviously lies within the province of the properly qualified expert. Therefore I shall limit my discussion to generalities and to a brief comment on its practical importance. The skin has always been an acceptable and fruitful field for functional and therapeutic studies and naturally will continue to be so. It is indeed an amazing experience to take account of the numerous investigations of medicaments, poisons and chemical agents in their effects on the skin and on the body. Some twenty-five years ago Unna, in his studies of chemistry of the skin, concluded that certain few solid and liquid substances (caustic acids and alkalis, phenols) as well as all gaseous and vaporous bodies, can penetrate the skin and, contrariwise, all soluble, indifferent substances, such as neutral salts, cannot. Dr. Macht has at least given us a serious incentive to improve this situation by suggesting additional methods of experimental study in the use of drugs and vehicles, volatile oils and their components. Whatever effects these studies may reveal on the cells, circulation, nerves and adnexa of the dermis from the physical, functional, chemical and pathologic standpoints must be deferred to future studies. The interpretation by pharmacologic methods, however, of changes and effects would seem to be more conclusive than the interpretation of purely biologic changes. Furthermore, in recording the results of penetration of the skin and mucous membranes the important factor of the limits of safety in the application of these experimental substances has been indicated or suggested by the author. Every practitioner realizes the indications for and the value of symptomatic, palliative and expectant therapy, particularly when the etiology remains obscure. Stimulating, inhibitory and destructive procedures, in other words radical therapy which aims to "change the soil" of pathologic conditions of the skin, appears to be the field for investigation to which Macht has drawn our attention.

DR. THEODORE CORNBLEET, Chicago: I was interested to hear that Dr. Macht found that the essential oils, ketones and their related substances do not penetrate as well through the pathologic skin as through the normal skin. I have tackled this problem in a somewhat different way, through a study of the ketone excretion in the urine. In this study I found that the amount of ketones in the urine increased proportionately to the size of the area of skin involved in any kind of a dermatitis. Now it appears that these ketones, which occur ordinarily on the skin surface in the sweat, penetrate the skin with difficulty when there is a dermatitis present and as a result are excreted instead through the urine. Inflamed skin acts, therefore, as a barrier to both materials at the surface and in the lymph and blood. My feeling is that this problem is related to a type of equilibrium between constituents of the blood and the secretions at the surface of the skin. For instance, there is some evidence at the present time that cholesterol and like products are excreted to the surface of the skin and then reabsorbed. In this way, perhaps, many substances are excreted and finally reabsorbed after modification. This process is interfered with at an inflamed site.

DR. DAVID I. MACHT, Baltimore: Dr. Pels mentioned greaseless creams. These are the worst vehicles of all and it is not surprising, as these are really soaps, soap suds with an addition of a little oil to make them stick and look nicer. I want to stress particularly a few words regarding the difference between normal and pathologic skin in relation to absorption, because I did not speak enough on the subject when I read my paper. It seems, as a result of all my experiments, that living tissues are more easily penetrated by chemicals than dead tissues, with one exception. If a burn is produced by an actual cautery, with a raw wound and open vessels, there occurs, of course, marked absorption, but if a burn is produced by scalding, there is coagulation of proteins and the absorption is practically nil. These facts with regard to the difference between normal and pathologic skin and mucous membranes in respect to penetration of drugs are parallel to the results of experiments reported by Dr. Anderson, Dr. Bell and me some years ago with regard to the penetration of ultraviolet rays through skin and mucous membranes, which most dermatologists are also interested in. We have shown that penetration of these rays, even of short ultraviolet rays, is much greater through living tissue than was supposed. The trouble was that previous experimenters made their experiments either on leather or on dead skin, and there, of course, that had altogether different conditions and results. I was interested in the statement made by Dr. Cornbleet regarding the ketones in relation to normal and pathologic skin surfaces, because that fits in very well with my observations.

EFFECTS OF VITAMIN B (B_1) THERAPY ON THE POLYNEURITIS OF ALCOHOL ADDICTS

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Prior to the recognition of the rôle played by vitamins, polyneuritis in the alcohol addict was usually attributed to the direct toxic action of alcohol. Shattuck,[1] Minot[2] and Wechsler[3] suggested that avitaminosis probably played an important rôle in the production of this type of polyneuritis. Several investigators then specifically indicted vitamin B. This opinion was based primarily on the following observations: first, that patients with "alcoholic" polyneuritis had as a rule an inadequate food intake; second, that "alcoholic" polyneuritis and beriberi showed similar clinical and pathologic manifestations.[4] In addition it was observed that these subjects improved when given diets rich in vitamin B and that when such diets were supplemented by vitamin B concentrates improvement occurred even while the subjects were given from a pint to a quart of whisky daily.[5]

Recent fundamental contributions have made possible a more direct approach to the study of the etiology of syndromes suspected of being on the basis of vitamin B deficiency. The first of these contributions was Cowgill's[6] determination of the vitamin B requirement of man and of a formula by which this requirement can be predicted. Cowgill's formula has been confirmed clinically by Baker and Wright[7] and

Owing to lack of space, this article is abbreviated in THE JOURNAL by omission of the tables. The complete article appears in the authors' reprints.

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From the departments of Medicine and Psychiatry, New York University College of Medicine, and the Psychiatric Medical Service of the Third (New York University) Medical Division, Bellevue Hospital.

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Van Veen [8] abroad and by Jolliffe, Colbert and Joffe [9] in this country. The next contribution was the production of crystalline vitamin B_1 in amounts sufficient for clinical investigation.[10]

Using Cowgill's formula, Jolliffe, Colbert and Joffe [9] in a study of reliable dietary histories of forty-two alcohol addicts showed, first, that the diets of alcohol addicts with polyneuritis failed over an effective period of time to contain adequate quantities of vitamin B; second, that the diets of alcohol addicts without polyneuritis, though the addiction was of long duration, contained adequate quantities of vitamin B; and, third, that certain subjects without polyneuritis consumed enough alcohol over a sufficient period of time to cause peripheral nerve involvement if alcohol per se was its cause.

Jolliffe and Colbert [11] then presented evidence that the rate and the degree of improvement in the objective signs of polyneuritis were roughly proportional to the vitamin B intake in twenty-eight alcohol addicts with uncomplicated polyneuritis who were given diets containing one time (group A), two times (group B) and four times (group C) the estimated vitamin B requirement of subjects weighing 60 Kg.

If the rate and degree of improvement of subjects treated by diets containing approximately four times their vitamin B requirement could be enhanced by a further increase in vitamin B, without otherwise changing the diet, the belief that polyneuritis in the alcohol addict is a manifestation of vitamin B deficiency would receive added support. This is our purpose in the present study.

We are cognizant of the fact that other factors than vitamin B deficiency may cause a peripheral neuritis. These may and do operate in the alcohol addict as well as in subjects not addicted to alcohol. We are also aware of the hazards of drawing conclusions as to etiology from therapeutic results. Improvement in these patients, or the degree of their saturation with vitamin B, cannot as yet be gaged by a practical laboratory procedure. Furthermore, peripheral neuritis is a chronic disease, subject to wide variations in degree of involvement, occurring in subjects who frequently have a multiple rather than a single deficiency and in whom the pathologic changes, because of extent or duration, may be so far advanced as to be irreversible. For these reasons, in a study of etiologic factors by therapeutic methods it is necessary that the subjects treated should present, at least clinically, no evidence of other deficiency diseases, and the changes in their peripheral nerves should at least appear to be reversible. We have accordingly chosen for this study patients who have a mild degree of involvement and whose polyneuritis we therefore believe, in the absence of a reliable history, to be of relatively short duration.

METHODS

The criteria we have used to designate mild polyneuritis are as follows: The signs must be limited to the lower extremities, with the knee jerks preserved and with no obvious muscle atrophy or foot drop; the patient must show absent ankle jerks plus some demonstrable sensory change such as muscle tenderness, skin hyperesthesia in a peripheral nerve distribution, and impairment of the vibratory or position sense. As in previous studies, the tendon reflexes are reported only as being present or absent, and sensory changes are reported as to extent but not as to degree. In an earlier study [11] the efficacy of treatment by varying amounts of vitamin B was compared at the end of twenty-one days. The thirteen subjects who were treated with a diet containing approximately four times their predicted requirement of vitamin B had various degrees of involvement, the severity rating of the polyneuritis being as follows: mild, three cases; moderate, eight; severe, two. As a group, ten (77 per cent) showed motor improvement, and eleven (85 per cent) showed sensory improvement at the end of twenty-one days. A review of the case histories disclosed, however, that at the end of ten days only four (30 per cent) showed motor improvement; the same four patients were also the only ones showing sensory improvement. If again increasing the vitamin B intake would advance recovery, a ten day period of observation offered an obviously better comparative basis than twenty-one days. We have therefore made the comparison of changes in objective signs of polyneuritis at the end of ten days.

On admission to the medical wards, each subject having a polyneuritis was given a basal diet [11] containing a vitamin calory ratio of 1.7, plus 18 Gm. of autoclaved vegex. As we have previously shown, this diet, which is of borderline adequacy in vitamin B for a subject weighing 60 Kg., results in no improvement in objective signs of peripheral neuritis. The subjects were maintained with this diet for from three to five days, during which time it was determined whether the patient was cooperative and whether complications existed. Conditions likely to increase the vitamin B requirement or prevent its absorption or utilization were considered complications. The subjects having these conditions are not reported. Jaundice, ascites or signs of liver cirrhosis did not cause exclusion from this study. If the patient was suitable for further study he was then given a weighed diet containing a vitamin/calory ratio of 5.5, plus 18 Gm. of unheated vegex, which increased the vitamin/calory ratio to 6.8, approximately four times the vitamin B requirement of the subject weighing 60 Kg. To alternate subjects we gave in addition 10 mg.[12] of crystalline vitamin B_1 [13] freshly dissolved in 2 cc. of physiologic solution of sodium chloride, by intravenous injection at daily intervals. This amount of crystalline vitamin B_1, calculating 1 mg. as equal to 6,660 mg. equivalents of Cowgill, increased the vitamin/calory ratio to 28.3, or about sixteen times the vitamin B requirement of a subject weighing 60 Kg. Of the subjects studied, seventeen fulfilled our criteria for a mild polyneuritis; eight of these received crystalline vitamin B_1, and nine dietary treatment alone. The latter group served as a control for those treated with the crystalline preparation. We have designated the control subjects group C, since their treatment was identical with that of group C in a previous study. The subjects receiving 10 mg. of crystalline vitamin B_1 daily for ten days we have designated group D. Observations were made by the same observer and checked at frequent intervals by the second observer during the ten day period.

8. Van Veen, A. G.: Het B_1-gehalte van Voedingsmiddelen, Geneesk. Tijdschr. v. Nederl.-Indië **75**: 2050-2064 (Nov. 26) 1935.

9. Jolliffe, Norman; Colbert, C. N., and Joffe, P. M.: Observations on the Etiologic Relationship of Vitamin B (B_1) to Polyneuritis in the Alcohol Addict, Am. J. M. Sc. **191**: 515-526 (April) 1936.

10. Williams, R. R.; Waterman, R. E., and Keresztesy, J. C.: Larger Yields of Crystalline Antineuritic Vitamin, J. Am. Chem. Soc. **56**: 1187-1191 (May) 1934. Williams, R. R., and Cline, J. K.: Synthesis of Vitamin B_1, ibid. **58**: 1504-1505 (Aug.) 1936.

11. Jolliffe, Norman, and Colbert, C. N.: The Etiology of Polyneuritis in the Alcohol Addict, J. A. M. A. **107**: 642-647 (Aug.) 1936.

12. One mg. of the crystalline substance is equivalent to 333 international units.

13. Courtesy of Merck & Co., Inc., Rahway, N. J. We have used both Vitamin B_1 Merck Natural Crystals, and their synthetic product Betabion.

RESULTS

Observations on the objective neurologic signs of peripheral nerve involvement in the nine patients in group C, and the results of maintaining them with a diet containing a vitamin/calory ratio of 6.8, are summarized in table 1. Observations on the eight patients in group D, maintained with the same diet as those in group C but who received in addition 10 mg. daily of crystalline vitamin B_1, are summarized in table 2. The results in the two groups at the end of the ten day period are compared in table 3. Subjects in group D, by every method of comparison, showed greater improvement than the control subjects in group C. At the end of the ten day period only one (11 per cent) of the subjects in group C was considered cured, but four (50 per cent) of the subjects in group D were so considered. Motor improvement was observed in two (22.2 per cent) of the subjects in group C, while five (62.5 per cent) in group D showed motor improvement. Sensory improvement occurred in four (44.5 per cent) subjects in group C, and in all of group D.

These results are remarkable, but the conditions of this study must be borne in mind. These subjects had but a mild polyneuritis and, as far as we are aware, presented no clinical evidence of another deficiency disease or other complications as previously defined. Patients manifesting evidence of a more severe polyneuritis, when treated as those in group D, occasionally exhibit dramatic improvement. Subject 7, previously presented by Jolliffe and Colbert [11] in table 4 of their paper, illustrates this dramatic response. This subject, following the administration of 20 mg. of natural crystalline vitamin B_1, showed within forty-eight hours a return of the knee jerks, a disappearance of the foot drop and striking improvement in the sensory status. Such dramatic response in a patient with more than a mild polyneuritis has not since been observed, though we have treated more than sixty patients with various diets and varying amounts of vitamin B. Because of the wide variations in the degree and duration of involvement, and the various complications present in the subjects having more than a mild polyneuritis, we have as yet too few cases in the several groups from which to draw any conclusions. However, since our results may suggest the correct solution of certain problems in vitamin B therapy, some of these problems will be illustrated in the following cases:

CASE 46.—An actress, aged 35, was brought to the hospital April 1, 1936, by her husband, who stated that she had been drinking heavily for eight or nine years and had been eating little during the past year. Six months prior to her admission, ascites developed. Three abdominal paracenteses were performed, the last a week before admission. On physical examination she showed a moderately severe polyneuritis with absent triceps, knee and ankle jerks. Vibratory sensation was absent in the ankles and below, and position sense was absent in the toes. There was calf muscle tenderness, stocking hyperesthesia extending to the midthigh, and glove hyperesthesia extending to the elbows. In addition, she had a hydrothorax, marked ascites and dilated abdominal veins. The spleen felt firm and was palpable three fingerbreadths below the costal margin; the liver was just palpable. There was no edema of the lower extremities, nor were there any signs of congestive heart failure, such as dilated veins in the neck, orthopnea or dyspnea. The heart was not enlarged on roentgen examination. The patient was given the diet and vegex received by group C, the fluid and salt intake was not restricted, and no medication other than sedatives was given. On the ninth day a gain in weight of 3½ pounds (1,587 Gm.) and increasing abdominal distention necessitated abdominal paracentesis. Twenty pounds (9 Kg.) of clear, straw colored ascitic fluid was removed. By this time improvement in the neurologic signs had occurred. The triceps jerks had returned; glove and stocking hyperesthesia had diminished, and the vibratory sensation had returned in the ankles, continuing to be absent only in the toes. The same regimen was continued. By the twenty-first day a gain in weight of 10½ pounds (4.8 Kg.) had occurred. Paracentesis was again performed and 8 pounds (3.6 Kg.) of ascitic fluid removed. Further neurologic improvement had occurred by this time in that the knee jerks had returned and the glove hyperesthesia had completely disappeared. Beginning on the twenty-second day, 10 mg. of natural crystalline vitamin B_1 was administered daily by intravenous injection for five consecutive days. By the twenty-eighth day the stocking hyperesthesia had diminished to the ankles, calf muscle tenderness was absent, and vibratory and position sense were intact, though the ankle jerks remained absent. The patient was now mentally clear. From the twenty-second day to the twenty-eighth day the patient gained 8 pounds (3.6 Kg.) and there was sufficient ascites so that a fluid wave in the abdomen could be elicited. But further increase in ascites did not occur; the weight first became stationary, and on the thirty-sixth day she began to lose weight. By the forty-eighth day she had lost 11 pounds (5 Kg.), and evidence of ascites had disappeared. During this period the neurologic signs remained unchanged from those of the twenty-eighth day. By the sixty-sixth day the patient had gained 4 pounds (1.8 Kg.), but there was no evidence of ascites or edema. The ankle jerks remained absent but the stocking hyperesthesia had diminished so that it now involved only the plantar surface of the feet. To note the effect on the remaining signs of polyneuritis, 10 mg. of natural crystalline vitamin B_1 was administered daily by intravenous injection for five days. By the seventy-second day the ankle jerks had returned and the hyperesthesia had disappeared. The patient was discharged June 15, 1936, without signs of polyneuritis or mental disease. The spleen remained palpable to the same extent as on admission, but the distended abdominal veins were now less prominent. She then was treated as an outpatient with a diet rich in vitamin B supplemented by three teaspoonfuls of vegex daily, and to the present (eleven months later) alcoholism, ascites or polyneuritis has not returned.

The response of this patient indicates that cirrhosis of the liver may not interfere with either the absorption or the utilization of vitamin B. During the first twenty-one days, when the treatment was entirely oral, the response was about the average obtained in other patients with as severe a neuritis but without clinical evidence of cirrhosis. The addition of crystalline vitamin B_1 on two occasions approximately quadrupled the vitamin B intake, and the increased response during those two periods can be attributed to that fact.

Patients having polyneuritis may show relatively little response to vitamin B therapy as judged by the objective signs of peripheral nerve involvement, especially in the motor phase. This lack of satisfactory response, granted that the etiology is vitamin B deficiency, is most likely due to an irreversible anatomic lesion. This irreversibility may be due to either a severe deficiency over a short period or a mild or moderate deficiency over a longer period.

CASE 47.—A policeman, aged 35, was admitted to the hospital Nov. 11, 1936, his third admission to this service because of alcoholism. His first admission, May 2, 1936, was occasioned by a hematemesis. At that time he showed signs of a mild polyneuritis with absent ankle jerks, absent vibratory sensation in the toes, marked tenderness of the calf muscles, and plantar hyperesthesia. The position sense in the toes was maintained, the gait was natural, and no muscle atrophy was noted. The patient received the house diet for hematemesis and was discharged, May 31, with the polyneuritis unimproved. He continued to drink a quart of whisky daily, ate poorly and was readmitted June 3, at which time the polyneuritis was still considered mild. He was discharged two weeks later and promptly resumed his intemperate habits. On the present admission, occasioned by inability to walk, the knee jerks were preserved, the ankle jerks were absent and vibratory sensation was absent in the pelvis and below. Position sense in the toes was intact, but

marked tenderness of the calf muscles, plantar hyperesthesia and atrophy of the calf muscles were present. The tongue was completely bald. There were dilated veins over the lateral walls of the abdomen extending up to the level of the axilla and down to the midthighs. The spleen was not palpable, but the liver extended to within a fingerbreadth of the umbilicus. There was no edema, ascites, jaundice or signs of congestive heart failure. The patient was given the same treatment as subjects in group C and in ten days showed sensory improvement in that vibratory sensation was now absent only in the toes. Continuing with the same diet, and beginning on the eleventh day of study, 10 mg. of synthetic crystalline vitamin B_1 was given by intravenous injection for thirty consecutive days. By the seventeenth day, i. e., following 60 mg. of crystalline vitamin B_1, the tenderness of the calf muscles had disappeared. By the twenty-sixth day, after 150 mg. of crystalline vitamin B_1, the plantar hyperesthesia had disappeared, but the ankle jerks had not returned and the vibratory sense remained absent in the toes. No further improvement occurred by the forty-third day, or after 300 mg. of crystalline vitamin B_1. At this time the dose of synthetic crystalline vitamin B_1 was increased to 50 mg. daily and continued for ten days, but there was no further improvement in the objective signs of polyneuritis. During his stay in the hospital the patient's weight increased from 132 to 155 pounds (60 to 70 Kg.), associated with a marked increase in strength. On admission it had been impossible for the patient to stand, but by the twenty-first day he could walk on a wide base, and on discharge the gait was considered normal.

The response in this subject, as measured by the objective signs of polyneuritis, was limited to improvement in the sensory status. Although objectively there was little improvement, functionally the ability to walk, probably occasioned by the marked gain in strength, is not to be ignored. The failure of the ankle jerks to return after 800 mg. of synthetic crystalline vitamin B_1 had been administered during forty-three days is due, we believe, to relatively irreversible anatomic changes in the peripheral nerves occasioned by the long duration of a mild vitamin B deficiency.

CASE 48.—A man, aged 35, a vagabond, admitted to the hospital Dec. 3, 1936, complained of marked weakness and pains in the legs and swelling of the ankles during the preceding few days. Because of the patient's mental status, a reliable history was unobtainable. Examination showed a moderately severe polyneuritis with absent ankle and knee jerks. The vibratory sensation was absent in the pelvis and below, but position sense was intact. There was marked tenderness of the calf muscles and plantar hyperesthesia but no muscle atrophy. In addition there was an icteric tint to the sclerae, and a firm but tender liver was palpable five fingerbreadths below the costal margin. There were a few dilated lateral abdominal veins, but ascites was not present and the spleen was not palpable. Edema of the ankles was noted on admission but disappeared by the next day, and there were no signs of congestive heart failure. The patient was given the same diet and vegex as the subjects in group C. At the end of ten days no improvement was noted. The patient was then given, in addition, 10 mg. daily of natural crystalline vitamin B_1 by intravenous injection for thirty consecutive days. On the forty-first day of study, after the administration of 300 mg. of crystalline vitamin B_1, the only improvement in objective signs of polyneuritis was the disappearance of the tenderness of the calf muscles. Beginning on the forty-second day, 50 mg. of natural crystalline vitamin B_1 was administered daily for five consecutive days. At the end of this period the plantar hyperesthesia had disappeared and the patient was able to walk unassisted but on a wide base; the knee jerks and ankle jerks, however, remained absent. Jaundice had disappeared but the liver remained palpable five fingerbreadths below the costal margin.

In this subject the improvement in the objective signs of polyneuritis was limited to the disappearance of muscle tenderness and plantar hyperesthesia. Functional improvement was limited to an improvement in strength. On admission the patient could not stand unassisted. At the end of forty-seven days of treatment, during which time he had received 610 mg. of natural crystalline vitamin B_1, he was able to walk unassisted, without a cane, but on a wide base. The lack of improvement in the objective signs of motor nerve involvement we believe to be due to relatively irreversible anatomic changes in the peripheral nerves occasioned by an acute vitamin B deficiency.

CASE 49.—A "man about town," aged 39, was admitted to the hospital Feb. 1, 1936, because of complete inability to care for himself. He had been drinking about one quart of whisky daily for the past ten years. His appetite had been maintained until five months prior to admission, when he noted its failure, and for the past month he had eaten very little. Examination six months prior to admission showed no evidence of polyneuritis, but on admission there was absence of all tendon reflexes in the upper and lower extremities, with a bilateral foot drop and weakness of the hand grips. There were no signs of congestive heart failure, but the liver was palpable, firm and slightly tender two fingerbreadths below the umbilicus. There were a few visible lateral abdominal veins. The spleen was not palpable. A fluid wave and shifting dulness could not be elicited. The patient was given the diet and vegex received by group C, plus 20 Gm. of a vitamin B concentrate[14] by mouth, bringing the vitamin/calory ratio up to 14. Within two weeks the foot drop, muscle tenderness and stocking hyperesthesia had disappeared. The biceps and triceps jerks had returned, but the knee jerks and ankle jerks remained absent. The vibratory sensation remained absent in the toes, but the position sense was intact. At the end of twenty-one days the knee jerks had returned and the patient was able to walk on a slightly widened base. He was then treated as an outpatient, taking approximately the same diet and vitamin B as in the hospital. By June 1 all signs of polyneuritis had disappeared except absence of ankle jerks. The liver was now palpable only on deep inspiration. This regimen was continued till December 15, at which time the patient was given 50 mg. of natural crystalline vitamin B_1 by intravenous injection three times a week for fifteen doses. The ankle jerks were still absent at the conclusion of this period.

This case illustrates an excellent sensory and motor response in a subject having an acute polyneuritis in all objective manifestations except a return of the ankle jerks. These are probably permanently lost, owing, we believe, to the severity of the vitamin B deficiency and the resulting irreversible neural lesion.

COMMENT

Additional evidence that vitamin B deficiency is the cause of the polyneuritis of the alcohol addict is furnished by a comparison of the response of subjects in group C and group D. The more rapid and complete improvement of the latter is definite. Since the two groups received identical weighed diets and oral vitamin B supplements, the greater response of group D can be attributed only to increasing the vitamin B intake over that received by group C, or to chance. In a previous study Jolliffe and Colbert[11] attributed the improvement of subjects in group B, as compared with the lack of response in group A, to doubling the vitamin B intake without otherwise changing the diet. They were at that time unable with certainty to attribute the greater improvement in group C than in group B solely to the increase in vitamin B, since not only the vitamin B intake of group C was doubled as compared with group B, but calories, protein, mineral salts and the other vitamins were also increased. Since group D in the present study received the same diet and oral vitamin B supplement as group C in this and in the previous study, we now believe that the greater improvement in group C as compared with

14. Rhyzamine B, Burroughs Welcome & Co., Inc., New York.

group B was due primarily to the increase in vitamin B; since the improvement was roughly proportional to the vitamin B intake, we do not believe that chance significantly influenced our results.

Although motor and sensory improvement occurred in patients receiving daily twice the predicted vitamin B requirement of a subject weighing 60 Kg., this was minimal. It was not until four times the predicted requirement was given daily that absent ankle jerks were observed to return within twenty-one days. We therefore believe that the dosage of vitamin B as frequently advised in the literature of many drug houses has been far too small. For curative results in vitamin B deficiency we believe that the intake of vitamin B should never be less than four times the patient's predicted requirement. We cannot say that 10 mg. of crystalline vitamin B_1 parenterally administered under these conditions is the optimum dosage. One-half the amount might have given equally good results, but doubling the 10 mg. dosage may still further enhance the results. These possibilities are under investigation. At present the determination of the optimum curative dose can be arrived at by clinical evidence only. A practical chemical procedure for the determination of vitamin B saturation, in place of the biological assay method of Harris and Leong,[15] is needed in order that each subject's vitamin B excretion in the urine may be followed at daily intervals over a long period of time. While such a method is desirable in following the mild cases of polyneuritis, it is almost indispensable in determining what the optimum therapeutic dose of vitamin B should be in those having a more severe polyneuritis. At present when the objective signs of polyneuritis fail to improve we are unable to decide whether the neuritis is on the basis of vitamin B deficiency, and, if so, whether the pathologic processes have gone on to irreversible changes or the patient is not yet saturated with vitamin B. Such problems occurred in subjects 47 and 48 after we had administered 300 mg. of crystalline vitamin B_1 intravenously, in addition to an oral intake of approximately four times the predicted requirement, and in subject 49 after eleven months of oral treatment. It may be that most of the vitamin B subsequently administered could have been recovered in the urine.

The rapid return of reflexes as noted in subjects 7,[11] 40 and 41 may occasion some surprise. This rapid recovery is not without precedent in the clinical experience of neurologists in other forms of neural disease, such as Landry's ascending paralysis.[16] In the avitaminotic B pigeon a complete inability to stand or fly may be replaced by normal activity within an hour following parenteral administration of vitamin B. When recovery follows so dramatically, it is inconceivable that actual nerve degeneration could be present. This statement is supported by numerous pathologic studies.[17] These observers rarely found significant histologic changes in acute experimental avitaminosis B. However, vitamin B unsaturation does lead to changes of the chemistry in the neural system.[18] These changes could reasonably produce physiologic alterations sufficient to cause areflexia and other signs of polyneuritis and, at the same time, be rapidly reversible following resaturation with vitamin B.

The disappearance of the ascites (in case 46) during the course of vitamin B therapy may have been due to a spontaneous remission. Though spontaneous remissions do occur in subjects having cirrhosis of the liver they are relatively rare, and we are inclined to believe that vitamin B played a part in this remission now lasting over eleven months. In subject 49 the liver was palpable below the umbilicus, but four months later it was palpable only on deep inspiration. This occurrence is not at all unusual in our alcohol addicts treated with vitamin B. It is possible that these large livers were not due to fatty cirrhosis but to congestive heart failure. If the latter is the true explanation, the large palpable liver was the chief or only sign of congestive heart failure in most of these subjects. We have treated five other subjects having cirrhosis and ascites. In four subjects, none of whom had polyneuritis, there was no clear evidence of beneficial response. In the fifth subject, who had polyneuritis, a beneficial response seemed to follow. Many subjects carefully studied and controlled over long periods will be required to establish the value of this therapeutic procedure in liver cirrhosis.

Although there was no reason to expect a difference in response to the administration of synthetic and natural crystalline vitamin B_1, we have, since the synthetic product was available, alternated our subjects between the two products. Equally good and negative results were obtained with the two, both in the subjects reported in this study and in our unreported cases.

SUMMARY

We have observed an additional group of seventeen alcohol addicts having uncomplicated mild polyneuritis who were given diets containing four times the predicted vitamin B requirement of a subject weighing 60 Kg. Alternate subjects were given by intravenous injection 10 mg. daily of either natural or synthetic crystalline vitamin B_1 for ten days. By every method of comparison the response of those receiving the crystalline supplement was better than that of the control group. Four histories selected from our group of subjects with more than a mild degree of polyneuritis illustrate problems encountered in the treatment of such subjects. Some patients having cirrhosis of the liver apparently respond by improvement to vitamin B therapy.

CONCLUSIONS

1. Vitamin B deficiency is the primary cause of the polyneuritis of the alcohol addict.

2. Improvement in the objective signs of polyneuritis in the alcohol addict varies directly with the vitamin B intake up to a point of optimum dosage, which, though not as yet determined, is definitely more than four times the predicted maintenance requirement.

ABSTRACT OF DISCUSSION

DR. GEORGE R. COWGILL, New Haven, Conn.: My experience in this field has been with experimental animals. I note that the patients were placed on basal diets with a fairly accurately determined vitamin B content, and known doses of the pure vitamin given in addition. These efforts to quantitize the clinical work constitute a real step forward. In our work with pigeons we learned that we could not obtain a satisfactory

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curative test unless we used a dose from three to five times the minimum daily weight-maintenance dose. It is perfectly obvious that the clinical experience just reported accords well with our animal experience. I have frequently had occasion to advise my clinical colleagues to use much greater doses of vitamin B in their work, and this advice was based on our experience with experimental animals. Drs. Goodhart and Jolliffe reported that occasionally a patient would show dramatic improvement following the administration of liberal doses of vitamin B. This is quite comparable to what has been observed in experimental animals. However, not all patients responded so well. The same dose of vitamin B administered to our dogs did not always yield the same results. Evidently we could not gage accurately enough the severity of the state of extreme vitamin B deficiency. It was for this reason that I gave up trying to assay chemical fractions for vitamin B by a curative method. Some of the patients received as much as 10 and in some cases 50 mg. daily of crystalline vitamin B. If it is assumed that the average man requires about 1 mg. daily, these seemingly large doses are from ten to fifty times the daily minimum. From experience I should say they are not excessive. Doses of this order of magnitude in relation to the minimum have been widely used with experimental animals usually with the desired success. If one were to attempt to give such doses of vitamin B in the form of vitamin-rich foods or the cruder concentrates, simple calculation will show that perfectly enormous amounts of these materials would have to be given. With the pure vitamin now available for clinical use, I have little doubt that trials of it in the clinic in these larger and appropriate doses will reveal numerous conditions as involving a serious lack of vitamin B as at least one feature of the syndrome in question. Can too much vitamin B be given? Recent tests by Molitor have shown that it is possible to kill mice, rats, rabbits and dogs by administration of enormous doses of crystalline vitamin B. The lethal dose appears to be from 25,000 to 50,000 times the daily normal requirement. If it is assumed that these results may be translated to the human species, it appears that the lethal dose for man would be from 25 to 50 Gm. of the pure vitamin.

DR. MARTIN G. VORHAUS, New York: Drs. Goodhart and Jolliffe have added another chapter to the work on alcoholism which has been in progress at Bellevue Hospital for some time. This paper is an important step forward toward a better understanding of vitamin B_1 therapy. The authors have presented convincing evidence that large doses bring a greater percentage of good results in polyneuritis than moderate or small doses. In our first communication my co-workers and I suggested a daily dose of 10 mg. of vitamin B_1 in severe cases or in those of long standing. This dose has been employed in many of the reported cases. Some questions with regard to vitamin B_1 therapy that have been raised are: What are the symptoms of an overdose of vitamin B_1? Is there a toxic dose of vitamin B_1? The authors have given 50 mg. of vitamin B_1 daily by intravenous administration and have not noted any signs or symptoms of toxic effect. This is in accord with our experience. We have given as high as 90 mg. daily by mouth without observing any untoward effect. From these clinical observations it may be concluded that very large doses of vitamin B_1 may be given safely. Of especial interest to me is the occurrence of certain side effects of vitamin B_1 therapy. I refer to such clinical observations as failure of reaccumulation of ascites and the reduction in the size of the liver in certain cases. That such changes may be only coincidental is admitted but it is very important to point out that the therapeutic value of vitamin B_1 is undergoing critical study at present and its limitations are still not clearly defined. Weiss and his associates have reported changes in cardiac function in some cases on vitamin B_1 therapy. We are studying alterations in bone structures in cases of gout and certain types of osteo-arthritis on large doses of vitamin B_1 over a long period of time. There is a great deal yet to be learned about vitamin B_1 therapy, but one point is becoming more definite—as the authors have indicated—that often the dose of vitamin B_1 is too small or administered for too short a period to serve as a basis for thoroughly evaluating its benefit in a given case.

DR. TOM D. SPIES, Cincinnati: In the past six years I have been making clinical observations along this line. I can corroborate almost everything that the authors have said. They have gone much farther than I in many respects. There are a few practical points that might be accentuated. I feel that the dose of 10 mg., or four times that, is very small. In other words, I think they have not gone far enough, because I have had to give as much as 500 mg. on several successive days to get an alteration in cases such as they classed as irreversible. There are two factors, I think, that enter into the treatment of these particular persons: one is the size of the dose and the other is the factor of time. I am not at all sure that the authors gave an adequate dose, and some forty-odd days is not long enough in many of the cases. It takes months, literally months. In general, I am sure that alcoholic polyneuritis is in part at least a nutritional disease, and I am equally certain that vitamin B_1 is a factor.

DR. ROBERT S. GOODHART, New York: We are attempting by various methods to determine the optimum dose of vitamin B. We are at present using 5, 20 and 50 mg. doses in an effort to determine this point more accurately. There is no reliable chemical method of analyzing the urine in determining whether or not these patients are saturated with vitamin B. There is evidence that the polyneuritis due to vitamin B deficiency is in the early stages a physicochemical phenomenon. We feel that when rapid improvement occurs following vitamin B therapy this is due to the action of vitamin B in rectifying these physicochemical alterations. When rapid response does not occur and there is no obvious change in the polyneuritis over a three to four weeks period we are inclined to believe that there has been some actual anatomic degeneration. We also wish to point out that these alcohol addicts are not on a diet deficient alone in vitamin B_1 and therefore other deficiencies may and do complicate the picture. For example, it has been demonstrated by men in this work that vitamin A deficiency may be responsible for a peripheral neuritis.

THE TEACHING OF BODY MECHANICS IN PEDIATRIC PRACTICE

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The purposes of this paper are first to reemphasize the importance of body mechanics as a necessary part of preventive pediatrics, second to review the mechanics of the body which determine efficiency and third to present a simplified and practical method of teaching which can be carried out in regular office practice and which has produced highly satisfactory results in my hands over a period of several years.

Efficient use of the body has so evidently a favorable effect on the general health and well being that it is accepted as an axiomatic point of departure by most writers on the subject. The bad effect of poor general health on body mechanics, with its attendant lack of muscle tone, lowered threshold of fatigue and lessened available mechanical and emotional energy, is also evident. It seems unnecessary to argue that poor body mechanics and ill health form a truly vicious circle, each in turn increasing the other.

The body, like any other machine, can be mechanically efficient only when all its parts can be most readily maintained in equilibrium. "Equilibrium maintained by the body in upright standing position is an active and not a passive one." [1] The starting point for efficient, graceful, strong movement must be equilibrium. Energy

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Owing to lack of space, the illustrations have been omitted here. They will appear in the author's reprints.

Read before the Section on Pediatrics at the Eighty-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 9, 1937.

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