THE USE OF BRITISH ANTI-LEWISITE (BAL) IN THE TREATMENT OF DIABETIC NEUROPATHY

Clinical Study — Preliminary Report

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BRITISH anti-lewisite (BAL) has been administered to 22 diabetic patients in the course of the last year, in an attempt to appraise its clinical value in the treatment of various neurologic complications of diabetes. This study was prompted in part by the report made by Furmanski[1] several years ago which indicated that some peripheral neuropathies other than those associated with heavy metal intoxication might be helped by the administration of BAL. At that time he reported 3 cases of peripheral neuropathy improved by its administration. It was postulated that neuropathies might represent biochemical disorders within the neuron, consisting of impairment of enzymatic function. Since the etiology and treatment of diabetic neuropathy require both clarification and improvement, it was decided to test the virtues of BAL in such cases.

This report summarizes the results obtained in these 22 patients, discusses briefly the theoretical aspects of the action of sulfhydryl compounds, interjects a word of caution regarding its use, and emphasizes its limitations.

Before the study was undertaken a number of important considerations required critical analysis. The first of these concerns the pharmacologic properties of BAL, only the more pertinent of which will be discussed. BAL (2, 3-dimercaptopropanol) is recognized as an extremely potent compound containing two sulfhydryl radicals; these sulfhydryl radicals have a great affinity for heavy metals. Many essential enzyme systems contain heavy metals within their chemical structures. Webb and Von Heyningen[2] studied the effects of BAL on enzyme systems, and showed that 7 were strongly inhibited by BAL. For example, polyphenol oxidase becomes inactivated in the presence of BAL but is reactivated when copper is added. Carbonic anhydrase, when inactivated with BAL, regains its activity upon the addition of zinc. BAL decreases the respiration of tissue slices and inhibits the activity of cytochrome C; in sufficient concentration it also destroys the activity of insulin,[3] apparently by interfering with its disulfide linkage.

Heavy metals usually produce toxicity because of their great affinity for sulfhydryl radicals present in the prosthetic group of many essential enzymes. For example: the concept has been accepted generally that trivalent arsenic blocks the metabolic function within the spirochete, as well as in human tissues, by combining with such sulfhydryl groups within enzymes. The application of BAL to the treatment of arsenical intoxication was based on its ability to

supply competing sulfhydryl radicals in order to protect, as well as to reactivate, previously affected enzyme systems. The reversibility of such biochemical processes is confirmed amply by studies such as those to which we have referred.

It is evident from animal experimentation[4] that the administration of heavy metals prior to the administration of BAL increases the tolerance of the animal for BAL. Toxic side effects, common in small doses in normal animals, do not result when much larger doses are given animals intoxicated by heavy metal. It is thus apparent that heavy metals are antidotes for BAL, and that BAL and other sulfhydryl compounds are antidotes for heavy metals. It appears evident, too, that the doses of BAL recommended for the treatment of heavy metal intoxication cannot necessarily apply to persons with diabetes, since it has not been ascertained that the neurologic manifestations of diabetes bear any relationship to heavy metal poisoning. The important initial consideration in this observation was the safety of BAL administration, particularly in the treatment of the diabetic patient. Throughout the entire investigation the doses employed were always maintained at a level far below the quantities recommended for the treatment of heavy metal poisoning. Exceptional care and precautions were observed throughout in the event that toxic manifestations (in terms of alterations in pulse, blood pressure, respiratory rate, and alterations in body chemistry) might become manifest.

Results

Twenty-two patients with diabetic neuritis have been treated with BAL during the course of the last year; each has been hospitalized during the period of therapy. Every patient had received varying periods of diabetic control with improvement in nutrition, and many had taken additional vitamins prior to BAL therapy. All had failed to respond to these customary measures of treatment. BAL was administered intramuscularly in an initial dose of 50 mg. on the first day and was increased to 100 mg. on the second day. The dosage generally remained at 100 mg. once or twice per day, although occasionally 3 doses were prescribed within a 24 hour period. The average duration of treatment was from 7 to 14 days. The results have been interesting and promising and, although not consistently favorable, have been sufficiently encouraging to justify a report. Among the 22 patients treated, 12 were definitely improved (table 1), and 10 were unimproved (table 2).

Among the 12 patients improved there were 9 (cases 1 through 8 and case 12) who had an accentuation of pain beginning from 5 to 15 minutes after the injection on almost every occasion. The intensification of the pain followed the distribution of the involved nerve or nerves, and persisted for from ½ to 2½ hours, following which the discomfort diminished or completely disappeared. Usually the pain became intensified following each subsequent injection and, as treatment continued, the pain disappeared completely except for the time immediately following injection. Occasionally it was noted that, after 4 or 5 injections (particularly if the size of the dose were kept constant), return

of the pain was not experienced until the size of the dose was increased, at which time the original type of pain might return. Patients did not always experience this phenomenon following each injection; it did not always appear after the initial dose, and sometimes not until after the second or third dose. This phenomenon was observed in 9 patients, none of whom were informed that such an occurrence might be anticipated. One of these was a physician (case 7) whose verbatim description of his subjective experience is included herewith:

"Fifteen minutes following each injection (timed by the clock) there was an abrupt modification in the subjective distress over the area afflicted. Anesthesia, or at times intense pain, occurred over the involved nerve segments as the reaction wore off; during the next 30 to 60 minutes the feet became warm and comfortable. Hyperesthesia and pain gradually diminished. At the termination of 11 injections some anesthesia is still present in the left great toe, but to a noticeably diminished extent. There is no hyperesthesia, no paresthesia, no burning, no deep-seated pain and no anesthesia of the remaining portion of the feet. There is no nocturnal exacerbation of symptoms. Minimal edema of the lower legs and ankles has disappeared. The skin of the feet and legs which showed trophic changes has assumed a healthy appearance."

Each of these patients experienced subjective improvement and some complete disappearance of pain after 10 to 14 days of treatment. Eight of the 9 have remained free of discomfort for periods of 1 month to as long as a year. The results have been uniformly satisfactory in this particular group with but one exception, a patient (case 12) who experienced an accentuation of the pain on 2 occasions, although treatment was conducted for a 13 day period. His symptoms disappeared but promptly recurred 2 days after treatment ceased, and he failed to respond to a second course of therapy. He has since committed suicide.

Among the 12 patients who improved, there remain 3 (case 9, 10 and 11) who obtained definite alleviation of pain, numbness, or burning in the lower extremities. None of these experienced accentuation of distress following any injection. In 1 patient (case 9) numbness recurred after 4 months and did not respond to a second course of treatment. In another (case 11) improvement has been maintained after a period of 4 months. The remaining patient (case 10) had complete relief from pain for a period of 6 weeks after which time it returned with original intensity; a second course of therapy was followed by complete relief for a period of 2 months, although she is at present under treatment for a third recurrence.

Among the 10 patients who were unimproved, there were 4 (cases 13, 14, 15 and 16) whose symptoms of numbness and paresthesiae had been present for 3, 4, 8 and 18 years respectively. Improvement was apparent in none, even though BAL was administered for periods of time similar to that of the first group. Therapy was interrupted in 1 person (case 21) after 5 injections had failed to cause significant alteration in the intensity of pain; this may have constituted an inadequate trial.

TABLE 1
SUMMARY OF 12 CASES SHOWING RESULTS OBTAINED IN THOSE RECEIVING GREATEST IMPROVEMENT FROM BAL THERAPY

Case	Age	Known Duration of Diabetes	Duration of Neuropathy	Duration of BAL Therapy	Total Amount of BAL Given	Immediate Result
1.	60	12 yrs.	7 mos.	13 days	1075 mg.	Accentuation of pain
2.	63	12 yrs.	6 mos.	9 days	1800 mg.	Accentuation of pain
3.	36	3 mos.	6 mos.	15 days	1700 mg.	Accentuation of pain.
4.	67	Found at time of first visit	18 mos.	10 days	900 mg.	Accentuation of pain
5.	64	14 yrs.	3 mos.	12 days	1150 mg.	Accentuation of pain
6.	56	7 yrs.	8 mos.	10 days	1300 mg.	Accentuation of pain
7.	43	9½ yrs.	2+ yrs.	11 days	375 mg.	Marked increase in pain. (See description.)
8.	54	7 mos.	1 week after diabetes was "controlled" 6+ mos.	8 days	850 mg.	Marked increase in pain each injection
9.	47	4 yrs.	3 mos.	8 days	975 mg.	Accentuation of pain
10.	58	3 yrs.	6 mos.	1st 13 days course	475 mg.	No accentuation of pain
				2nd 11 days course	1375 mg.	No accentuation of pain
11.	69	19 yrs.	5 mos.	20 days	1900 mg.	No accentuation of distress
12.	67	10 mos.	4 mos.	13 days	800 mg.	Intensification of pain after 2 injections

One patient (case 20) presented clinical evidence of severe peripheral vascular insufficiency accompanied by cyanosis of the feet upon assuming a dependent position. Advanced degrees of arteriosclerosis were demonstrated roentgenologically.

TABLE 1 (continued)

Results at End of Therapy		Ultimate Result
Sensory	Motor	
Complete absence of pain and numbness. Stopped codeine 5th day.	No change. Absent patellar and achilles reflexes.	No return of pain after 6 months.
Complete relief of pain and numbness.	Gait improved reflexes unchanged, vibratory sense unchanged.	No return of pain after 10 months.
Marked improvement. Occasional brief periods of pain.	No alterations.	No recurrence after 6 months.
Complete relief of pain, burning and numbness.	No alterations.	No recurrence after 4 months.
Complete relief of pain and burning.	No alterations.	No recurrence after 5 months.
Complete relief of pain and burning.	Diplopia improved.	Slight numbness returned after 10 mos. No pain after 1 year.
Complete relief of pain, burning and paresthesiae.	Trophic changes in skin and toe nails disappeared.	No return after 9 mos. in spite of acute peritonsillar abscess 5 mos. after therapy.
Complete relief of pain, burning and numbness.	No changes.	Therapy just completed. No return after 1 month.
Complete relief of pain and burning.	No changes.	Returned after 4 mos. Did not respond to second course.
Complete relief of pain.	No changes.	Returned after 6 weeks.
Complete relief.	No changes.	Returned after 2 months.
Complete relief of pain, coldness, dysesthesiae and feeling of constriction.	Loss of sensitivity of flesh, no motor changes.	No return after 4 months.
Complete relief of pain.	No changes.	Recurred after 2 days. No response to second course.

Another patient in the group of failures was a man whose first neurologic symptoms appeared upon awakening in another hospital after a 3 day period of unconsciousness due to insulin shock. He was thought to have suffered extensive cortical damage incident to his hypoglycemia, since he had noted

retrograde amnesia and a poor memory dating from that time. There was loss of two-point discrimination sense and astereognosis as well. Vurpas' sign, indicative of frontal lobe degeneration, was strongly positive.

Improvement failed to occur in still another patient (case 18), a man of 67 years, in whom neuritis had been present for a period of 6 months. He was totally uncooperative and objected to all forms of therapy from the beginning. There was evidence of advanced arteriosclerosis obliterans of the lower extremities, loss of vibratory sense and position sense below the knees, and absent patellar and Achilles tendon reflexes. Spinal fluid protein measured 85 mg. per cent. Repeated caudal blocks with 1 per cent procaine failed to effect relief of his pain; vascular exercises and vasopneumatic therapy were without benefit. A trial on BAL suggested initial improvement, but the patient complained so bitterly of pain at the site of injection that treatment was discontinued. A transorbital leukotomy failed to produce relief. He left the hospital under protest.

An additional patient (case 19) who failed to respond to BAL had an intercostal neuralgia with a zone of anesthesia comparing to the 9th dermatome. X-rays of the dorsal spine showed an extensive osteoarthritis. His pain was diagnosed as a parietal neuralgia, either secondary to osteoarthritis or possibly the result of diabetic neuritis. A 12 day course of BAL failed to relieve the pain, but it was immediately alleviated by the introduction of novocain into the contralateral cervical sympathetic chain. It is not clear whether diabetic neuritis or radiculitis caused by osteoarthritis occasioned the pain. This case is included, nevertheless, as a failure.

The remaining patient in this group (case 22) may not have had diabetic neuritis because fever, a rapid sedimentation rate, and a questionable destructive lesion in the 3rd lumbar vertebra were observed. Her pain was relieved by x-ray therapy.

Toxic Reactions

No serious toxic reactions occurred in a single instance. Local discomfort at the site of the injection varied from no pain at all to a severe, burning variety. The local distress was usually of short duration and not of sufficient intensity (except in the foregoing case) to discourage further injections. Inflammatory reactions at the site of injection were not evident. Intensification of the pain, which appeared at first to indicate an undesirable side effect, may actually represent a good prognostic sign, since the persons experiencing this reaction obtained the greatest amount of improvement and have shown the least tendency toward recurrence. Alterations in respiratory rate, blood pressure, or pulse and body chemistry did not occur under BAL therapy. There was no alteration in insulin requirements in a single patient. This conceivably might not be true should larger doses of BAL be employed, but this investigation was not for the purpose of ascertaining the maximum level of tolerance of diabetic persons to intramuscular BAL therapy.

Discussion

The frequent occurrence of neurologic abnormalities in diabetic patients prompted earlier students to consider the central nervous system as the site of the basic lesion in diabetes. In 1864 De Calvi first postulated that the neurologic manifestations were complications of the diabetic state. Since that time much has been written concerning the nervous system in diabetes. Lesions have been described in the brain, the spinal cord, posterior nerve roots, sympathetic ganglia, and peripheral nerves. It would appear that no part of the nervous system is entirely immune, although symptoms are noted more often in the lower extremities.

Little is known concerning the etiology and pathology of diabetic neuropathy. The neurologic features evident in diabetic patients represent a far from clear-cut syndrome. Because this syndrome may be diffuse or disseminated, often representing a bizarre picture, it is difficult to evolve an accurate clinical classification of diabetic neuropathy. It may occur with many symptoms and few signs, with few symptoms and many signs, or a combination of both. It is for this reason, in part at least, that any new approach at therapy makes accurate evaluation impossible.

Widespread involvement of the nervous system may be manifested by such distressing symptoms as neuropathic foot simulating Charcot's joint, nocturnal diarrhea, bladder paralysis, abnormal pupillary reaction, and ocular muscle palsy. Complications that have advanced to this degree are probably irreversible.

A number of explanations for the neurologic manifestations of diabetes have been offered, including vitamin deficiency, dehydration, toxic factors, hyperglycemia, cachexia, ketosis, and arteriosclerosis, either within the nutrient vessels of the brain or spinal cord or within the vasa neurorome. More than one factor is undoubtedly important and the pathogenesis of diabetic neuritis cannot be fully appreciated until examination of considerable histologic material has been made from patients intensively studied during life. While considerable attention has been devoted to the use of vitamin B and other food supplements in treatment of this complication, results have not been encouraging.

Careful histologic studies of the nervous system in diabetes made by Woltman and Wilder[5] disclose the presence of arteriosclerosis of the nutrient vessels of the nerves which they consider an important factor in the production of diabetic neuritis. While undoubtedly important, arteriosclerosis may be the principal limiting feature in the development of any therapeutic procedure capable of producing uniformly good results until vascular degeneration can be prevented or overcome. Thus the cause of the complication is as obscure as the pathogenesis of the underlying disease.

A further limiting factor which prevents any accurate conclusion in the establishment of a new therapeutic tool for the treatment of diabetic neuritis is the variability in the behavior of the complication. It is unrelated to the severity of the diabetes or to the insulin requirement. Neuritic symptoms may

TABLE 2
SUMMARY OF 10 CASES TREATED WITH BAL SHOWING LITTLE OR NO IMPROVEMENT

Case	Age	Known Duration of Diabetes	Duration of Neuropathy	Duration of BAL Therapy	Total Amount of BAL Given	Immediate Result
13.	50	6 yrs.	4 yrs.	11 days	2100 mg.	? Improvement
14.	58	11 yrs.	3 yrs.	8 days	860 mg.	? Improvement
15.	65	3 yrs.	18 yrs.	10 days	2400 mg.	None
16.	61	9 yrs.	8 yrs.	10 days	2100 mg.	None
17.	57	13 yrs.	8 mos.	10 days	550 mg.	None
18.	67	4 yrs.	6 mos.	5 days	300 mg.	None. Refused further doses
19.	62	10 yrs.	3 mos.	9 days	1200 mg.	None
20.	69	3 yrs.	2 yrs.	9 days	1600 mg.	None
21.	53	21 yrs.	4 mos.	4 days	350 mg.	None
22.	54	4 yrs.	1 mo.	24 days	4800 mg.	None

be the first indication of the presence of diabetes, may never occur during a lifetime of diabetes, or may appear only as a late manifestation. Once present, diabetic neuritis may improve slowly with the management of the underlying hyperglycemia and glycosuria. Conversely, it may make its first appearance after the disease has been brought under control; however, in the majority of instances, it runs a chronic course which appears to be its most constant feature. Seldom do the symptoms change appreciably over the period of a few weeks but rather slowly over a period of months or years. This particular feature of diabetic neuritis is emphasized when reviewing the results of cases treated with BAL.

Since diabetic neuritis occurs among well-controlled diabetic patients as well as among those who are poorly controlled, diet and insulin, still the basic essentials in the management of any complication of diabetes, are often inadequate methods of treatment. Vitamin therapy has not produced recovery

TABLE 2 (continued)

Results at End of Therapy	Ultimate Results	Remarks
None	None	Neuritic symptoms present 4 years.
Pain gone	Symptoms returned in 2 weeks	Neuritic symptoms present 3 years.
None	None	Neuritic symptoms present 18 years.
None	None	Neuritic symptoms present 8 years.
None	None	Onset of symptoms dated to insulin shock. Retrograde amnesia, loss of 2 point discrimination astereognosis + Vurpas' sign.
None	None	Uncooperative. Failed to secure relief from caudal blocks, vasopneumatic therapy and transorbital leukotomy.
None	None	Extensive osteoarthritis dorsal spine. Pain relieved by novocain injection of contralateral cervical sympathetic chain.
None	None	Extensive arteriosclerosis of leg vessels. Dependent cyanosis. Oscillometric readings ¼ right, ½ left.
None	None	Discontinued because pain was atypical and no altered by injections (inadequate trial).
None	None	Diagnosis questioned. Had rapid sed. rate, fever, ? destructive lesions lumbar spine. Pain relieved by x-ray therapy.

either uniformly or consistently and, in general, has been disappointing. Because of the multiplicity of the problem of diabetic neuritis and the lack of uniformly satisfactory therapeutic procedures for its relief, the investigation of any new adjunct to therapy seemed desirable and justifiable.

The experience gained in the study of these 22 cases does not permit final conclusions. Several observations, however, appear to be of sufficient importance to justify further investigation of the real value of BAL therapy. The first of these is the intensification of the pain following the injections of BAL in those patients who received maximum benefit. Experiments wherein radioactive BAL is administered[6] demonstrate its rapid elimination, the greater part being quickly metabolized and excreted in the urine. It enters the circulation from an intramuscular site within 5 minutes and reaches a maximum blood level within an hour. A constant blood level is obtained for the first 2 hours, is reduced by one-half at the end of 3 hours and to one-third at the end

of 7 hours. Eighty per cent enters the circulation and is distributed throughout the body 1 hour after injection. It is entirely gone from its intramuscular site at the end of 6 hours. Only a minute amount is excreted by the lungs. Forty-five per cent of the total is in the urine within 6 hours, and 81 per cent within 24 hours. Hence it is not significantly cumulative in 4 hour doses. Side effects, when they appear, are transient and when symptoms do occur disappear in 2 to 3 hours.

When one compares the rate of absorption of BAL and its known blood concentrations after administration with the time of appearance and the duration of the intensification of pain in patients who obtained the greatest improvement from treatment, the correlation seems more than mere coincidence.

The other feature deserving further consideration is the degree of improvement manifest within a short period of time. Gradual disappearance of pain over a period of 7 to 14 days of BAL therapy demonstrates a striking contrast to all other therapeutic measures employed in the past. The reappearance of pain at intervals following a course of therapy, and the subsequent response to a second course, at least in some patients, are matters of additional interest.

These observations suggest that whatever benefit sulfhydryl compounds may exert in management of painful neuropathy of diabetes must come about through a biochemical change rather than by a regeneration of damaged nerve tissue. The complete failure experienced in some cases although disappointing is not necessarily surprising, particularly if multiple factors are responsible for the development of the neurologic complications. It is understandable that, where arteriosclerosis is the major factor responsible for nutritional changes within the nerve fibers, anatomic and structural changes may well have advanced to an irreversible stage.

An especially disappointing feature is the inability to demonstrate improvement in the neurologic signs. Although vibratory sense improved in some patients, and muscle tone in many (together with diminution of tenderness along the peripheral nerves and muscles), no constant improvement in reflexes or other neurologic signs could be elicited.

Subjective improvement in symptoms of numbness and paresthesia often could be noticed by the patient from day to day; with continued therapy, the numbness which originally might have extended to the knees would gradually become more and more peripheral, tending to persist in the feet and toes for the longest period of time. Occasionally it would remain in these areas for some days before abating, or persist in the toes permanently. Frequently, the patient would report that he was able to sleep comfortably throughout the night, that he could tolerate the weight of bed clothing against his limbs, and that his feet were no longer cold.

In one person trophic changes in the skin and nails of the lower extremities underwent profound alteration. The atrophic skin became normal in color and began to desquamate in normal fashion. Yellow discoloration of the toenails, which had been present for 2 years, gradually disappeared as the new nail grew in.

One patient with diplopia due to ocular muscle palsy experienced im-

provement but not complete disappearance of the double vision. Two patients in whom codeine addiction had been feared voluntarily discontinued the use of narcotics after 4 and 7 days respectively.

Summary

Conclusions as to the ultimate value of BAL in the management of diabetic neuritis are at present unjustifiable. The results obtained in the 22 cases reported, however, are encouraging. BAL in the doses employed was well tolerated by patients with diabetes; there was no evidence that the underlying diabetes was intensified or that the insulin requirement was altered. Undesirable side effects were limited to pain at the site of injection. Because serious side effects (known to accompany larger doses of BAL) were avoided, the maximum tolerance for BAL by patients with diabetes was not established. Since the drug is rapidly disseminated and eliminated within a period of 6 hours, it is theoretically possible that its administration every 6 hours might prove more beneficial than under the schedule employed.

The possible merits of other sulfhydryl compounds, such as glutathione, cysteine, and BAL-glycoside (BAL intrav) should be studied, particularly since the latter has a much lower LD-50 than does BAL. The great difference in response to BAL in these 2 groups of patients suggests that a better classification may be possible in cases of diabetic neuritis, and its real therapeutic value may be limited to those who experience intensification of symptoms. Inasmuch as several of the more protracted cases of neuropathy failed to respond, early treatment may be important for a better therapeutic score. Possibly the combination of earlier treatment and more frequent doses of BAL or some other sulfhydryl compound may aid materially in the management of this complication. BAL must be considered only as an adjunct to the treatment of the neuritis and the underlying therapy must consist of the management of the diabetes itself.

It is natural to assume that zinc, a constituent of all commercial insulins, might be the agent responsible for the production of the neuritis. This seems unlikely, however, since neuritis has occurred in patients who have never taken insulin, and existed long before its advent. Presumably the mechanism of BAL action in such cases bears no relationship to the removal of heavy metals from the nervous system itself.

Conclusion

Twenty-two patients with diabetic neuropathy have been treated with BAL; 12 have been relieved of their pain and, to a large extent, the subjective distress attending the neuritis. Eight of these experienced an intensification of pain following almost every injection and have remained free of recurrences. Four showed no intensification of distress but tended toward relapse. Ten patients experienced no benefit. A possible explanation for failure has been presented and a recommendation for early treatment has been advocated.

Note of Caution

For the present the size of each individual injection of BAL should be maintained at a low level until further experience indicates that larger doses can be employed safely. Since this highly volatile substance loses much of its potency upon exposure to air, the unused portion of the ampule should be discarded and a fresh ampule used for each injection. The accepted standards in the management of diabetes, including diet and insulin, should not be disregarded. BAL must be considered a possible adjunct to the management of this complication, and reserved only for those patients in whom established forms of therapy have proved ineffective.

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