PYRIDINE NUCLEOTIDES IN THE PREVENTION DIAGNOSIS AND TREATMENT OF PROBLEM DRINKERS A Preliminary Report

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The author has successfully utilized the pyridine nucleotides, particularly the Diphosphopyridine Nucleotide, in its oxidized form, in the prevention, alleviation and removal of the acute and chronic symptoms of alcoholism. The capacity of a group of severe chronic alcoholics, to metabolize rather large quantities of alcohol without the development of loss of control and toxic symptoms previously manifested on much smaller quantities of alcohol, was restored.

Not only was this effect achieved while the pyridine nucleotides were being administered, but with the administration of the proper dosage and concentration of Diphosphopyridine Nucleotides, it was also possible for the patients on several subsequent days following the administration of a single treatment, to drink rather large quantities of alcohol without developing their characteristic toxic response, namely decelerate conducts, loss of control over their drinking and the insatiable craving which is so typical of this group of patients.

The pyridine nucleotides were administered to the patients chiefly through the intravenous and intramuscular routes, since these methods make possible a more accurate and rapid evaluation of the response of the patient to the therapy. Other methods of administration are being investigated.

PROBLEM DRINKING

Alcoholism is a disease it has been officially defined as a disease by the American Medical Association. In the United States it ranks fourth as a most serious public health problem. It has nearly 6 million victims in the United States alone and by its nature, deeply affects the lives of about 24 million people who comprise the immediate family. This number is being increased annually at the rate of at least 250 000 persons.

It is estimated that one out of every 16 persons who drink is, or will become, and alcoholic. Alcoholism is no respecter of persons, male or female, nationality or creed. It is evenly distributed throughout the social drinkers of all levels of society. Contrary to public opinion, only 7% of alcoholics are to be found at the skid road level.

What is more shocking is that less than 10% are receiving therapy of any kind. This means that there are more than 4 500 000 hidden alcoholics in the United States alone, hidden from all but their immediate families and associates. They

are hiding and suffering and dying because they and their families are ashamed of their disease, ashamed to face it and seek help. They are ashamed because most people believe that alcoholism is a moral, personality and character weakness.

This misconception and resulting stigma developed because of failure of the writers and scientists to differentiate between alcoholism and drunkenness, between the sick alcoholic and the deliberate drunkard. The true alcoholic fights desperately for control of his drinking and hates to become drunk. The drunkard cares little for control, and strives chiefly for the oblivion of drunkenness. As pointed out by Lemere the common denominator of all problem drinkers is the inability to drink in a controlled manner.

In addition to the 6 million recognized and accepted problem drinkers, there are the uncounted millions of "heavy social drinkers" in the twilight zone of problem drinking whose health is being adversely affected in varying degrees and whose general course is slowly and surely progressing toward the state of overt alcoholism. A more detailed study of this group is in the process of being written and will be published by the author as soon as completed.

THE INTOXICATED STATE

Problem drinkers are of two classes: Class A is a true type alcoholic. This individual suffers from an innate constitutional intolerance to alcohol. Progression of alcoholism in this type is markedly constant from the beginning of social drinking. Symptoms and findings develop on a time-ordered basis and can be measured or predicted with a reasonable degree of accuracy. This author's research findings indicate that this group represents 65% of problem drinkers.

Class B this is the escape drinker. Here the intolerance of alcohol is acquired by sheer frequency and volume of intake over many years. This individual exhausts body metabolic capacity for alcohol and thereafter the intolerance is permanent.

In 1940, the author, working with Voegtlin, Lemere, and Chas. A. Shadel+, planned a research program whose scope was to cover investigation of all possible facets of causation of alcoholism, from a physical, physiological, biochemical, neurological, psychological, sociologic and hereditary standpoint. The ultimate goal was to be the development of a specific therapy for the

intoxicated state. The author believes that Diphosphopyridine Nucleotide therapy is a major advancement toward the achievement of his goal.

The first major project completed was the glucose tolerance study done on 303 alcoholic patients (3 op.cit.) This study failed to reveal any consistent pattern of variance from the normal glucose tolerance curve, which could be correlated with the severe intoxicated state manifested by the patients who were studied.

Numerous glucose tolerance studies on alcoholics by other workers since that time have revealed a wide variation of results.

A battery of liver function tests which included from 9 to 12 of the most widely accepted and commonly used tests now in use, was also begin, at that time. Although the profile which these tests developed was positive in the more advanced cases, and in spite of the fact that the number of individual tests which we have now performed is in excess of 85 000, the overall results of the program from a standpoint of specific information have been disappointing. However, in some cases the liver function profile proved quite useful as a warning of impending liver failure and was positive frequently enough to prove to our satisfaction that the liver, along with the central nervous system, was one of the two organs chiefly involved in the disease of problem drinking.

Concurrently, the author and Lemere were conducting extensive investigation in the psychological and neurological phase of the causation through a continuing program of narcoanalysis and narcotherapy. Although this program was started in 1941, and is continuing as of this date and the series of patients so studied now numbers over 4 000, we have as yet failed to find a psychological factor common to the majority of patients, which could be considered of major etiologic importance.

From a sociologic standpoint, Wellman in a study of 830 patients, found the subjects to be quite evenly distributed throughout the entire stratum of society from the highest to the lowest, from a social, economic and intellectual standpoint.

It was in the physical examination that this author consistently elicited the findings, which he believes is a reflection of the true etiology of the disease of problem drinking. These are the neurological findings of nervousness, restlessness, irritability and tremor of the upper extremities and extended tongue, which are almost invariably present in a problem drinker early in the withdrawal phase. A detailed discussion of these and other pertinent physical findings elicited from the physical examinations performed on 10 000 alcoholic patients has been published elsewhere.

THE PYRIDINE NUCLEOTIDES

Early in the experience of the writer it became apparent that the major part of the toxic state and symptomatology was not due to the "alcohol" effect alone, but rather to the accumulation of the more toxic metabolites of alcohol in the system of the patient. Specific reference is made to the acetaldehyde, to acetoacetic acid, oxaloacetic acid, lactic acid and other metabolities which follow consumption of alcohol, and whose presence in the system of these patients precipitates such gross evidence of a severe toxic state of the nervous system.

Since these substances are metabolized late in the process of oxidation of alcohol, the author chose coenzymes, namely the pyridine nucleotides, as the substances most likely to succeed in rapidly removing these toxic metabolities from the nervous system of a patient suffering from their presence. Since dehydrogenation is a major step in their removal, the oxidized form Diphosphopyridine Nucleotide was chosen for the preliminary investigation although other forms have been used.

Because evaluation and equilibration are most rapidly and accurately achieved by the intravenous and intramuscular routes of administration these were the methods chosen for the initial patients. However, the oral and other routes of administration are currently being studied. The dosage varied from 300 to 1000 mg. intravenously, depending upon the need of the patient. Intramusularly, the dosage varied from 50 to 150 mg. per dose being given only after the patient's tolerance level had been determined.

TECHNIQUE

A group of 20 of the most severe types of chronic alcoholic patients was chosen for the initial study. Diphosphopyridine Nucleotide in the oxidized form was given in dosages ranging from 300 to 1000 mg. The coenzyme was dissolved in a solution of sterile normal saline to a concentration of 3 mg. per cc. and was administered by slow drip.

The rate of administration depends strictly upon the individual patient's ability to absorb the coenzyme but the average rate of tolerance for this solution was from 20 to 30 drops per minute. Most of the patients could tolerate 20 drops per minute with no difficulty. If the solution is administered too fast, the patients complain of headache and marked shortness of breath, which quickly disappears when the rate of flow is slowed to below 20 drops per minute. Care should be taken when first starting the intravenous solution that this rate is not exceeded, then the medication can be administered with no distress whatsoever to the

patient. To date there has been no toxic effect whatsoever from the administration of the coenzyme.

RESULTS

Two of the patients were in delirium tremens and one of these was also having alcoholic convulsions of grand mal proportions at the rate of 3 to 4 convulsions per hour. This patient was given 1 gram of the coenzyme at the rate of 24 drops per minute. In one hour's time the convulsions had ceased and did not recur, the delirium had disappeared, the patient's temperature which was 103° when the I.V. was started, had dropped to 100° and the patient was mentally clear, cooperative and well oriented as to time, place and persons. This I.V. was

administered in the evening and after it was discontinued the patient had approximately 6 hours of normal restful sleep. The following morning he was hungry, ate a good breakfast, and was able to shave himself without difficulty. The second gram was then administered at the same rate and dosage. Following this treatment, the facial oedema, which had been massive disappeared; the patient ate a hearty lunch and was permitted to be up and about the room. That evening he complained bitterly because he was not permitted to attend to some bookwork, which he had neglected.

The second, a 31 year old white male, had been in delirium tremens, but was in a state of alcoholic stupor at the time the medication was started. The patient was given 0.5 gram. Of the coenzyme in 165cc. of sterile normal saline by I.V. drip at the rate of 28 drops per minute. In exactly 35 minutes this patient was completely sober, mentally clear and on objective psychometric and neurometric tests which were given to him immediately, his average score was 90% of normal function. He also complained of severe hunger and immediately after treatment partook of a general diet with liberal servings. There was no recurrence of his delirium tremens, and he expressed complete freedom from the craving for additional alcohol, which is so common in the withdrawal phase with other types of therapy .

The remaining 18 patients were in various stages of intoxication, ranking up to the sober state. A detailed analysis of the chemistry and results obtained in this group will be published as soon as completed.

In addition to the above, 2 healthy male nonalcoholic were give 100 and 200 cc. of alcohol on successive nights, both with and without the coenzyme intravenously. They were given 1 gram of the coenzyme intravenously and 200 mg. intramuscularly in divided doses previous to the intake of the alcohol. Briefly, it was learned that without the coenzyme, intoxication and severe "hangover" were

inevitable. With the coenzyme the alcohol effect was obtained but the intoxication and "hangover" were completely absent.

DISCUSSION

In order to evaluate and equilibrate objectively the dramatic, clinical and metabolic effect of the coenzyme, an alcohol tolerance test has been developed. This accurately correlates and calibrates the blood alcohol curve resulting from a given amount of alcohol with the blood acetaldehyde curve resulting from that. Technique and details, as well as results obtained with this test, will be published soon. Briefly the tests of the acetaldehyde level of the blood employ the enzymatic degradation technique developed by Kline and Kortzis in Frankfurt, Germany. We are well pleased with the accuracy and effectiveness of the test in our experience so far. The test clearly demonstrates that the coenzyme

thoroughly and with remarkable rapidity, either removes or reduces to negligible quantities the acetaldehyde from the blood stream of the patient.

As an additional objective calibration of the effect of the coenzyme upon the brain and central nervous system, in a particular effort aimed at testing intracellular activity of the coenzyme, the Diphosphopyridine Nucleotide was administered intermittently during the process of electroencephalography with the following results. A white male patient, aged 45, with a history of recent convulsions secondary to chronic alcoholism was prepared for electroencephalography using an 8 channel standard Grass machine, a disorganized low voltage rapid rhythm type of tracing, seen in this type of patient was obtained in all leads. While the encephalograph was running the standard I.V. solution of the coenzyme was started at the rate of 24 drops per minute. In exactly 19 minutes, normal alpha rhythm appeared in the left hemisphere, the voltage increased to normal and the rate dropped from 20 to 30 cycles per second to 12 cycles per second. Upon discontinuing the I.V. solution of coenzyme after a dosage of only 211.5 mg. there was a deterioration in the quality of the tracing to a rate of 16 to 18 cycles per second. There was also a reduction in the amount of alpha rhythm and organization present, but even the photo stimulation failed to completely reverse the improvement which had taken place in the tracing following the administration of the coenzyme.

CONCLUSION

- Dramatic improvement has followed the administration of Diphosphopyridine Nucleotides to patients suffering from acute and chronic alcoholism.

- Evidence has shown that by proper administration in adequate dosage, the coenzyme greatly reduces, and in some cases completely removes the

"craving for alcohol" which is responsible for alcohol addiction and which

is so characteristic of this disease.

- An alcohol tolerance test has been developed which has proven extremely useful, not only in diagnoses but as a guide to therapy. This test also offers possibilities as a screening device for the detection of the undeveloped alcoholic.

- By use of the alcohol tolerance tests for early detection and the Diphosphopyridine Nucleotides prophylactically there is real hope for preventing addiction in the undeveloped alcoholic.

- Administered either intravenously or intramuscularly at the proper rate, no side effects or toxic reaction has been noted to date from

Diphosphopyridine Nucleotides.

- Objective evidence of the beneficial effect of Diphosphopyridine Nucleotides has been demonstrated by the Alcohol Tolerance Test of Freund.

- Further evidence of the beneficial effect of Diphosphopyridine Nucleotides on the brain has been demonstrated by rapidly converting abnormal electroencephalograms to normal tracings by the administration of the coenzyme to patients both during and after the process of electroencephalography. Subsequent rechecks of these electroencephalograms show the tracings to be remaining normal.

- Administration of the coenzyme to social drinkers consuming large quantities of alcohol on an empty stomach, while not influencing the normal alcohol effect, greatly reduced intoxication and prevented hangover completely!

- It should be thoroughly understood that the use of this coenzyme is in no way intended to make social drinkers out of alcoholics! Rather, its use is aimed at restoring their health, removing the craving for alcohol and assisting them in maintaining complete sobriety!