The NAD Deficiency Diseases

John P. Cleary, M.D.[1]

Introduction

Vitamin B3 occurs in two forms, nicotinamide and nicotinic acid. They were first isolated from liver in 1937 by Conrad El-vehjem and shown to be what was then called the PP factor or pellagra preventative factor. The name was later changed to vitamin B3, commonly called *niacin* for the nicotinic acid form and *niacinamide* for the amide form. Soon after, a synopsis of the early research on the compound was published in 1941 by the Merck Company. The coenzymes NAD and NADP which niacin makes are essential for many enzyme reactions in the energy production systems of all cells. Before a total picture of the importance of NAD could be discussed, research was apparently interrupted by World War II.

Low cell energy levels cause disease. Multiple etiologies cause low cell energy; for example, low NAD levels, lipophilic toxins like HCB, DDT and other chlorinated hydrocarbons, and the newly discovered w3EFA deficiency, are known causes of energy deficiency at the cellular level. Cellular transport of hydrogen ions and electrons across lipid membranes like the cell membrane and mitochondrial membrane can be damaged by the presence of large numbers of HCB or DDT molecules. These act as insulators to the transmission. Likewise the absence of w3EFA would impair electron and hydrogen ion transfer. However, several diseases can be cured at their early stages by raising NAD levels, which corrects impaired cellular energy production caused by low NAD. These diseases include what are now diagnosed as alcoholism, pellagra, diabetes, hypertension, heart failure, and some early porphyrias.

[1] 2937 Monroe Street Madison, WI 53711

Meat is Most Abundant Source of B_3.

In the thousands of years which preceded the advent of agricultural societies, our ancestors apparently derived over a third of their average daily calories from meat. Eaton and Konner (1985) studied contemporary hunter-gatherers and compared studies from archaeology and paleontology to estimate that the pre-agriculturalist consumed ten times the amount of red meat, a large portion of which was liver probably, that the average American now consumes. Coronary heart disease, hypertension, diabetes, and some types of cancer have emerged as dominant health problems only in the past century and are virtually unknown among the few surviving hunter-gather societies, according to Trowell. Since the development of agriculture, humans have been susceptible to what I call the niacin deficiency or NAD deficiency diseases, through a partial adaptation to less meat in the diet. As even the Krebs cycle does not function without the coenzymes NAD and NADP a steady supply is necessary, and is obtained through niacin, as niacin makes NAD. An active man would have had to eat 5000 calories of skeletal meat per day to obtain 125 mg of niacin, but the partial substitution of liver would reduce calories and increase abundantly the amount of niacin. The recommended daily allowance is a mere 20 mg of niacin, and this false assumption is the basis for much disease today.

The Predator Response Mechanism Hypothesis.

Man is carnivorous, man is a predator, and the struggle is an old one. Built onto the primitive part of the brain is a simple mechanism to regulate the behavior of the predator. It is a trigger which is activated when levels of NAD become low, and NAD receptor sites are left uncovered. The predator seeks niacin at this point. One could

say the need is a purely chemical one, a need to cover those receptor sites. The early agriculturalists quickly found a means of subduing the unwanted predator response, with alcohol, which forms tetra-hydrisoquinone, a substance which binds to opiate receptors in the brain.

It appears that about 10% of our genetic pool is severely NAD deficient. Modern day society no longer benefits from that percentage of humans who are better hunters than the rest; leadership in the hunt now gives us instead the violence and drug addiction of that group's inability to deal with its extreme predator response.

When intake of niacin is needed, humans are also able to compensate with prolonged exercise, which generates endorphins to saturate the NAD receptor sites and thereby relieve the restlessness and irritability of the predator response mechanism. Nicotine in tobacco is a vaso-constrictor that relieves the pangs of niacin deficiency or hunger, but alcoholics and drug addicts exhibit a highly visible predator response when unable to obtain more alcohol or drugs to saturate the receptors. If we understand this predator response mechanism and the role of niacin, we can have a means of treating and preventing the addiction.

Discovery of the Niacin Treatment for Alcohol Addiction.

In the course of treating twelve alcoholic patients with 500 mg nicotinic acid daily it has become apparent that this dosage is an effective, inexpensive and rapid correction of the metabolic disorder which we label alcoholism (Cleary, 1985). Searching the literature, we find that the research to prove this has already been done. At the International Titisee Symposium held in the Black Forest in Germany, Lieber (1982) showed that the chemical reaction which breaks down ethanol to acetaldehyde is accelerated in chronic alcoholics. The second step in the chemical breakdown of acetaldehyde to acetic acid is decreased or slowed down in chronic alcoholics. The net result is an elevation of acetaldehyde in the alcoholic patients as compared to control subjects. Davis and Walsh (1970) showed that this acetaldehyde condenses with dopamine in the brain to form a morphine-like substance called tetrahydropapoveroline. They postulate that this substance is the cause of addiction in the alcoholic.

Lyon and Anthony (1982) have shown that a morphine antagonist, naloxone, is able to relieve coma caused by alcohol ingestion. Dr. Vastola, Madison, Wis., has successfully used intravenous morphine to relieve the symptoms of withdrawal in alcoholic patients. I believe alcohol addiction is caused by morphine-like substances believed to be generated from acetaldehyde and dopamine in the brain. Nicotinic acid is needed to oxidize alcohol and reduce acetaldehyde levels, as well as provide enough niacin to make in addition adequate extra NAD to saturate receptors in the brain.

Probably the first physicians to treat acute alcoholism with niacin, successfully, were Mainzer and Krause (1939), who reported that success in the British Medical Journal. Dewan (1943) published that nicotinic acid was essential for the oxidation of alcohol by rabbit brain tissue. Eriksson (1974) published that in rats, giving excess nicotinamide will cause the acetaldehyde level to be cut in half as compared with control animals. The same effect occurs in humans, and I am convinced this is the way to break the addiction cycle in alcoholics, because I have done so for two years, using 500 mg NIC daily on alcoholic patients (Cleary 1985).

NAD Used Parenterally to Treat Alcohol and Drug Addictions.

Paul O'Holleran (1961) published to an unreceptive medical audience his results of a study supported by Abbot Laboratories at the Shadel Hospital Research Department, in Seattle, Washington. He reported that he was able to treat both alcohol addiction and all types of drug addiction with the coenzyme Diphosphopyri-dine Nucleotide, which is the old name for NAD, a coenzyme which the body makes out of the vitamin nicotinic acid (niacin). His study was on 100 patients addicted to heroin, pantopone, morphine, dihydro-morphine, meperidine, codeine, cocaine, amphetamines, barbiturates, and

tranquillizers. He used NAD, or Diphospho-pyridine Nucleotide, which he called DPN, intramuscularly or intravenously in a slow drip in quantities of up to 1000 mg per day for a period of four days. He stated that the addict experienced no symptoms of withdrawal on this treatment and had no desire for addicting substances following treatment while in the hospital. He was unaware that niacin supplement would be necessary on a continuing basis and the saturation of the brain receptors was only temporary. He discusses experiments by Beer and Quastel (1958) which showed that DPN (NAD) was important in the dehy-drogenation of acetaldehyde. In their study, the inhibition of respiration of rat brain cortex slices by low concentrations of acetaldehyde was shown to be abolished by the increase of DPN (NAD). Although O'-Holleran did not fully understand the action of NAD in opiate addiction, clinically it worked. Davis and Walsh (1970) provided research results in 1970 which elucidate the problem. They showed that there is a similar mechanism in alcohol and opiate addiction because alcohol condenses to form opiates in the brain tissue. When acetaldehyde, which is a product of alcohol metabolism, was incubated with dopamine and brain homogenate, morphine-like substances were formed. This substance was a tetrahydrisoquinone, a substance very similar to morphine and it is addictive, and it was hypothesised that this substance went to the brain receptors to cause the addiction to alcohol. Beer and Quastel also noted that "the behavior of acetaldehyde on brain respiration in vitro re-sembles that due to a number of narcotics". But more importantly, in 1982, at the All-Union Research Institute of General and Forensic Psychiatry, in Moscow, USSR, experiment showed that there was a reduction in opiate binding sites in the brain of rats after chronic treatment with ethanol. The binding sites in the brain tissue were measured by homogenizing the brain tissue and adding radioactive opiates, and measuring the amount that bound to the brain tissue. Chronic ethanol treated rat brain tissue had fewer unoccupied binding sites, so that when measurement is taken after addition of radioactive opiates, less of these opiates are able to bind in the ethanol treated rat brain tissue. Levine et al. (1983) discuss the converse. Ethanol treated rat brain tissue, which would be devoid of adequate NAD as acetaldehyde reduces NAD, is more receptive to Naloxone. Apparently Naloxone is a stronger binder to the receptors than the alcohol condensation products acetaldehyde and dopamine in the absence of adequate NAD. Enkephalin is a weaker binder than the alcohol condensation products, acetaldehyde and dopamine. Taborkoff (1983) measured the effect ethanol had on the binding capacity of mouse brain by dihydromorphine and enkephalin. The binding capacity of enkephalin and dihydromorphine go down as the alcohol concentrations (acetaldehyde and dopamine) go up. Dihydromorphine shows a short term ability to bind over acetaldehyde and dopamine but after a rise to 50mM of alcohol the opiate dihydro-morphine is unable to displace acetaldehyde and dopamine. These research projects prove Davis and Walsh's hypothesis that the condensation products of alcohol bind to the opiate receptors. Niacin will displace the condensation products of alcohol (acetaldehyde and dopamine) and can thus relieve the addiction by supplying the normal binding substance to the brain receptors, namely NAD.

The Predator Response Mechanism.

I hypothesize that NAD and the endorphins are the only two physiological substances that bind the so called opiate receptors in the brain. Endorphins are produced by the brain in response to physical exercise and pain. Low brain NAD levels cause the predator response and the animal begins to exert itself in the hunt of prey. It is very important that pain and fatigue do not stop the hunt; therefore the endorphins are secreted to fill the NAD receptor sites temporarily until the hunt is completed and the animal can absorb the needed niacin to regenerate brain NAD levels. The NAD then saturates the receptor sites and displaces the endorphins. Normal brain NAD levels shut off the predator response. Physical exertion such as jogging and running is therefore often addicting. This kind of addiction will also

respond to nicotinic acid saturation of the brain receptor sites.

O'Holleran had earlier shown NAD to be effective in detoxing acute alcoholic patients. Clinically I have seen that nicotinic acid given orally in dosages of 500 mg per day will not only relieve acute intoxication but permanently relieve alcohol addiction. This same dosage will relieve drug addiction and the endorphin addiction on a continuing basis, because nicotinic acid is needed in a continual supply in this group of patients. Ottenello's (1948) use of nicotinamide to cure addiction to morphine supports this very logical conclusion. I believe much criminal and anti-social behavior may be caused by the lack of sufficient nicotinic acid.

Early Research into Other NAD Deficiency Diseases.

In 1937, Elvehjem's work resulted in the availability of niacin for the first time for trial treatment on various diseases. A little known publication from that time by Tom Spies (1938) discusses that in pellagra there is an excretion of abnormal amounts of porphyrins in the urine, and that when niacin is given the secretion of those porphyrins stops. He went on to test other types of diseases for porphyrinuria. He found that diabetics had this problem and painters suffering from lead poisoning (Spies and Bean, 1938) had it. Patients with cirrhosis of the liver had it and even cardiac patients who were in heart failure had it. He treated these porphyrinuria patients with niacin 500 mg per day and the porphyrinuria disappeared.

It was known that niacin was important in biochemical reactions as a coenzyme but why would giving niacin change the excretion of abnormal porphyrins? There are other causes of porphyrinuria that have been found since then. PCB and HCB are organic chemical compounds that are known to cause porphyria and this is because they interfere with the cell energy production by distortion of lipid membranes in the cell. Compounds that activate poly-(ADP-R) synthetase use up all the NAD and no NAD is left over to produce ATP. Such compounds include the alkylating agents alloxan, streptozotocin and mycotoxins. Low energy production in the cells is what all the porphyria diseases have in common.

Spies and his coworkers found they could cure the porphyrinuria of diabetes, cirrhosis, heart failure, and lead poisoning with niacin, so he also measured NAD levels (Vilter, Vilter and Spies, 1939) at a time when the other physicians were preoccupied with the low insulin levels. He found that in the ketoacidosis of diabetes NAD levels were very low (Vilter, Vilter and Spies, 1939) the same as they were in pellagra, which ameliorates with niacin. Diabetes is probably, initially, a low NAD disease. Yamada (1982) describes the preventive effects of Nicotinamide injections on Diabetes Insulitis. Vilter (1940) reported that low values of the coenzyme NAD concentration of whole blood were observed in diabetes mellitus, leukemia, roentgen sickness and pneumococci pneumonia. The red blood cell can almost double in coenzyme content following the ingestion of nicotinic acid, according to Kohn (1938). A British physician, Neu-whal (1943), did treat diabetes with nicotinamide and found he could actually take patients off insulin if he got to them in the early stages of diabetes. Other diabetics required much less insulin if given nicotinamide. Later in the 1980's, Yamamoto (1981) and other Japanese researchers found that nicotinamide inhibited production of experimental diabetes in animals if given before or right after a dose of diabetogenic chemical. Exploring this lead, it was discovered that the diabetogenic chemicals were alkylating agents that caused breaks in DNA strands and caused a reaction in beta cells of the pancreas which shut down insulin production. Breaks in cell DNA activate a poly (ADP-ribose) synthetase enzyme. All the intracellular NAD is split and inactivated by this reaction and cell function is stopped. Certain compounds inhibit the poly (ADP-ribose) synthetase like zinc ion, nicotinamide, benzemids. Zinc ion is the most active inhibitor at physiological levels. Other researchers found that diabetics suffer from zinc deficiency, as do alcoholics and pellagrins. We know that niacin deficiency can lead to zinc deficiency and the link is the same as in porphyria, low energy,

which results in poor reabsorption of zinc from the gut and it is also lost in the urine for the same reason, low NAD, and low energy. The link between alcohol addiction and diabetes has long puzzled medical scientists, but now the common etiology is known: they are both niacin deficiency diseases.

NAD Shown to be a Neurohormone in 1983.

As a neurohormone, NAD could affect the hypothalamic centers that regulate appetite. C. D. Richards et al. (1983), in what will prove to be a landmark biochemical publication, showed that NAD is a neurohormone as well as a coenzyme. In this view, Sutton's (1940) discussion of two cases of pellagra that failed to respond to treatment with nicotinic acid, liver extract, and adequate diet is pertinent. A trial of anterior pituitary extract called "polyansyn" produced remission in both cases without any dietary supplements of niacin. It suggests that the low levels of NAD of pellagra cause dysfunction of the pituitary-hypothalamic mechanism and this dysfunction can be corrected in most cases by giving nicotinic acid and thereby raising NAD levels, but that in a few cases the dysfunction is more severe and requires anterior-pituitary extract to correct it. Further evidence to support this hypothesis is given by DeRosa et al. (1984) who reported on their endocrine study of anorexia nervosa. They found multiple endocrine abnormalities consistent with hypothalamic dysfunction. These were: reduced basal glucose levels and flat glucose curves after oral loads of glucose, reduced serum insulin levels with slight response to glucose stimulation, elevated basal growth hormone levels with a fair response to L-dopa stimulation, elevated serum cortisal with loss of circadian rhythm and slight inhibition after dexa-methasone suppression testing, decreased T3 and FT3, slightly increased T4 levels, and testosterone levels were elevated in female anorexics and decreased in male anorexics.

Schizophrenia: A Substrate Pellagra with a Combined Trace Omega 3 Essential Fatty Acid Deficiency.

Rudin's (1981) discussion of his "pellagraform physical disorders" which ameliorate "not so much with vitamins as with supplements of a newly discovered trace omega 3 essential fatty acid (w3EFA)" refers to its use on schizophrenia, manic-depressive psychosis, and agoraphobia-like phobias, and to those disorders as being basically deficiencies in the w3EFA. The w3EFA "provides the substrate upon which niacin and other B vitamin holoenzymes act uniquely to form the prostaglandin 3 series tissue hormones regulating neuro-circuits en block." This all takes place in the pituitary-hypothalamic mechanisms. He proposes "that a mixed deficiency with a statistically dominant pellagraform picture showing a non-definitive response to multivitamin therapy can *also* be produced by (i) excessive reliance on a pure corn diet — the main cause of classical pellagra because corn is low not only in the niacin-tryptophan enzyme cofactor but also in the omega-3 essential fatty acid (w3EFA) substrate converted by the niacin holoenzyme uniquely to the prostaglandin (PG) 3 tissue hormones or (ii) by consumption of modern refined foods which contain hardly 20% of traditional w3EFA levels ..."

His work is perhaps the key to the last and least understood facets of the NAD deficiency spectrum, which probably includes the diseases which are listed as having extreme zinc loss in the urine and feces, i.e. schizophrenia, diabetes, alcoholism, pellagra, porphyria, and to some extent multiple sclerosis. The hypothalamic dysfunction of the severe NAD deficiency in schizophrenia is apparently corrected with adequate B vitamins and NAD and the proper amount of the new trace omega 3 essential fatty acid (w3EFA). His paper formulates this new substrate pellagra, and differentiates it from vitamin pellagra and compound pellagra, and discusses Fiennes' work (1973) with Capuchin monkeys which were reared without w3EFA and developed the classical Three Ds, of pellagra. A synergistic action is apparent, for the diseases under his discussion, but no studies

have been done to show that using just the w3EFA on early diabetes, pellagra, alcoholism, and porphyria will correct low NAD levels and correct apparent pituitary dysfunctions and those chemical reactions for which NAD is a virtual ringmaster. The Capuchin primates did have adequate vitamin B diets; *adding* the w3EFA at that point only points out a synergistic reaction. Normal energy transmission in the cell depends on the essential fatty acids being present in the membranes. When niacin deficiency diet is given to animals it takes about 60 days for any signs or symptoms to develop, in the dog. Anorexia comes first, then lesions of the mouth, then severe diarrhea and finally death in a matter of weeks. In Fiennes' Capuchin primates, pellagra induced by w3EFA deficiency took two years to develop. The newborn monkeys would have died within months on a niacin deficiency diet. Since these deficiencies take different time limits, one two months, the other two years, how can they be studied together? Lipids in the cell membranes are changed gradually over the two years in the w3EFA deficiency diet so that energy transmission across cell membranes is impaired. Hex-achlobenzene, HCB, induced porphyria is an example of induced porphyria caused by the same alteration of cell membranes. The deficiency in w3EFA is just as disabling to cell membranes but apparently takes a longer period of time to develop and is more variable and subtle. Rudin treated schizophrenia, which he correctly labels substrate pellagra, with linseed oil (his LSO) and niacin and other vitamins, with excellent results.

Anorexia and Schizophrenia are Examples of the Different Forms of Pellagra

V. L. Evans (1939) discussed anorexia in the late 30's in an early attempt to separate the vitamin pellagra from the substrate pellagra (Schizophrenia). The patient reported "weakness, headache, undernourishment and anorexia." In the hospital she became "suspicious, hostile, disorientated and violent." She seemed to be having vivid visual hallucinations. The mucous membranes of her mouth and tongue were "rather more red than the normal, but nor markedly so." The only physical symptoms of pellagra noted were moderate glossitis and stomatitis; she, however, recovered completely from her mental symptoms after four days on the therapeutic dose of 500 mg niacin per day. Two weeks later her blood pressure was down and her weight up 12 pounds. Evans had in fact found a case of anorexia nervosa which progressed to full blown psychosis while she was hospitalized. He indicates that she probably would have been diagnosed as schizophrenic if he had not treated her for pellagra. There is indeed a striking similarity between the prepsychotic stage of the pellagrin patient of Dr. Evans and what in recent times is called the borderline psychotic state of pseudoneurotic schizophrenia. I saw hundreds of cases of schizophrenia (substrate pellagra) as a psychiatric resident physician and as a ward physician in a large psychiatric hospital and I do believe that the borderline stage is often a sub-clinical case of pellagra, and could well be described by the same initial symptoms that Frostig and Spies (1940) have applied to early pellagra. In a possible subclinical stage of vitamin pellagra the therapeutic trial of niacin 500 mg daily should be offered. Petrie et al. (1981) have published that chronic schizophrenics improved on nicotinic acid, 300 mg daily, or Pyridoxine 75 mg daily, but not on a supplementation of the combined vitamins. It is the therapeutic dosage which is important here. The two or three grams of niacin daily which Hoffer (1954) used gave him excellent results in the treatment of schizophrenia. Personal correspondence from Dr. Hoffer indicates that he also very successfully used NAD orally in a special preparation, enteric coated to release after passing through the stomach. This points out the advantage of nicotinic acid in treating NAD deficiency diseases; because it is an acid it can be given orally and be well absorbed in the acid media of the stomach. In fact if nicotinic acid is given along with ascorbic acid there seems to be an even better absorption or there is an increased storage of energy at the cellular level.

Subclinical Pellagra: Term Coined by Dr. V. L. Evans in 1939.

Dr. Evans published a second paper in which he emphasized that there are two types of pellagra, the full-blown textbook cases and a "subclinical" type. He presents 13 cases in which none was the "frank classical type", but their prompt response to nicotinic acid, the specific for pellagra, established the diagnosis. The 13 cases all had mental illness, which did not improve in all of the cases after the pellagra symptoms improved, as he did not have the advantage of Rudin's recent work with w3EFA. However, two of the cases, for example #9 below, diagnosed as mental illness were recognized as pellagra, and treated for such, recovered completely.

His case #3 was given only 120 mg of nicotinic acid daily. In three days the lesions of the mucous membranes had entirely healed, while the depression and agitation remained the same. The dosage was not enough to adequately treat pellagra; otherwise she may have been completely cured in time also.

Case #11 was given 300 mg of nicotinic acid, a borderline dosage for pellagra. She showed gradual improvement of mental symptoms, which was however attributed to psychotherapy.

Case #9 was given 500 mg of niacin per day and had a clearing of mental symptoms in four days. This is an example of adequate treatment of pellagra.

Another example of a research project which also did *not* use an *adequately* high level of dosage of niacin is that conducted by Hekimian, Friedhoff, and Alpert (1966). Responding to the proposal that the accumulation of acetaldehyde derived from alcohol could be minimized or prevented by the administration of NAD, since this compound is a cofactor in the metabolism of alcohol, the research proceeded with a double-blind study on acute brain syndrome caused by alcoholism. The assigned dosage was 100 mg NAD, administered intramuscularly at 9:30 AM. The NAD patients showed no improvement, and even three NAD patients were considered "worse" after three days. The dosage was much below the required 500 mg spread over 24 hours. O'Holleran used up *to 1000 mg of NAD* in a *slow IV drip* to treat his patients for a period of four days.

The following year after Hekimian's study, E. Majchrowicz (1967) published in the same journal on the same subject. His work using 2 mg per kg was not only below adequate niacin dosage levels but was not administered intravenously by slow drip. The time release capsules now available would have worked as effectively as the slow drip intravenously. Majchrowicz's inadequate dosage level and the acceptance of his department's publication effectively stymied research on NAD as a treatment for acute alcoholism for the following fifteen years.

Clinicians Save the Day.

The early clinicians, practicing medicine, did discover these viable treatments for addiction only to be ignored. Russell Smith reported (1974, 1978) his treatment of 500 cases of alcohol addiction over a five year period, using nicotinic acid 3 grams or more per day. He experienced a 50% to 60% remission of the alcoholism over the five years, which is most remarkable in view of the usual single digit percentages of cure experienced by most treatment programs. Why he was ignored, and O'Holleran and others were ignored, is due to the extreme prejudice that exists in the medical community toward the use of nutritional therapy for the cure of disease. Apparently no one could believe these favorable results were possible.

Conclusion.

Oral nicotinic acid therapy provides an effective biological treatment for addiction to both alcohol and opiate drugs. In order to be effective it must be given in daily doses of 500 mg or more. The time release capsule or tablet is more convenient since it can be given twice daily and thus reduce the chances for poor compliance by the patient. There is considerable evidence that this same treatment is effective for other manifestations of the NAD deficiency disease like anorexia nervosa, early diabetes mellitus, heart failure, essential hypertension, and even the problems of predatory behavior like crime and violence.

Rudin's substrate pellagra (schizophrenia) responds when the w3EFA is added to the niacin treatment program.

References.

ANOKHINA, I. P.: Effect of Acute and Chronic Ethanol Exposure on Rat Brain Opiate Receptor Function. Ann 1st. Super. Sanita. 18, 31-34, 1982.

BEER, J. H. and QUASTEL, C. T.: The Effect of Aliphotic Aldehydes on the Respiration of Rat Brain Cortex Slices. Canad. J. Biochem, and Physiol. 36, 531-41, 1958.

CLEARY, J. P.: Etiology and Biological Treatment of Alcohol Addiction. Jour. Neuro. Or-tho. Med. Surg. 6, 75-77, 1985.

DAVIS, V. and WALSH, M. J.: Alcohol, Amines and Alkaloids, a Possible Biochemical Basis for Alcohol Addiction. Sci. Feb. 13,167,1005-1007, 1970.

DEROSA, G.: Endocrine Study of Anorexia Nervosa. Exp. Clin. Endocrinl. 82, 1983.

DEWAN, J. G.: An Alcohol Detoxification Mechanism in the Central Nervous System. Amer. J. Psych. 99, 565-568, 1943.

EATON, S.: Paleolithic Nutrition. New Eng. Jour. Med. 312, #5, 1985.

ERIKSSON, C. J.: Increase in Hepatic NAD level — Its Effect on Redox State and on Ethanol and Acetaldyhde Metabolism. FEBS LETTERS 40, 317-20, 1974.

EVANS, V. L.: Pellagra with Psychosis and Minimal Physical Symptoms. JAMA, Apr. 1, 1939.

FROSTIG, J. and SPIES, T. D.: The Initial Nervous Syndrome of Pellagra and Associated Deficiency Diseases. Am. J. Med. Sci. 199, Feb. 1940.

FIENNES, R. N., SINCLAIR, A. J. and CRAWFORD, M. A.: Essential Fatty Acid Studies in Primates: Linolenic Acid Requirements of Capuchins. J. Med. Prim. 2,155-169,1973.

HEKIMIAN, L. J.: Treatment of Acute Brain Syndrome from Alcohol with Nicotinamide Adenine Dinucleotide and Methamenodiazepoxide. Qrtly. J. Studies Alcohol. 27,1966.

HOFFER, A., OSMOND, H. and SMYTHIES, J.: Schizophrenia: A New Approach II. Results of a Years Research. J. Ment. Se. 100: 29-45, 1954.

KOHN, H.: The Concentration of Co-Enzymelike Substances in Blood Following the Administration of Nicotinic Acid to Normal Subjects. Bio. Chem. J. 32, 2075, 1938.

LEVINE, A. S.: Alcohol and the Opiate Receptor. Alcoholism Clinical and Exper. Res. 7, 83-84, 1983.

LIEBER, C. S.: Changes in Blood Ethanol Consumption and Acetaldehyde After Chronic Ethanol Consumption. Int. Titisee Sym. Black Forest Ger. Jan. 1982.

LYON, L. J. and ANTHONY, J.: Reversal of Alcoholic Coma by Naloxone. Ann. Inter. Med. 96(4): 464-465, 1982.

MAINZER, F. and KRAUSE, M.: Nicotinic Acid in the Treatment of Delirium Tremens. Brit. Med. J. Aug. 12, 331, 1939.

MAJCHROWICZ, E.: Nicotinamide Adenine Dinucleotide and the Metabolism of Ethanol and Acetaldehyde, Qrtly. J. Studies on Alcohol, 28, 1967.

MERCK COMPANY: Nicotinic Acid. 1941.

NEUWAHL, F. J.: The Lancet, Sept. 18, 348-51, 1943.

O'HOLLERAN, P.: DPN in the Prevention, Diagnosis, and Treatment of Problem Drinkers. West. J. Surg. Obst. Gyn. 69, 101-104, 1961.

O'HOLLERAN, P.: DPN in the Prevention, Diagnosis, and Treatment of Drug Addictions. West. J. Surg. Obst. Gyn. 69, 213-15, 1961.

OTTENELLO, P.: II Complesso Aneurina-Vi-tamina PP Nella Cura del Morfinismo e di Altre Intossicazioni Voluttuaire. Minerva Medica. 1948.

PETRIE, W. M.: The Use of Nicotinic Acid and Pyridoxine in the Treatment of Schizophrenia. Int. Pharmacopsychiat. 16, 245-250, 1981.

RICHARDS, C. D.: Nicotinamide Adenine Dinucleotide Depresses Synaptic Transmission in the Hippocampus and Has Specific Binding Sites on the Synaptic Membranes. Br. J. Pharmco. 79, 1983.

RUDIN, D. O.: The Major Psychoses and Neuroses as Omega - 3 Essential Fatty Acid Deficiency Syndrome: Substrate Pellagra. Biol. Psychiatry 16, 837-850, 1981.

SMITH, R. F.: Status Report Concerning the Use of Megadose Nicotinic Acid in Alcoholics. Orthomolecular Psych. 7, 1, 1978.

SPIES, T. D. and BEAN, W. B.: The Role of Nicotinic Acid in the Prevention of Pellagra, Roentgen Sickness and Increased Porphyrinuria. J. Clin. Inv. 17, 1938.

SPIES, T. D., GROSS, E. S. and SASAKI, Y.: Effect of Yeast and Nicotinic Acid on Porphyrinuria. Proc. Soc. Exper. Biol. & Med. 38: 178-181. 1938.

SUTTON, D. C: Interrelation between the Vitamin B Complex and the Anterior Lobe of the Pituitary Gland. J. Lab. Clin. Med. 25, #11, 1940.

TABORKOFF, B. and HOFFMAN, P.: Alcohol Interactions with Brain Opiate Receptors. Life Sci. 32, 197-204, 1983.

TROWELL, H.: Hypertension, Obesity, Diabetes Mellitus and Coronary Heart Disease. In: Trowell, H. C. Burkitt, D. P. (eds), Western Diseases: Their Emergence and Prevention. Cambridge, Mass: Harvard Press. 3-32,1981.

VILTER, R. W., VILTER, S. P. and SPIES, T. D.: Relationship Between Nicotinic Acid and Codehydrogenase (Cozymase) in Blood of Pellagrins and Normal Persons. JAMA 112:420-422, Feb. 4, 1939.

VILTER, R. W., VILTER, S. P and SPIES, T. D.: Determination of Codehydrogenases I and II (Cozymase) in Blood of Diabetics in Severe Acidosis." Am. J. M. Sci. 197:322-326, Mar. 1939.

VILTER, S. P.: Coenzymes I and II in Human Blood. Jour. Lab. Clinical Med. 26, p. 31, 1940.

YAMADA, K.: Preventive and Therapeutic Effects of Large-dose Nicotinamide Injections on Diabetes Associated with Insulitis. Diabetes 31, 749-753, 1982.

YAMAMOTO, H.: Streptozotocin and Alloxan Induce DNA Strand Breaks and Poly (ADP-ribose) Synthetase in Pancreatic Islets. Nature, 294, Nov. 19, 1981.