Niacin and Nicotinamide Adenine Dinucleotide ("NAD") Therapy
A Brief History

The Discovery of Niacin

Niacin was first described by Hugo Weidel in 1873 in his studies of nicotine. The original preparation remains useful: The oxidation of nicotine using nitric acid. Niacin was extracted from livers by Conrad Elvehjem who later identified the active ingredient, then referred to as the "pellagra-preventing factor" and the "anti-blacktongue factor."

When the biological significance of nicotinic acid was realized, it was thought appropriate to choose a name to dissociate it from nicotine, to avoid the perception that vitamins or niacin-rich food contains nicotine, or that cigarettes contain vitamins. The resulting name 'niacin' was derived from **ni**cotinic **ac**id + vitam**in.** Niacin is referred to as vitamin B_3 because it was the third of the B vitamins to be discovered. [1]

1960 - Early Treatment of Alcohol Abuse with Vitamin B

The man who would co-found Alcoholics Anonymous was born to a hard-drinking household in rural Vermont. When he was ten, his parents split up and Bill was raised by his maternal grandparents. He served in the Army in WW I, and although not seeing combat, Bill Wilson had more than ample opportunities to drink. In the 1920's, Wilson achieved considerable success as an inside trader on Wall Street, but a combination of drunkenness and the stock market crash drained what was left of his fortune and his capability to enjoy life.

Hard knocks, religious experience, and a growing sense that by helping other alcoholics he could best help himself led Bill to create one of the world's most famous introductions: "My name is Bill W., and I'm an alcoholic." Even as Alcoholics Anonymous slowly grew, many of Bill's financial and personal problems endured, most notably depression. Abram Hoffer writes: "I met Bill in New York in 1960. Humphry Osmond and I introduced him to the concept of megavitamin therapy. Bill was very curious about it and began to take niacin, 3,000 mg daily. Within a few weeks fatigue and depression which had plagued him for years were gone. He gave it to 30 of his close friends in AA. Of the thirty, 10 were free of anxiety, tension and depression in one month. Another 10 were well in two months.[2]

1961 - Paul O'Hollaren and Addiction Therapy

In 1961, Paul O'Hollaren M.D. authored a report titled Diphosphopyridine Nucleotide in the Prevention, Diagnosis and Treatment of Drug Addiction. The article reported that O'Hollaren had successfully utilized the diphosphopyridine nucleotide, in its oxidized form (then commonly referred to as DPN, now known as NAD) in the prevention, alleviation and removal of the acute and chronic symptoms of drug addiction.

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[1] http://www.news-medical.net/health/Niacin-History.aspx

[2] From *Vitamin B3: Niacin and Its Amide*, by A. Hoffer, M.D., Ph.D.; Wilson B: *The vitamin B3 therapy: The first communication to AA's physicians* (1967); *A second communication to AA's physicians* (1968).

The forms of addiction which were reported to have responded successfully to this coenzyme therapy by total, immediate and permanent discontinuance included heroin, opium extract (Pantopon), morphine, dihydromorphine, meperidine, codeine, cocaine, amphetamines, barbiturates and tranquilizers. These results were obtained in patients whose addictions ranged from 2 to 28 years in duration. He goes on to state that in treating over 100 cases of drug addiction, withdrawal is achieved with very few (and in some cases none) of the characteristic withdrawal symptoms, usually experienced with other treatments and that the evidence strongly suggests that complete freedom from craving can be sustained by administration of the coenzyme at proper dosage and intervals, through a continuing program of management (as in diabetes).[3]

1962: United Nations Office on Drugs and Crime (UNODC)

In an article dated January 1, 1962, author Malachi Harney asserts that, "Cocaine abuse is not at present a problem in the U.S.A. While there is an extensive use of cannabis, generally smoked as marijuana, this is usually in the form of intermittent, sporadic and occasional dissipation. The heavy constant use of this drug, characteristic in some other countries, is here somewhat rare."

He goes on to cite methadone as a substitute drug leading to rapid reduction of narcotic intake, providing a less severe reaction when the methadone is discontinued, calling it "a revolutionary accomplishment in the humane disintoxication of a narcotic addict." The article laments the lack of a non-addicting opiate and lack of a chemical cure for addiction, but mentions the O'Hollaren article cited above as a possible beneficial development.

The O'Hollaren Patents

1964: U.S. Patent No. 3,158,540 is issued to Paul O'Hollaren captioned: "Method for Alleviating the Withdrawal Symptoms of Drug Addicts"

1966: U.S. Patent No. 3,266,989 is issued to Paul O'Hollaren captioned: "Treatment of Alcoholism"

Note: Both of these patents have long-since expired.

1980's: Development of Treatment Protocols

Working from a clinic in Tiajuana, Mexico, Dr. William Hitt, in association with physicians and researchers from South Africa, developed protocols to administer DPN (the old term for nicotinamide adenine dinucleotide or "NAD") to ease the withdrawal from drug and alcohol addiction and as reported in the earlier research, leaving the patient free of the craving for the addictive substance and with improved cognitive ability better able to make good decisions that improve future behavior.

Dr. Hitt's therapy becomes popular in Southern California and he becomes the best-known provider of withdrawal support to the stars. With the patent protection of

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[3] West. J. Surg., Obst. & Gynec. May-June 1961: Diphosphopyridine Nucleotide in the Prevention, Diagnosis and Treatment of Drug Addiction - A Preliminary Report by Paul O'Hollaren, M.D., Seattle, Washington *From the Research Department, Shadel Hospital*

the O'Halloren works expired, Hitt had no means to protect his therapeutic approach but strict secrecy. He labels his IV solutions as amino acids, and similarly documents his files. But the active ingredient is in fact NAD. Dr. Hitt later began to provide the product to clinicians in the US who adopt the therapy and begin to provide it to patients.

1986: Further Research into NAD Deficiency Diseases Emerges

In his 1986 paper The NAD Deficiency Diseases, published in the Journal of Orthomolecular Medicine[4], John Cleary traces the history of Vitamin B3 (niacin) and its role in the predator response in man. The article suggests that 10% of the modern genetic pool is severely NAD deficient. The paper expounds upon the treatment of alcohol addiction with NAD and references the history of prior work of Paul O'Holleran at Shick-Shadel Hospital in Seattle, Washington.

Furthermore, Cleary references the work of Kohn (1938) that suggesting that if treated in the early stages, NAD could relieve the need for insulin in diabetes, and could greatly reduce the needed dose of insulin in other patients, and the work of Evans (1939) suggesting that NAD could benefit patients suffering from such diverse diseases as pellagra, schizophrenia and anorexia.

Cleary believes that "Before a total picture of the importance of NAD could be discussed, research was apparently interrupted by World War II." The work apparently was not resumed following the conclusion of the conflict.

2001: Broadened Clinical Availability of the Therapy

In 2001, Paula and Dr. Richard Mestayer opened Equipoise Wellness Center, originally located in Slidell, Louisiana, and relocated after 2005 to the current Springfield, Louisiana facility.

In 2006, having been treated for addiction by Paula and Dick Mestayer, Mike Sanders opens the Execucare Addiction Recovery Center in the suburbs of Atlanta, Georgia.

2000's: The Research Continues

In a paper titled Alcohol, Oxidative Stress and Free Radical Damage,[5] Defeng Wu and Arthur Cederbaum identify and describe the role of oxygen species (ROS) in the body, small, highly reactive, oxygen-containing molecules that are naturally generated in small amounts during the body's metabolic reactions and can react with and damage complex cellular molecules such as fats, proteins, or DNA. They report that alcohol promotes the generation of ROS and/or interferes with the body's normal defense mechanisms against these compounds through numerous processes, particularly in the liver. For example, alcohol breakdown in the liver results in the formation of molecules whose further metabolism in the cell leads to ROS production. Alcohol also stimulates the activity of enzymes called cytochrome P450s, which contribute to ROS production. Further, alcohol can alter the levels of certain metals in the body, thereby facilitating

[4] Journal of Orthomolecular Medicine, Volume 1, No. 3, 1986 at page 149.

[5] Alcohol, Oxidative Stress and Free Radical Damage, Defeng Wu and Arthur Cederbaum, Alcohol Research and Health, Vol. 27 No. 4, 2003 pp 278-284.

ROS production. Finally, alcohol reduces the levels of agents that can eliminate ROS (i.e., antioxidants). The resulting state of the cell, known as oxidative stress, can lead to cell injury. ROS production and oxidative stress in liver cells play a central role in the development of alcoholic liver disease. The authors describe the significant role of NAD in the reduction of oxidative stress through the reduction of free radicals and improvement of cellular oxygenation in the body.

In his paper NAD+ and Vitamin B_3: From Metabolism to Therapies[6], Anthony A. Sauve (Department of Pharmacology ofWeill Medical College of Cornell University, New York, New York) reported that the role of NAD^+ metabolism in health and disease is of increased interest as the use of niacin (nicotinic acid) has emerged as a major therapy for treatment of hyperlipidemias and with the recognition that nicotinamide can protect tissues and NAD^+ metabolism in a variety of disease states, including ischemia/reperfusion. In addition, a growing body of evidence supports the view that NAD^+ metabolism regulates important biological effects, including lifespan.

NAD^+ exerts potent effects through the poly(ADP-ribose) polymerases, mono-ADP-ribosyltransferases, and the recently characterized sirtuin enzymes. These enzymes catalyze protein modifications, such as ADP-ribosylation and deacetylation, leading to changes in protein function. These enzymes regulate apoptosis, DNA repair, stress resistance, metabolism, and endocrine signaling, suggesting that these enzymes and/or NAD^+ metabolism could be targeted for therapeutic benefit. This review considers current knowledge of NAD^+ metabolism in humans and microbes, including new insights into mechanisms that regulate NAD^+ biosynthetic pathways, current use of nicotinamide and nicotinic acid as pharmacological agents, and opportunities for drug design that are directed at modulation of NAD^+ biosynthesis for treatment of human disorders and infections.

In a November 2008 presentation to the Society for Neurosciences titled "Neurotransmitter Restoration Therapy for the Treatment of Substance Abuse[7]" authors Owen et.al. conclude that neurotransmitter restoration using NAD measurably improved stress, depression, anxiety and cravings ratings and, in contrast to methadone and suboxone, does not show any potential for abuse.

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[6] The American Society for Pharmacology and Experimental Therapeutics, by Anthony A. Sauve, Department of Pharmacology, Weill Medical College of Cornell University, New York, New York Received June 14, 2007 and Accepted December 27, 2007.

[7] Presentation to the Society for Neurosciences, "Neurotransmitter Restoration Therapy for the Treatment of Substance Abuse", S. Owen, MD, P. Norris, M.Ed., LPC, DAPA, S. Broom Gibson, Ph.D. and R. Mestayer, M.D.