

ABOUT THE AUTHOR

Professor Georg D. Birkmayer, M.D., Ph.D. is a world renowned biochemical researcher, who was the first to identify the importance of NADH in cellular development and energy transmission for all bodily functions and organs. He is the Medical director of the Birkmayer Institute for Parkinson's Therapy in Vienna, which has treated thousands of patients suffering from Parkinson's disease, Alzheimer's disease and depression. He is founder and Chairman of Birkmayer Pharmaceuticals and the Birkmayer Laboratories, also in Vienna. Dr. Birkmayer is the author of more than 150 research papers and more than 100 scientific articles in the areas of cancer diagnosis, neurochemistry and neuropharmacology related to Parkinson's and Alzheimer's diseases. He is a professor at the University of Graz in Austria, heading its Division of Neurochemistry at the Department of Medical Chemistry. He is also a visiting professor at the University of Beijing and Canton, China, and Secretary General of the International Academy of Tumor Marker Oncology in New York. He is the European Editor of the Journal of Tumor Marker Oncology and a member of the editorial board of the Journal of Experimental and Clinical Cancer Research and a number of other scientific journals. He is a member of many international scientific societies such as the New Academy of Sciences and the American Association of Cancer Research. He is also a Fellow of the American College of Nutrition.

THE BIRKMAYER CONTRIBUTION: A LEGACY OF INNOVATION IN HEALING

The story of NADH is intricately linked to the story of the Birkmayer family. It began in postwar Vienna at the Hospital for the Brain Injured (Wiener Hirnverletzten-Lazarett). There the young professor Walther Birkmayer saw over 3,000 braininjured patients as chief physician. Grasping the importance of neurorehabilitation as a special discipline, he began a journey to explore the neurobiological reactive mechanisms within the brain. His observations led to the realization that injuries must create an imbalance between various reactor substances or neurotransmitters, resulting in a wide range of patient behaviors or symptoms.

His subsequent research with Parkinson's patients during the late '50s and early '60s, using L-dopa, the precursor to the substance dopamine, led to one of the crucial events of neurology. He succeeded in demonstrating that a pharmacological effect could be counteracted by another chemical substance producing a specific physiological or psychic result. In the years that followed, Dr. Walther Birkmayer was to receive four honorary doctorates from leading European institutions in recognition of his outstanding lifetime contributions. He was also highly regarded by his patients for his help and his humanity

Walther's son Georg also became a doctor. After fighting at the forefront of cancer research, Georg was to follow his father, making his own contribution to the development of neurorehabilitative therapies. He went on to discover and implement the therapeutic usage of NADH or coenzyme 1, the topic to be explored in this booklet.

In 1993, Dr. Georg Birkmayer developed the first and only stable and absorbable oral tablet form of NADH. His discovery, recognized with worldwide patents, made NADH available to the general public as a nutritional supplement, licensed and available only under the brand name Enada®.

Research continues in the U.S.A. and abroad to explore Enada's full potential. FDA-approved clinical trials are currently being conducted under the auspices of leading American research hospitals.

NADH

The

Energizing

Coenzyme

How an important, yet little-known coenzyme enhances cellular energy in brain and body functions

Prof. Georg Birkmayer, M.D., Ph.D.

Foreword by Richard A. Passwater, Ph.D.

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FOREWORD

The health research community is especially excited that practical way to increase cellular levels of an important compound called NADH has been found. A simple dietary supplement containing a stabilized form of NADH has been developed by Dr. Georg Birkmayer. Why is this so exciting? Because NADH, which is the biochemist's abbreviation for nicotinamide adenine dinucleotide, is extremely important to health. The reason that it hasn't been widely discussed before is that until now, there was no way to do anything about improving the level of NADH in cells. It was like the weather. Why talk about it if you can't do anything about it. How important is NADH? While there is no such thing as a singularly "most important" compound in the body, or even a "most important antioxidant", NADH comes as close as a single compound can. NADH is both the primary coenzyme that drives reduction and oxidation reactions in cellular metabolism and the most powerful antioxidant. An extraordinarily complex molecule, NADH is essential to produce energy from food. NADH is the principal carrier of electrons in the oxidation of molecules that produce energy in the cell. The more NADH available in the cells, the more energy can be produced.

As the body's most powerful antioxidant, NADH can regenerate other important antioxidants to protect the body from damaging free radical attack. Free radicals are involved in more than 80 diseases, including heart disease, cancer, arthritis and neurodegenerative diseases of aging. As an example of the importance of NADH to the antioxidant cycle, NADH can supply a molecule of oxidized glutathione to form the cell's major antioxidant, reduced glutathione. This action can be repeated along the antioxidant chain.

Reduced glutathione can regenerate spent vitamin C back to active vitamin C, which in turn can regenerate spent vitamin E back into active vitamin E. Thus, a few molecules of NADH can have a profound influence on the body's antioxidant defenses against disease-causing free radicals.

NADH's amplification effect can be seen in other ways as well. Each molecule of NADH can produce three molecules of ATP, a major compound for storing energy in the body. Another example is that each molecule of NADH can produce six molecules of dopamine, which is extremely important to mental function and to patients with Parkinson's disease. This amplification effect is due to the fact that NADH is a coenzyme that helps power many different enzymes to be catalysts in thousands of reactions in the body. The NADH plus the appropriate enzymes can cycle over and over to drive essential reactions. Thus, a few additional milligrams of NADH in the body can often bring about major improvements in body function as verified by several recent clinical studies.

Dr. Birkmayer, the pioneer in using NADH to treat Parkinson's disease, has extended his research to include other scientists at universities such as Georgetown University Medical Center, Washington, D.C. and Lenox Hill Hospital, New York City. He describes this exciting research in this book in a clear, understandable manner. Research is expanding into new areas, but at this writing I have been following the research in Parkinson's disease, chronic fatigue syndrome and Alzheimer's disease. The value of NADH in treating these disorders is discussed in this book. In addition, Dr. Birkmayer discusses the potential utility of NADH to improve cellular metabolism and energy levels in those not suffering from overt disease states, but also not producing optimal levels of NADH in their bodies. There is much of interest about NADH for everyone.

Richard A. Passwater, Ph.D.
Berlin, Maryland
September 1997

NADH: COENZYME NUMBER ONE

NADH is the abbreviation for the biological substance nicotinamide adenine dinucleotide. The “H” stands for high-energy hydrogen and indicates that it is the reduced form of coenzyme 1, another term for NADH.

Enzymes catalyze biological processes and create products in our body which we need to survive. They can be compared to production machinery in a factory which transposes one material into another one. In living cells they catalyze the breakdown and turnover of food components into smaller units, ultimately converting food into water and energy. Enzymes can perform their work only if an additional essential factor combines with the enzyme itself. This factor is called a coenzyme.

Without a complementary coenzyme, the majority of enzymes will not work. Hence a coenzyme is a necessary component for an enzyme to become active. Unlike DHEA and melatonin, NADH is not a hormone but a coenzyme. You can compare enzymes and coenzymes with an engine and its fuel. The enzyme is the engine and the fuel is the coenzyme. Without its coenzyme the enzyme will not work. The deficiency of a needed coenzyme will actually slow down the enzymatic production process. A deficiency of NADH will result in an energy deficit at the cellular level, the symptom of which is fatigue. For the body to be deficient of NADH is the same as a car running out of gasoline. The more NADH a cell has available, the more energy it can produce. Unfortunately, the level of NADH in our body declines with aging and so do the NADH-dependent enzymes, in particular those for energy production.

HISTORY OF NADH

NADH was discovered in 1905 in yeast and was originally named cozymase, indicating that it is an essential factor for an enzyme. For over 90 years it has been described extensively in all biochemistry textbooks. NADH is also known under a number of synonyms. The synonyms for NADH are:

Chemical Name: β -nicotinamide adenine dinucleotide, reduced form

Synonyms: Nadide, disodium salt, reduced form
Diphosphopyridine nucleotide, reduced form
Adenine-D-ribose-phosphate-phosphate
D-ribose-nicotinamide, reduced form
Cozymase, reduced form
Coenzyme 1, reduced form
Codehydrogenase, reduced form
Enzopride

Abbreviated Name: NADH, DPNH, ARPPRNH, Co 1

NADH IN FOOD AND DIETARY SOURCES

NADH is present in every living cell, animal or plant. Hence it is present in our daily food. Meat, poultry, and fish contain the highest amount of NADH (Table 1). Vegetables, fruits and other vegetarian food have a much lower NADH content than meat.

Food type	NADH content in mg/kg of tissue
Meat	50
Poultry	40
Fish	35
Yeast	2
Potatoes	0.2

It should be noted that most of the NADH we take in from foods is destroyed during the cooking process. The situation would not be much improved even if our diets consisted mostly of raw meat or fish, as the greater part of the NADH present in these foods is degraded by the stomach gastric acid system in our bodies.

Animal cells do produce more NADH, because they need more energy for movement and locomotion. The highest content of NADH is found in the heart and flight muscle of birds. Plants are unable to move from one place to the other, so they do not need that much energy. Therefore they produce much less NADH than animal cells. Because of the low NADH content from plant sources, a vegetarian's intake of NADH is significantly less than that of people with a mixed meat-containing diet. It is known that vegetarians can develop an NADH deficiency over time. However, they may overcome their potential NADH deficit by a simple daily supplement tablet of the stabilized form NADH (Enada).

HOW NADH WORKS

The most important biological functions of NADH are as follows:

1. The cellular fuel for energy production
2. Key role in cell regulation and DNA repair
3. Enhancer of the cellular immune System
4. A potent antioxidant
5. The stimulator of dopamine, adrenaline and norepinephrine production

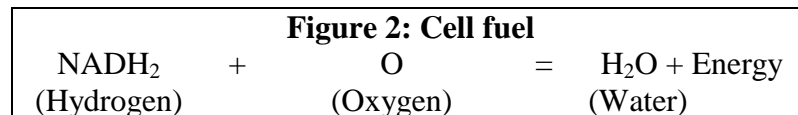
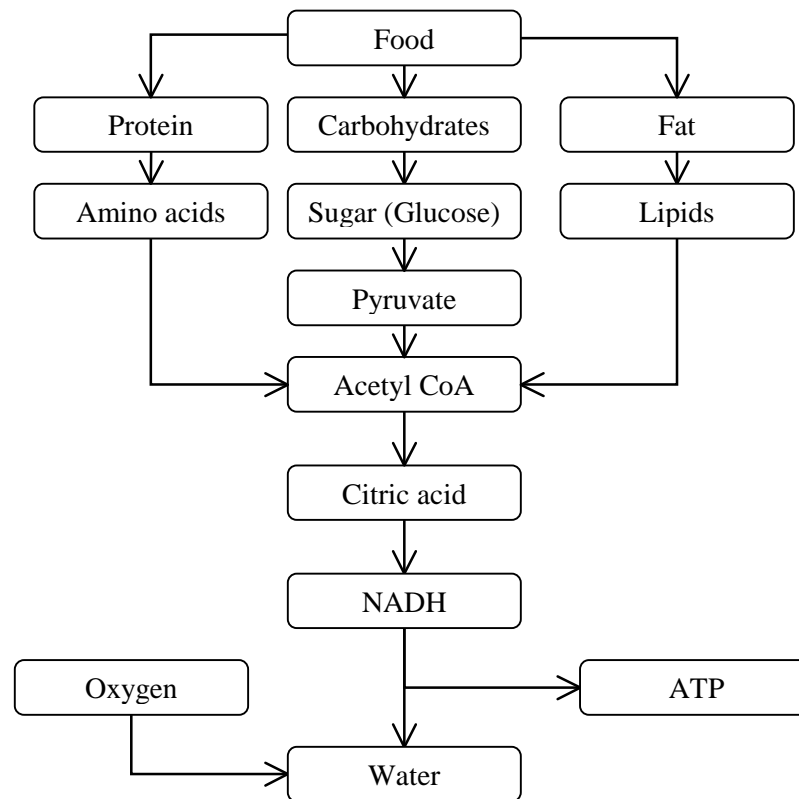
NADH: THE CELLULAR FUEL FOR ENERGY PRODUCTION

All living cells require energy to stay alive. Without energy a cell dies because energy production represents the essential prerequisite for every living cell. How is energy produced in the living cell? As shown in Figure 1, food is taken in, digested, and its components, proteins, carbohydrates and fat, are reduced into smaller molecules such as amino acids, sugars and lipids. They are further processed, leading to a reducing power in the form of NADH, the reduced form of coenzyme 1. NADH reacts with oxygen to produce in a cascade of reactions water (H₂O) and energy. This energy is stored in the form of the chemical compound adenosine triphosphate, abbreviated ATP. In other words the hydrogen in NADH, derived from splitting our food, combines with molecular oxygen present in all living cells (Figure 2) to form water and energy. Living cells use a rather sophisticated approach in order to conserve the energy. The very active hydrogen is bound to a bigger molecule, namely NADH, where it is less reactive than in pure form, but still retains its reaction (reducing) power. One molecule of NADH yields three molecules of ATP, an energy-rich compound present in all living cells. The more NADH a cell has available, the more energy it can produce. The amount of NADH a cell contains depends on the amount of energy it requires. Heart muscle cells, which have to contract themselves every second for an entire life time (3,600 times an hour or 86,400 times a day), contain 90 micrograms (µg) of NADH per gram of tissue. Brain and muscle cells contain 50 µg. This suggests that the brain needs at least as much energy as muscle cells, which is approximately 30 percent of the entire energy produced by an individual. In summary, the more NADH a cell has available the better it can perform its functions such as energy production, and therefore the longer it can survive.



The more NADH a cell has available, the more energy it can produce.

Figure 1: Simplified diagramm of the stages of metabolism that lead from food to NADH
 The series of reactions produces ATP, which is then used to drive biosynthetic reactions and other energy-requiring processes in the cell.



NADH CONTROLS CELL REGULATION AND CELL DAMAGE REPAIR

The genetic code of all cells resides in the deoxyribonucleic acid, abbreviated DNA. The DNA in the nucleus is well protected by histones and other macromolecules. Nevertheless, it can get damaged by exposure to various agents such as radiation, ultraviolet light, ozone and chemical toxins such as cytostatics, antibiotics or anti-inflammatory drugs.

It is important to note that the chemical industry produces more than 20,000 new chemical compounds every year, often without fully knowing how potentially toxic they may be. Yet they are being marketed in a variety of ways, pure or combined with other chemicals, usually without any toxicological studies done beforehand. Needless to say that people are continually exposed to these new chemicals usually without realizing their toxic potential.

These potentially harmful agents can react with our chromosomes. If our DNA is affected and damaged by one of these agents our genetic material will be altered. Replication of altered, defective DNA causes changed features in newly divided cells provided cell division can still occur. The greater the DNA damage the more extensive alterations in the cell and tissue occur. Genetic damage is the biochemical basis for a number of chronic diseases such as cancer, rheumatoid arthritis, immunodeficiencies and arteriosclerosis. Hence it is imperative that our genetic material remains unaltered in order to guarantee that any new progenitor cells developing after cell division occurs are identical to their parent cells. If the DNA is altered

by physical or chemical agents, the newly developing progenitor cells may be different from their mother cells and will not function in the programmed way. If this happens in heart cells, which must have the inherited feature to contract every second, they will lose their ability and a heart insufficiency at cellular level is the consequence.

In order to avoid the fatal consequences of DNA damage, both mammalian and human cells have developed a system which is able to repair alterations to their genetic material. This so-called DNA repair System needs NADH to gain full functionality. Therefore, the more NADH you have in your body the better the DNA repair system functions and the better you are protected from potentially developing diseases.

NADH: CELLULAR IMMUNE SYSTEM ENHANCER

Human cellular immune response is based on the activities of special white blood cells, in particular the T-lymphocytes, the B-lymphocytes and the macrophages. Macrophages are responsible for the direct elimination of foreign bodies. They take them in and degrade them, a process comparable to eating and digestion.

A direct relationship exists between the intake process of these specialized white blood cells and the activation of the immune system. The first step in the elimination of bacteria is the perturbation of the plasma membrane of these phagocytic (cell-eating) cells. As a consequence the metabolic activity is markedly increased, including the oxygen consumption within the cells. Most of the oxygen is converted to superoxide and hydrogen peroxide. This phenomenon, known as the “metabolic burst,” appears to be the first and most critical step leading to the destruction of the invader. During this metabolic burst and in cytotoxic activity of the macrophages, high amounts of NADH are used.



NADH is directly involved in the cellular immune defensive system.

Therefore, the coenzyme NADH is directly involved in the cellular immune defensive system, and the more NADH you have available in your body the more protection your autoimmune system can provide.

NADH: A POTENT ANTIOXIDANT

An antioxidant is a substance which acts against oxidation. The opposite of oxidation is reduction. A compound with a very high reduction potential exhibits a strong antioxidant power. NADH, the reduced form of coenzyme 1, has the highest reducing power of any biological material. Therefore it has an enormous antioxidative capacity. Well-known antioxidants are vitamins A, C and E, selenium and glutathione as well as the enzymes glutathione peroxidase and superoxide dismutase. Biological antioxidants are present in all living cells to protect the cell and its membrane from destruction by free radicals.

Free radicals are extremely reactive molecules which interact with many compounds in our cells, in particular with lipid-containing structures such as the cell membrane. For example, free radicals react with lipids surrounding the cell membrane, thereby violating the integrity of the cell wall, causing leakage and release of essential cellular component which usually results in cell death. Free radicals have been shown to be involved in the development of cancer, coronary disease, atherosclerosis, diabetes, neurodegenerative disorders such as Parkinson's and Alzheimer's diseases, and other autoimmune diseases.

Free radicals are formed in our cells by agents knocking out electrons from a molecule. These agents can be x-rays, ultraviolet light and other forms of high-energy radiation. Also ozone, smog, industrial pollution, smoking, environmental toxins, alcohol, heavy metals found in food and water, and many drugs including antibiotics and cytostatics trigger free radical formation.

Small amounts of free radicals are also produced in normal cells by metabolic reactions. The body, however, possesses a defense system to protect the cells from being irreversibly damaged. This System is called the antioxidative protection shield. The first and most important antioxidant component in this system is NADH, because it has the highest reduction potential of any compound in the cells.

In the presence of free radical inducers, such as radiation or cytostatics, the intracellular content of free radicals increases considerably. The antioxidative protection system can cope with the usual natural amounts produced in the body; however, it can become overwhelmed by large amounts of free radicals produced from the outside environment. The more free radicals present in a cell, the more damage a cell suffers, leading to earlier cell death, which contributes to premature tissue degeneration.

It is vital that the body have a sufficient supply of free radical antioxidant scavengers such as NADH in sufficient levels to eliminate these free radicals. Again, one of the most potent antioxidants and free radical scavengers is NADH.

Seniors may especially benefit from NADH supplement replenishment, since we now know that the NADH within our bodies declines with aging, leaving the elderly more vulnerable to damaging free radicals. Therefore, the more NADH they have available in their body the better the opportunity is for maintaining their health.

NADH AS DOPAMINE, ADRENALINE AND NOREPINEPHRINE STIMULATOR

Laboratory studies using neuron cell cultures prove that dopamine production can be increased by the addition of NADH to the culture medium. In a dosage-dependent manner, NADH yields up to a sixfold production of dopamine. Furthermore, NADH stimulates tyrosine hydroxylase (TH), the key enzyme for the production of dopamine, up to 70 percent . Additionally, studies performed in France found that NADH stimulates the production of dopamine and norepinephrine in certain brain areas by more than 40 percent. Also, a recent double-blind placebo-controlled study performed at a German university hospital with parkinsonian patients receiving NADH showed an elevated level of L-dopa and dopamine in their blood. These data suggest that NADH stimulates adrenaline and dopamine production and should therefore have a positive effect on all physiological functions which are stimulated by adrenaline or dopamine, namely: strength, movement, coordination, alertness, cognitive functions, mood, sex drive and growth hormone secretion.

Dopamine seems to be an important mediator of sexual functions, as dopamine agonists improve disturbances of libido, orgasm and ejaculation at least in some parkinsonian patients. As NADH is increasing the production of L-dopa and dopamine respectively, it may have a similar effect on sexual functions.

Dopamine also reduces prolactin secretion and a person's overall appetite. The higher the dopamine level in the blood, the lower the appetite. This may be of particular interest to overweight individuals, especially if they are using NADH as a supplement.

 ***The more NADH you have in your body the better the DNA repair System functions.***

Finally, the positive impact of dopamine on growth hormone secretion is most relevant, since growth hormone is regarded as a key factor for regeneration of cells and tissue.

REPORTED EFFECTS OF NADH

Protecting the Liver from Alcohol Damage

As alcoholic beverages are consumed, they are metabolized in the liver by the enzyme alcohol dehydrogenase, which needs NADH as a coenzyme to activate. Additional NADH may

improve the efficiency of liver enzyme functions, resulting in faster oxidation, shortened exposure, and reduced liver damage.

Preventing Alcohol-Induced Inhibition of Testosterone Biosynthesis

Under the influence of alcohol the biosynthesis of the sex hormone testosterone is inhibited. In other words the more alcohol you consume the lower your sex drive becomes. In the presence of NADH this alcohol-induced inhibition of testosterone is diminished or absent.

NADH Lowers Cholesterol Levels

In a double-blind trial it was demonstrated that NADH lowered the cholesterol level in spontaneous hypertensive rats after 8 weeks of 5 mg Enada (NADH) administered orally. Cholesterol levels were reduced by 30 percent after 10 weeks of treatment. These preliminary studies will help determine the applicability for longer-term human studies using Enada (NADH).

NADH Lowers Blood Pressure

Previous clinical studies indicated a trend for blood pressure to decrease significantly in patients taking supplemental Enada, the only oral stabilized, absorbable NADH available. A double-blind research study utilizing spontaneously hypertensive rats was conducted at a prestigious American medical hospital. In groups of 10, rats were given either a placebo or Enada (NADH) (5 mg). Over the first week systolic BP was slightly higher in the NADH group, but rapidly decreased significantly to average 15 mm Hg below the placebo group. At the end of 11 weeks, systolic BP in the placebo group averaged 201 mm Hg \pm 2.8 (SEM—Standard Error Mean), while averaging only 184 mm Hg \pm 2.8 (SEM) in the NADH group. Again, this study demonstrates the potential that NADH supplementation may actually lower blood pressure.



NADH may retard cell death and tissue degeneration.

NADH Inhibits Dopamine Auto-Oxidation

The neurotransmitter dopamine is spontaneously oxidized in the body, a phenomenon which is called auto-oxidation. During this process cytotoxic agents are formed which may damage certain areas of the brain. Auto-oxidation is found to be significantly higher in older individuals. Since NADH can inhibit the auto-oxidation of dopamine it represents a useful tool in reducing or preventing damage to certain areas of the brain. Therefore, NADH may retard cell death and tissue degeneration.

NADH Protects against AZT Toxicity

Azathymidine (AZT) is a drug used as an antiviral agent in HIV-infected individuals. However, AZT induces several severe side effects. It has been found that 19 days after administration of AZT, the energy-producing compartments in the cell, known as the mitochondria, change, becoming abnormal. Particularly affected is muscle cell tissue, which leads to severe muscular weakness in patients. Furthermore, it was found that NADH cytochrome C reductase, the key enzyme in cell energy production, was significantly decreased. As AZT is a DNA chain terminator it acts as a muscle toxin. It is anticipated that NADH may help minimize or even prevent the AZT induced changes and damage to the mitochondria leading to a possible normal functioning with regard to energy production.

There are a number of cancer-inducing quinones, such as cumene. NADH is able to protect the organism from the cancer inducing effect of quinones. Furthermore, NADH inhibits lipid peroxidation, which is induced by cumene hydroperoxide.

An interesting observation has been reported: that HIV infection decreases intracellular NAD and its counterpart NADH. In tissue culture reviews it was found that the more virus present, the lower the intracellular NADH pool. Hence HIV infection consumes a significant amount

of NADH, resulting in the HIV-infected cells having a lower NADH content than normal, uninfected cells. This rapid depletion of NADH can cause cell death. Furthermore, it has been noted in animal brain tissue studies that NAD, the oxidized form of Coenzyme 1, to which NADH is readily converted, prevents apoptosis (cell death) induced by the toxic AZT.

ENADA: NADH FOR ORAL USE

Enada is the only stabilized, ingestible, absorbable form of NADH for oral application, and has been recognized with a worldwide patent. Only Enada can maintain the right potency over an extended period of time (two years) and exhibit all the beneficial effects described in this booklet.

In February 1995, Enada became available in the U.S. as a nutritional supplement. It is marketed in two potencies, 2.5 mg and 5.0 mg in tablet form, packaged 30 tablets per box. This is generally a month's supply.

Since February 1995, thousands of customers have purchased Enada and are continuing to experience the benefits of this important energizing coenzyme. Hundreds of physicians in the U.S. have been using Enada with their patients suffering not only from Parkinson's or Alzheimer's disease, but also from depression and chronic fatigue syndrome and overall lack of energy. Remarkable beneficial effects have been reported by them. Doctors have reported that Enada is the best antidepressive substance they have ever experienced with their patients. Virtually no side effects have been observed.

Enada is a natural approach to energy, drive and health. Enada (NADH) energizes both body and brain activity, improves alertness, concentration, emotion, drive, hormone secretion and overall mood enhancement. It helps to improve brain cell performance and helps keep cells alive for a longer period of time. The more Enada (NADH) a cell has available, the more energy it can produce to perform its process efficiently. Enada (NADH) is available to everyone whose lifestyle demands increased energy, vitality and mental activity.

ENADA (NADH): SAFETY AND TOLERANCE

Although Enada (NADH) is marketed as a nutritional supplement, Birkmayer Pharmaceuticals has launched two clinical trials to prove scientifically that Enada is effective. Before these studies could get started they had to also prove to the Food and Drug Administration (FDA) that the stable oral form of Enada (NADH) is a safe substance.

Since the mid-'80s more than 3,000 parkinsonian patients have received NADH, either as intravenous infusion or in the form of oral tablets. No adverse or side effects have been observed in these patients. Additionally, 205 patients suffering from depression received NADH also, either parenterally or in tablet form. All patients reported an improvement of their symptoms. No adverse or side effects or interference with other antidepressive drugs they were taking were observed.

There are a number of patients who have been receiving treatment with Enada daily for over three years. Their only observation is that they feel better and are realizing increased physical and mental energy. No side effects have been observed with this continuing long-term use.

Extensive toxicology studies have been performed in order to demonstrate the safety of Enada (NADH). In one study rats received 1,000 mg/kg of NADH as a single intravenous dose, and the animals were observed for 14 days. All rats survived. Immediately after dosing, their respiration was elevated and there were signs of lacrimation. However, one hour after dosing the signs were no longer apparent and during the remainder of the 14-day observation period all rats appeared normal. If we transfer this dose to the human level it would mean that a single injection of 70,000 mg to a person weighing 70 kg (154 pounds) can be tolerated without complication. If we compare this amount with the 5 mg of Enada daily our patients usually take, this value is 14,000 times higher than the daily dose.

In fact, Enada (NADH) is considered so safe that individual dosage levels, regardless of age, may be custom tailored to suit individual health or training needs.

ENADA (NADH): NUTRITIONAL APPLICATIONS

ATHLETIC PERFORMANCE AND ENERGY ENHANCEMENT

In 1995 a study was conducted among competitive-level cyclists and long-distance runners. A significant range of performance improvements was recorded. Effects observed included increased oxygen capacity, decreased reaction time and greater mental acuity and alertness. The group of competitive athletes were given one Enada tablet 5 mg daily for one month. Five athletes experienced improved reaction time by up to 10 percent; eight athletes improved 10 to 20 percent, and three athletes experienced over 20 percent improvement. These represent impressive improvements for young, well-conditioned competitive athletes.

Recently a study with a European champion soccer team was performed. All players were taking Enada 5 mg for one month. Blood samples were collected before and after the four-week treatment period. The L-dopa blood level increased in all the athletes between 30 and 100 percent. L-dopa is instantly converted to the neurotransmitter dopamine, and dopamine is responsible for muscle strength, instinct movements, spontaneous reactions, libido and emotional drive. All but three athletes increased their noradrenaline levels. Noradrenaline increases vigilance, alertness, concentration and stress capacity. The players reported these features to have increased after taking Enada.

Given the positive data from the above studies and to test the potential energy-enhancing effect of Enada (NADH), among a group of competition long-distance runners and triathletes, a double-blind placebo study is being conducted. The study is under way at the Nicholas Institute of Sports Medicine and Athletic Trauma (NISMAT) at Lenox Hill Hospital in New York City, a world recognized Sports medicine institution. The objective is to further determine the beneficial effects of Enada (NADH) in young, healthy individuals performing normal, regular physical exercise.

Dr. Gilbert Gleim, Director of Research at NISMAT, stated that they have been approached by a number of nutritional supplement companies in the past who were interested in having NISMAT test their products, but they declined all requests. However, in the case of Enada they felt that the prior research warranted their involvement in conducting the double-blind study. Published findings from this study will be available in early 1998.


A POTENTIAL MEMORY ENHANCER

Memory is not a single function, but rather is composed of multiple systems of processes. Memory can be defined as the storage of information, signals and stimuli received by our five senses and the retrieval of this stored information. The brain is regarded as the central site of memory. However, it is a highly specialized and differentiated organ with many different regions such as the brain stem, the basal brain area, the midbrain and the brain cortex. There is a close link between information perception, processing, storage and retrieval. Only information storage and retrieval are regarded as memory.

The major prerequisite for memory is cognition. Cognition is the process of receiving signals from outside of the organism via our five senses. Stimuli from outside trigger biochemical reactions in the cells of the central nervous system and certain molecules transduce information from one form to another. These neurotransmitters are responsible for vegetative as well as cognitive performance. The best-known neurotransmitters are adrenaline, its precursor, noradrenaline, and dopamine. If the production of these neurotransmitters can be increased, cognitive performance will improve.

The rate limiting enzyme for dopamine and adrenaline biosynthesis is tyrosine hydroxylase. This enzyme can also store information received from an outer stimulus and can remember the same stimulus later on.

Using the definition of memory given above, the enzyme tyrosine hydroxylase is a memory molecule, and an increase of its cellular concentration and activity should amplify the memory capacity of the individual. Studies performed at our institute revealed that NADH is able to stimulate tyrosine hydroxylase and dopamine production in cultured nerve cells up to six times.

 ***More than 80 percent of patients exhibited a beneficial clinical effect with regard to cognitive abilities.***

Further evidence of the memory-enhancing effectiveness of NADH is derived from in vivo trials where NADH was injected into rats and a dose-dependent increase in L-dopa accumulation in a distinct brain area was found. The most convincing evidence that NADH stimulates dopamine production comes from clinical research on Parkinson's and Alzheimer's patients. More than 80 percent of these patients exhibited a beneficial clinical effect with regard to cognitive abilities.

Our observations with parkinsonian patients have been confirmed by a double-blind study performed at the University Clinic in Germany. Researchers found that not only did patient's disability improve, but also that their levels of L-dopa and dopamine were significantly increased.

In conclusion, NADH stimulates the production of the neurotransmitters dopamine and noradrenaline and also the activity of the enzyme tyrosine hydroxylase, which as explained above is a memory molecule. Hence NADH can be regarded as a memory enhancer.

A number of anecdotal cases confirm these biochemical explanations of memory enhancement. Here is one from a physician:

For most of his life Richard Madsen had been a big reader, but lately he had not been able to read more than five minutes without losing interest. He could not concentrate - he could not focus. He also had frequent memory lapses. At age 69, Richard's memory and concentration had been getting progressively worse for four years. I could not promise him anything, but I believed I knew of a treatment that could help. I put him on 2.5 mg a day of the natural coenzyme Enada (NADH). He took one tablet a day for a week, two tablets a day for the second week, then, for a third week, three tablets. Something startling happened! After the third week, Richard's ability to focus his attention had suddenly returned! Now he was able to read and concentrate for an hour or more! Additionally, his energy improved and his memory became significantly better! I could barely believe my eyes! I'm a doctor - a scientist - and I'd never seen such a tremendous improvement. I wanted to make sure it was the Enada (NADH) that had really caused these changes, so I had Richard lower the dosage for a week. Sure enough, Richard sank back to his original mental state. When he resumed the 3-tablet dosage, his concentration and memory returned again! Friends, I hope you can see as well as I can what incredible potential lies within this natural substance.

(Robert Atkins, M.D., Dr. Atkins' Health Revelations Supplement)

ANTI-AGING POTENTIAL

Aging is a highly complex biological process associated with a progressive decline in the performance of many, if not all, organs in the body. As we age, the NADH and energy levels in our cells decrease. In other words, aging is loss of energy. When the cellular energy declines below a certain threshold the cell dies and the tissue degenerates. However, if the energy production in the organs of elderly people can be kept at the same level as that of a

younger person this may translate to feeling younger and more active than actual biological age would indicate.

☞ NADH's further anti-aging potential is derived from its nature as one of the strongest biological antioxidants.

NADH plays a key role in the energy production of all living cells, as described at the beginning of the section "How NADH Works". If the cell has enough energy, it can perform all its processes more efficiently. The more NADH a cell has available, the more energy it produces and the longer it will stay alive. Less cellular energy means shorter cell life, faster aging, and potentially earlier cell death. The more NADH a cell has available, the better the DNA repair System will function, protecting the individual from degenerative chronic diseases such as arteriosclerosis, cancer, diabetes, rheumatoid arthritis, and immunodeficiencies. NADH's further anti-aging potential is derived from its nature as one of the strongest biological antioxidants. Due to this feature NADH can prevent damage to the cells by scavenging free radicals.

ENADA (NADH): MEDICAL APPLICATIONS

PARKINSON'S DISEASE

Parkinson's disease is characterized by the three major symptoms: tremor (shaking), rigidity (stiffness), and akinesia (inability to move). The organic cause of this disease lies in the brain. Certain areas in the basal part of the brain called black substance (substantia nigra) and the striped core (striatum) degenerate. First symptoms of Parkinson's disease are observed when 50 percent of these areas are irreversibly damaged.

This damage causes a deficit in one of the most important messenger substances of the central nervous system, dopamine. This neurotransmitter is responsible for muscle tone, upright position, muscle strength, libido and emotional drive. In many patients the tremor of one arm or one leg is the very first hint of the disease, particularly at its early stage. Later periods of stiffness in the legs and other parts of the body are recognized by the patient as well as a slow and shuffling walk. Akinesia, a common symptom of the parkinsonian, is described as slowness in initiation of willed, voluntary movement. Parkinsonian patients also have difficulty changing from one movement pattern to another and sustaining repetitive movements. Additionally, simultaneous acts, such as extending the hand to shake hands while rising from a chair, are difficult to perform. Rigidity, a constant uniform increase in resistance to passive movement while the person tries to relax, is a classic symptom of alterations in the basal brain. These symptoms should not be ignored, as there is a reasonable and efficient treatment available for PD and it should be emphasized that the life expectancy can be normal if the appropriate treatment is given.

The classical therapy for Parkinson's disease is Sinemet, which is L-dopa combined with a decarboxylase inhibitor. This treatment, which was first discovered by Professor Walther Birkmayer in 1961 is a pure substitutional therapy designed to resupply dopamine due to an insufficient level in the brain.

By taking L-dopa, many patients are relieved of their symptoms and become more mobile and less rigid. The classical tremor is usually reduced but does not disappear in all the patients. L-dopa, however, has certain drawbacks. First of all, it stops the body's own production of L-dopa in the brain due to a "feedback" mechanism. Feedback inhibition is a general biological phenomenon by which cells stop producing a compound if they have enough available, so that the therapeutic supply of L-dopa reduces the activity of the dopamine-producing enzyme. This is true for hormones, for neurotransmitters, and many other biological substances. The other drawback of L-dopa is that it is absorbed in unphysiologically high amounts, causing an overloading of the body and the brain with L-dopa and dopamine respectively. Dopamine is

then oxidized, forming enormous amounts of free radicals. Radicals are highly active molecules which do react with every substance in a cell, in particular the lipids of the cell membrane, resulting in damage to the cells. In other words, dopamine can cause further harm to the already degenerated brain area. This has been observed in parkinsonian patients, in particular after a long-term treatment of ten or more years. This prompted the thinking and development of a completely new approach. The new approach for Enada (NADH) is to stimulate the body to produce its own L-dopa rather than substituting for the deficit level with drugs such as Sinemet. From the biological point of view this approach represents a much better principle.

Therefore, in an open-label trial, 470 Parkinson's patients received a daily dose of 5 mg Enada. The treatment was given every other day for 14 days. Mobility, in particular walking, pushing, posture, speech as well as the ability to mimic another person's behavior or speech, improved after two weeks of Enada. The beneficial effect of NADH was confirmed by a university clinic in Germany in a double blind, placebo-controlled trial with the peroral form of 5 mg NADH every second day for 4 weeks to 60 patients. The improvement in the NADH group was significant at 2.9 points, compared to only 0.7 points in the placebo group, again demonstrating the beneficial effect of NADH.

DEPRESSION

Depression is a neuropsychiatric disorder which disturbs behavior, physical and mental activity, emotional effectiveness, overall mood and many other features which are essential for a person's normal active life. The main symptoms are listed in Table 2. A number of studies revealed that certain neurotransmitters, in particular adrenaline, dopamine, serotonin and their metabolites, play a role in the evolving depression symptoms.

Table 2: Symptoms of Depression	
1. Lack of enterprise	11. Loss of libido
2. Lack of enjoyment	12. Remission in the evening
3. Lack of interest	13. Compulsive brooding
4. Lack of initiative	14. General pessimism
5. Lack of concentration	15. Self-reproach
6. Reduced work capacity	16. Feelings of guilt
7. Loss of sleep	17. Anxiety
8. Loss of appetite	18. Suicidal tendencies
9. Loss of weight	19. Hypochondriac ailments
10. Constipation	20. Feelings of the futility of life

The improvement in the NADH group was significant

The coenzyme NADH has been used in an open-label trial as medication in 205 patients suffering from depression with various clinical symptoms. NADH was given either orally as Enada, or by intramuscular or intravenous injection. The duration of therapy ranged from 5 to 310 days; 93 percent of the depressed patients exhibited a beneficial clinical effect. An improvement up to 44 percent with a mean value of 11.5 was observed.

DEMENTIA AND ALZHEIMER'S DISEASE

Dementia can be defined as loss of intellectual functions such as thinking, remembering, and reasoning of sufficient severity to interfere with a person's daily functioning. It cannot be defined as a disease itself, but rather as a variety of symptoms which may accompany the physical condition or disease. The most common of the dementing disorders is Alzheimer's disease, affecting as many as 4 million Americans. Approximately 5 percent of the population over 65 years is affected. The clinical profile of dementia consists of a) loss of memory, b)

deterioration of intellectual functioning, and c) impairment in the activities of daily living. Symptoms of this disease include a gradual memory loss, decline in ability to perform routine tasks, disorientation in time and space, impairment of judgment, personality change, difficulty in learning, and loss of communication skills.

In an open-label trial 17 patients were studied. All had been diagnosed at various neurological clinics as having presenile and senile dementia of the Alzheimer's type. They received NADH. The total dosage was two tablets of Enada 5 mg per day, which was given in the morning 30 minutes before their first meal.

After a three-month treatment period an improvement as measured by the Mini Mental State Examination (MMSE) and the Global Deterioration Score (GDS) could be observed.

On the basis of these results an FDA-approved clinical study of Enada (NADH) was launched at the Department of Neurology of Georgetown University Medical Center. Directed by Stanley Cohan, M.D., Ph.D., Professor and Chairman Department of Neurology, Georgetown University Medical Center in Washington, D.C., this study is now well under way.

“NADH is a naturally-occurring compound with few side effects that has shown promise in Europe in preliminary trials with Alzheimer's disease patients,” says Dr. Cohan. “Currently, FDA-approved proven treatments and therapies for people with Alzheimer's disease are inadequate and this is a first step toward determining if this coenzyme is of potential benefit to Alzheimer's patients.”

CHRONIC FATIGUE SYNDROME

Chronic Fatigue Syndrome is characterized by a combination of various symptoms and complaints not necessarily related. It affects millions of Americans, 70 percent of whom are women. CFS is not as well defined as diseases such as diabetes, which can be diagnosed with 100 percent certainty by testing the blood sugar level. There is no specific test to prove a syndrome; it is therefore very difficult to diagnose. The Centers for Disease Control (CDC) have defined criteria for Chronic Fatigue Syndrome, which are listed in Table 3.

1. Fatigue for at least 6 months	7. Fatigue that lasts 24 hours or longer after exercising
2. Mild fever or chills	8. Headaches
3. Sore throat	9. Joint pain without swelling
4. Painful lymph nodes in the neck	10. Short-term memory problems, forgetfulness, inability to concentrate
5. Unexplained muscle weakness	11. Depression
6. Muscle pain	12. Sleep disturbance

These symptoms have to persist for at least 6 months in order to comply with the definition of Chronic Fatigue Syndrome. The CDC have not stated whether all or how many of the symptoms have to be present in order to fulfill the definition of CFS.

Most of the symptoms characteristic of chronic fatigue could also be caused by chronic diseases such as cancer, heart failure, immunodeficiency, rheumatoid arthritis and many other chronic conditions. All these diseases have to be excluded before a definitive diagnosis of Chronic Fatigue Syndrome can be made. A variety of blood tests are required in order to find out what might be the cause of the debilitating fatigue. They are listed in Table 4.

1. Blood cell counts	5. Potassium
2. Hemoglobin	6. Magnesium
3. Hematocrit	7. Thyroid hormones
4. Iron	8. Tumor markers

A possible cause of chronic fatigue syndrome is a depletion of the cellular energy-storing molecule ATP. An ATP deficiency is accompanied by severe fatigue, muscle weakness and muscle pain. Rest and sleep offer no relief as minor exertions result in a continued debilitating tiredness.

Based upon the metabolic theory, an FDA-approved double-blind placebo-controlled crossover study was launched at Georgetown University Medical Center using Enada (NADH). The proposed mechanism of action for NADH is to replenish the depleted cellular stores of ATP, thus improving the fatigue and cognitive dysfunction. Dr. Bellanti, the principal investigator in this study, and Director of Georgetown's International Immunity Center, states that "some CFS patients participating in the study show marked improvement over time." Based on these preliminary findings, Georgetown's Immunology Department is expanding the double-blind CFS study.

ENADA (NADH): IMPORTANCE FOR PEOPLE TODAY AND IN THE FUTURE

Enada (NADH) is the world's first and only stabilized, absorbable, patented, tablet-form NADH dietary supplement. It is now available to everyone whose lifestyle demands increased energy, vitality and mental clarity. In other words, it is beneficial not only for patients suffering from chronic fatigue syndrome, Alzheimer's disease, depression or Parkinson's disease, but for any normal, healthy individual whose lifestyle demands more energy. Even highly competitive athletes can benefit from the energy-enhancing potential of Enada. On the basis of its biological functions, Enada (NADH) will safely improve the quality of life for the majority of consumers. However, this is only one part of Enada (NADH)'s importance. The other part is the long-term preventive potential that Enada (NADH) offers, especially since preventive health care is a significant economic issue for all of us. Take, for example, Alzheimer's disease. The Alzheimer's Association says that four million Americans are afflicted and that the disease costs 90 to 100 billion dollars a year. If taking Enada (NADH) as an Alzheimer's preventive treatment helps delay the onset of the disease by only one year in just 10 percent of the Alzheimer's candidates, not only will we improve the quality of life for these Americans, but we could also save 10 billion dollars a year in direct health-care costs. Significant health-care savings can also be obtained with patients suffering from chronic fatigue syndrome. The Centers for Disease Control estimate the number of patients in the U.S. at 8 percent of the population. This is approximately 20 million people. Based on a conservative projection health-care cost savings would total several billions of dollars annually.

Enada (NADH) is one of the first nutritional supplements whose medical efficacy is being demonstrated in FDA approved clinical trials. This new approach should motivate other nutritional supplement companies to follow the Enada testing protocol. These substances will be regarded as the missing link between nutritional supplements and pharmaceuticals; in other words they can be classified as nutraceuticals. This paradigm shift taking place today is intended to speed up the process of bringing life-improving products more quickly to the marketplace. Enada (NADH), on the basis of its many physiological functions, will be one of the most important nutraceuticals - if not the most important. The scientific potential and benefits of Enada (NADH) are being recognized, especially when we consider its energy-generating potential at the cellular level, its function as an enhancer of the cellular immune system or as a potent antioxidant. Further clinical trials will confirm that the capacity of the immune system can be increased by supplementing with Enada (NADH).

Also the antioxidative features of Enada (NADH) offer new protection from chronic diseases caused by the influence of free radicals attacking the body. If preliminary findings obtained recently that Enada (NADH) lowers cholesterol and blood pressure are confirmed by

extensive clinical studies in humans, the relevance for the public will be enormous. Imagine targeting hypertension with a safe natural substance such as Enada! This certainly is an excellent alternative, due to its biological origin and its high degree of safety to most of the antihypertensive drugs presently available. If the lifesaving effects of NADH observed in some anecdotal cases of stroke and heart failure are confirmed in a larger group of patients, the consequences for their life expectancy and their overall quality of life will be remarkable.

ENADA (NADH): ACTUAL CONSUMER USAGE EXPERIENCE

The majority of its users take Enada every day; however, a growing number have discovered that they derive satisfactory benefits even when taking it every other day. This includes individuals who have been taking Enada (NADH) daily for more than three years. With this long-term usage experience, individuals continue to report that they just feel better. They have not experienced any side effects, even after this long term regimen. Also, a growing number of physicians in the U.S. have been using Enada (NADH) with their patients. Feedback has been very positive, one doctor stating that Enada is the best antidepressive substance he has ever experienced. Another doctor commented that the effect of Enada with his Parkinson's and Alzheimer's patients has been remarkable. At our institute we have treated a number of Alzheimer's patients who have moderate to severe symptoms. They continue to realize increased physical and mental energy. No side effects have been observed in these patients, even after long-term treatment for more than two years.

The actual experience of consumers and patients receiving Enada (NADH) tablets provides the most convincing evidence about the safety of this biologically ubiquitous coenzyme:

I am an attorney and have been taking 5 mg of Enada daily. My ability to "zero in," concentrate, and focus on issues has improved. I feel like I did when I was in law school years ago. (Lynn L., Illinois, customer comment from *The Supplement*, July 1996.)

My experience with Enada goes back a year ago and in my consulting practice I have found it to be very helpful in fibromyalgia & chronic fatigue syndrome. Along with this many of my clients have also reported improvements in mood and in general well being. (Tony X., Natural Health Consultant, Lodi, New Jersey.)

I heard of Enada through a friend who is a triathlon runner and swears by it. . . it has reduced his recovery time and has given him a longer runner's high. (Rudy B., Syracuse, New York.)

I found out about Enada when researching the Internet for my father's Alzheimer's. He has gone from being incoherent in a wheelchair to normal! People want to know how! (Barbara M., Greenville, Texas.)

I began my research (Harvard Parkinson's Disease Forum on the World Wide Web) reading everything I could find available concerning the development, clinical experiments and personal testimonies. I decided to order your company's Enada. Within the first week, my family and I began to see a drastic change in my facial masking and rigidity. I decided to start my NADH slowly, beginning with only one 2.5 mg tablet. After a week, I increased my dosage and now, only a month into the NADH therapy, I am taking 12.5 mg without any Sinemet. I thought it would be interesting for you to know how this natural supplement has aided me in my management of this disease. I can only hope that the FDA will continue to support it through research. My only regret is that I did not know sooner, but without it I would hate to imagine where I would be. My deepest thanks to your company. (William C., Fayetteville, Tennessee.)

I heard about NADH from one of my instructors (Southwest College of Naturopathic Medicine). I knew about NADH and its role in cellular energy metabolism from Biochemistry but was not aware of it being available as a supplement. I have suffered from chronic fatigue and adrenal burnout from increased stress since I started school three years ago. I decided to try the product. I have been taking ENADA, 5mg. daily in the a.m. for a little over one month

now and have had absolutely phenomenal results. Prior to beginning the ENADA, I had no energy reserve at all, as I became very stingy of how I was going to spend my energy in any given day. I needed more and more coffee to remain somewhat alert. I had what I called “brain fog“. I felt sluggish kind of like a cloud hanging over my body, could not concentrate, sometimes forgetful and felt that my body was falling apart. On many mornings, I found it very difficult to get up; my body felt heavy and couldn’t wake up. It was difficult to get through the long hours that I keep to get through my training. Even with taking an adrenal glandular supplement and dessicated thyroid, it did not help much. From the first day that I took ENADA, I noticed the difference immediately. I all of a sudden had mental clarity with a sharp state of mind, was able to think clearly, and felt more energetic. I started exercising on my stationary bicycle just about every day for at least 30 minutes. I am amazed at how easy it has been. My muscles seem to have an endless supply of energy to keep going (I would get very fatigued very quickly before). My muscles don’t get tired or painful and I could easily keep going longer than 30 minutes without feeling tired afterwards or needing to rest. It has definitely increased my energy reserve for exercising. I no longer need coffee to get me through the day. If I drink coffee now, its by choice, not because I need it for the caffeine boost. My energy has shifted and I definitely feel more alive. It’s easy for me to get out of bed in the morning at my usual 6 a.m. My mind and body feel alive from right when I get up without needing this overwhelming sluggishness, my mood has also improved. So what more can I say. I am so excited about the merits of this product as it has worked so well for me, I will continue to use it for myself and recommend or perscribe it to the many people I work with, as I already have. (Ciara G., Scottsdale, Arizona)

My energy level is much improved. My mental outlook is more positive since starting my Enada protocol as recommended by Professor George Birkmayer. Congratulations to an outstanding scientist. (Joseph C., Las Vegas, Nevada).

ENADA (NADH): HOW AND WHEN TO TAKE

Dosage requirements and response time vary from individual to individual. Optimal dosage should be established individually. A daily dosage of 2.5 mg shows results in healthy people; people with neurological disorders may require higher amounts. Enada tablets should always be taken whole with half a glass of water only on an empty stomach, 20-30 minutes before a meal, preferably in the morning.

Enada is available as a dietary supplement in the U.S.A. in 2.5 mg and 5 mg tablet form.

Nutritional and Energy Enhancement

2.5 to 5 mg daily or every other day depending upon individual response.

Therapeutic Treatment

10 to 15 mg daily, depending upon individual requirements and the guidance of your physician or health-care professional.

These recommendations are intended for information only. Always seek the advice of a qualified physician or health-care professional when taking any nutritional or pharmaceutical substance.

CONCLUSIONS

This booklet is intended to provide the reader with the most current data available for NADH, the natural coenzyme 1, including the significance and therapeutic benefits of Enada, the only stabilized, absorbable, oral (tablet) form of NADH available. At Birkmayer Pharmaceuticals our only mission is to develop safe, reliable and effective products which will improve the quality of life for all people. We believe that Enada (NADH) represents a quantum leap forward in our continued quest. We accept the challenge of proving the efficacy of our products through sound, quantifiable, scientific principles and clinical research studies. . . not

marketing hype. We have invested millions of dollars in research to achieve Investigative New Drug (IND) status for Enada by the Food and Drug Administration, enabling us to conduct FDA-approved clinical trials at prestigious medical institutions such as Georgetown University Medical Center and the Nicholas Institute for Sports Medicine at Lenox Hill Hospital. Our objective is to demonstrate beyond a shadow of doubt that Enada increases cellular energy in the body. To achieve this we went to both ends of the medical and athletic spectrum. We are testing patients suffering from chronic fatigue syndrome (a total loss of energy) to highly conditioned, competitive athletes who compete in triathlons (a total need of energy). By scientifically demonstrating and validating increased energy performance through double-blind clinical trials, we will also provide energy enhancement and improvement for the benefit of all people who know, trust and experience our Enada (NADH).

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