The NAD Deficiency Diseases

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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.

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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.

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NAD+ metabolism in health and disease

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Nicotinamide adenine dinucleotide (NAD^+) is both a coenzyme for hydride-transfer enzymes and a substrate for NAD^+-consuming enzymes, which include ADP-ribose transferases, poly(ADP-ribose) polymerases, cADP-ribose synthases and sirtuins. Recent results establish protective roles for NAD^+ that might be applicable therapeutically to prevent neurodegenerative conditions and to fight *Candida glabrata* infection. In addition, the contribution that NAD^+ metabolism makes to lifespan extension in model systems indicates that therapies to boost NAD^+ might promote some of the beneficial effects of calorie restriction. Nicotinamide riboside, the recently discovered nucleoside precursor of NAD^+ in eukaryotic systems, might have advantages as a therapy to elevate NAD^+ without inhibiting sirtuins, which is associated with high-dose nicotinamide, or incurring the unpleasant side-effects of high-dose nicotinic acid.

The biology and biosynthesis of NAD^+

Nicotinamide adenine dinucleotide (NAD^+) and its phosphorylated and reduced forms, $NADP^+$, NADH and NADPH, have central roles in cellular metabolism and energy production as hydride-accepting and hydride-donating coenzymes. Discovery of the coenzymatic activity of NAD^+ is reviewed in Box 1 and the redox chemistry that is mediated by NAD^+ is schematized in Figure 1. Such reactions are not destructive in the sense that NAD^+ and NADH are interconverted by hydride transfer. As with all phosphorylated natural products, NAD^+ is biosynthesized from smaller units and is broken down. Whereas NAD^+ breakdown was thought once to be a nonspecific process, we now realize that NAD^+ consumption is linked intrinsically to signaling reactions inside and outside cells that control gene expression, Ca^{2+} mobilization, cell death and aging. In this review we provide a detailed overview of NAD^+ metabolism with emphasis on the potential for NAD^+-boosting therapies to maintain health and treat diseases.

Tryptophan is the *de novo* precursor of NAD^+ in all vertebrates and almost all eukaryotes investigated. People who subsist on tryptophan-poor diets run the risk of developing the nutritional deficiency pellagra unless their diet is supplemented with one of the classical vitamin precursors of NAD^+, nicotinic acid (Na) or nicotinamide (Nam), which are collectively termed niacin. As shown in Figure 2, the salvage pathways for the two niacins are encoded by different genes and, thus, might not be expressed equally in all vertebrate tissues. The blood–borne bacterium *Haemophilus influenza* can not synthesize NAD^+ *de novo* or salvage niacins (see Glossary). Instead, it depends on uptake of nicotinamide riboside (NR) and a bacterial pathway that converts NR to NAD^+ by phosphorylation and subsequent adenylylation [1]. Recently, it has become apparent that fungi and vertebrates encode eukaryotic NR kinases (Nrk isozymes) to salvage NR, a third vitamin precursor of NAD^+, which occurs in milk [2]. Precisely how and where, intracellularly and extracellularly, NR is produced is unknown and a matter of active research.

The abundance of NAD^+ in human cells is controlled by many factors. For example, genes such as *IDO*, which encodes the *de novo* biosynthetic enzyme indoleamine 2,3 dioxygenase, are under transcriptional control [3], whereas nicotinamide mononucleotide (NMN) adenylyltransferases (Nmnats), Nmnat1, Nmnat2 and Nmnat3, are localized differentially [4]. NAD^+ is partitioned into reduced (NADH), phosphorylated ($NADP^+$) and reduced, phosphorylated (NADPH) pools, in addition to the NAD^+ pool. Each pool resides differentially in membrane-bound compartments and is partially sequestered from free NAD^+ by binding to proteins.

Three classes of NAD^+ consumers

The abundance of NAD^+ is also regulated by breakdown, largely because the molecule is not only coenzyme for oxidoreductases but also a substrate for three classes of

Glossary

Ecto-enzymes: membrane-bound enzymes with an extracellular active-site.
Flushing: a painful condition that consists of 'hot flashes', reddening and heat in the extremities.
Reverse cholesterol transport: the multi-step process by which HDL particles deliver cholesterol to the liver for excretion through bile acids.
Salvage and *de novo* biosynthesis: biosynthetic pathways are termed salvage if the distinctive piece of the final product is recovered from breakdown products and *de novo* if the distinctive piece is produced from units that require large rearrangements. NAD^+ consists of an ADP-ribose group linked to Nam. Whereas the AMP moiety of ADP-ribose always derives from ATP, the distinctive piece of NAD^+ is nicotinamide, which is either salvaged or synthesized *de novo*. The three vertebrate salvage and one *de novo* NAD^+ biosynthetic pathways are depicted in Figure 2.

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Disclosure statement

C.B. is inventor of intellectual property related to nicotinamide riboside kinases and uses of nicotinamide riboside. The intellectual property is owned by C.B.'s employer, Trustees of Dartmouth College, and therapeutic uses are licensed by Sirtris Pharmaceuticals, a firm for which C.B. serves on the Scientific Advisory Board.

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Box 1. History of the NAD$^+$ coenzyme

In the early 20th century, Arthur Harden and co-workers reconstituted cell-free glucose fermentation with two fractions, one termed 'zymase' that was heat-labile and retained by dialysis, and one termed 'cozymase' that was heat-stable and passed through dialysis. Zymase was not a purified enzyme but a protein fraction that contained glycolytic enzymes. The cozymase fraction contained ATP, Mg^{2+} and the NAD$^+$ coenzyme, the structure of which was determined by Otto Warburg. In glucose fermentation, NAD$^+$ functions as the hydride acceptor in the step catalyzed by glyceraldehyde-3-phosphate dehydrogenase, producing NADH and diphosphoglycerate. Similarly, NADH functions as the hydride donor for alcohol dehydrogenase, which is required for the reduction of acetaldehyde to ethanol, regenerating NAD$^+$. Numerous hydride transfer enzymes or oxidoreductases interconvert either NAD$^+$ and NADH or NADP$^+$ and NADPH to reduce or oxidize small-molecule metabolites (see Figure 1 in the main text).

enzymes that cleave NAD$^+$ to produce Nam and an ADP-ribosyl product. Although, historically, these enzymes have been called NAD$^+$ glycohydrolases, NAD$^+$-dependent ADP-ribosyl transferase is a more precise term [5]. However, to avoid confusion with dedicated protein mono(ADP-ribosyl) transferases, we refer to the enzymes historically termed NAD$^+$ glycohydrolases as NAD$^+$ consumers. As depicted in Figure 3, the three classes of NAD$^+$ consumers are (i) ADP-ribose transferases or poly(ADP-ribose) polymerases, (ii) cADP-ribose synthases and (iii) sirtuins (type III protein lysine deacetylases).

The substantial flux through NAD$^+$-consuming pathways explains why people require niacin supplementation when tryptophan is limiting. If NAD$^+$ were only a coenzyme (i.e. not consumed but merely interconverted between oxidized and reduced forms by hydride transfer), the nutritional requirement to support ongoing synthesis in excess of that provided by the *de novo* pathway would be difficult to explain. Thus, we now believe that either dietary niacins or NR in conjunction with niacin and/or NR-salvage are required to maintain NAD$^+$ in cells that are undergoing rapid NAD$^+$ breakdown (Figure 2).

ARTs and PARPs

ADP-ribose transferases (ARTs) and the more numerous, poly(ADP-ribose) polymerases (PARPs) consume NAD$^+$ to create an ADP-ribosyl protein modification and/or to form the ADP-ribose polymer, PAR (Figure 3). In a comprehensive review of the function of ARTs and PARPs, de Murcia describes numerous conditions that induce this type of NAD$^+$ catabolism and the consequent ADP-ribose reaction products in DNA-damage responses, epigenetic modification, transcription, chromosome segregation and programmed cell death [6]. Because of the roles of PARPs in cell death, there are substantial pre-clinical and investigative efforts to inhibit PARP to protect against cardiac, inflammatory and neurodegenerative conditions [7]. However, because PARP has complex roles in cell survival and repair signaling in addition to mediating cell death, it might be difficult to develop neuroprotective strategies that involve chronic inhibition of this essential enzyme [7]. Moreover, much of the benefit associated with inhibition of PARP might be related to protecting cellular NAD$^+$, such that NAD$^+$-boosting therapies targeted to tissues in which PARP is activated might be safer and as effective.

cADP-ribose synthases

cADP-ribose synthases are a pair of ecto-enzymes also known as the lymphocyte antigens CD38 and CD157, which produce and hydrolyze the Ca^{2+}-mobilizing second-messenger cADP-ribose from NAD$^+$ [8–10] (Figure 3). CD38 catalyzes a base exchange between NADP$^+$ and Na to form Na adenine dinucleotide phosphate (NaADP) [11], which is also a hydrolytic substrate [12]. All the products of CD38 (cADP-ribose, ADP-ribose and NaADP) have distinctive roles in Ca^{2+} mobilization.

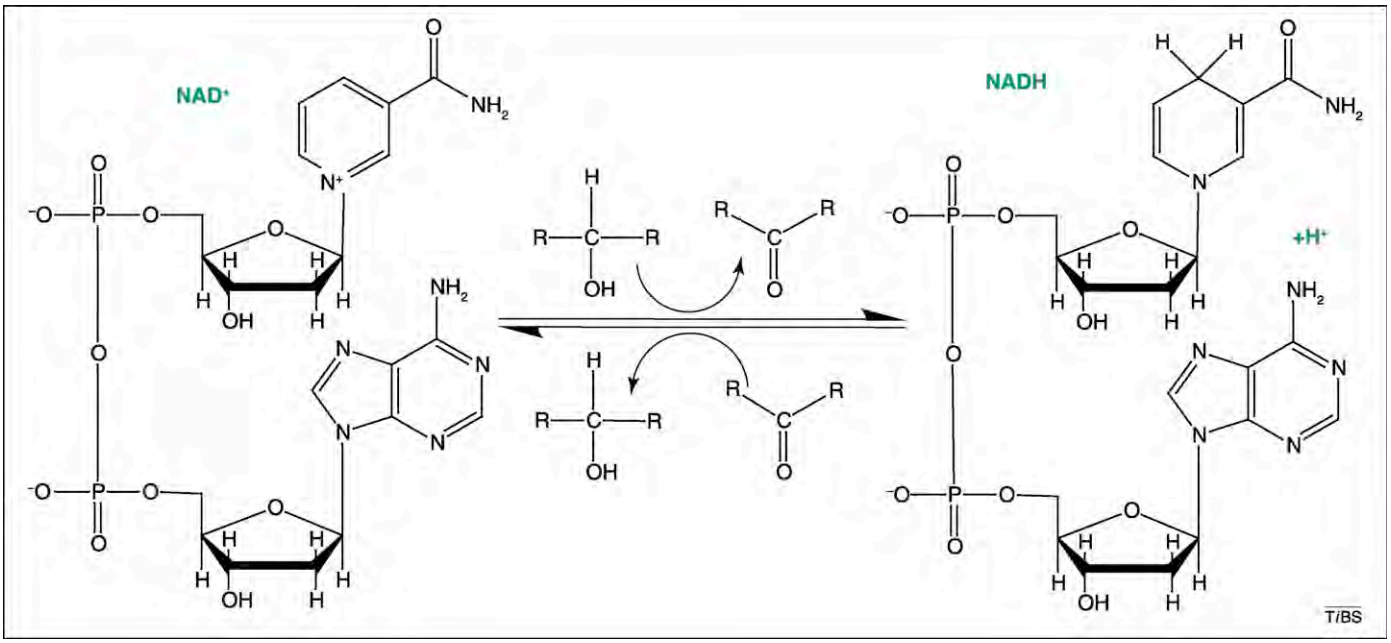

Figure 1. NAD$^+$ as a coenzyme for reversible hydride transfer. In a typical NAD$^+$-dependent oxidation, an alcohol is converted to the corresponding aldehyde with the production of NADH plus a proton. In the NADH-dependent direction, an aldehyde is reduced to an alcohol, which regenerates NAD$^+$.

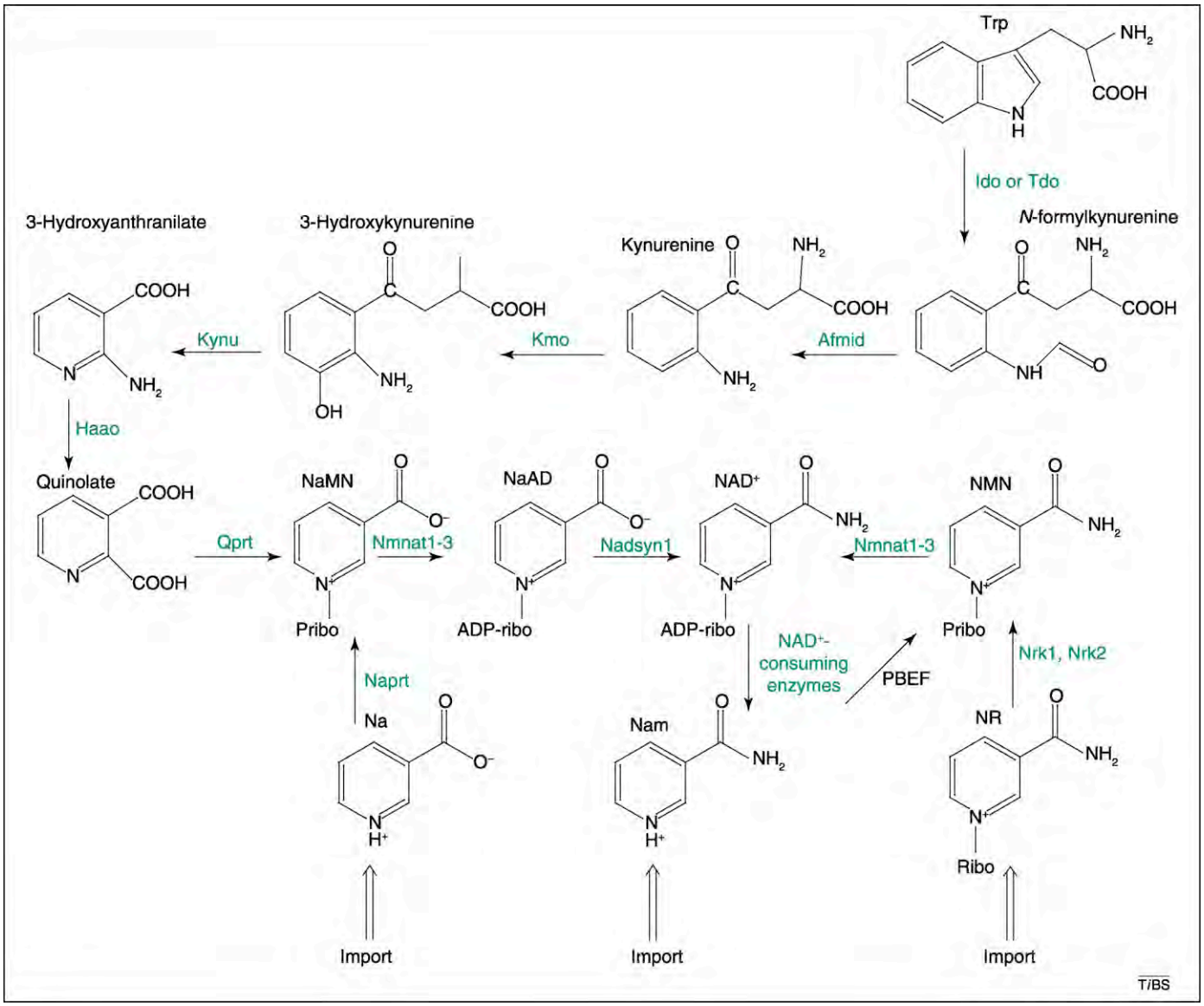

Figure 2. Intracellular NAD^+ metabolism in vertebrates. *De novo* synthesis begins with the conversion of tryptophan to *N*-formylkynurenine by either indoleamine dioxygenase (Ido) or tryptophan dioxygenase (Tdo). Arylformamidase (Afmid) then forms kynurenine, which is used as substrate by kynurenine monooxygenase (Kmo) to form 3-hydroxykynurenine. Kynureninase (Kynu) then forms 3-hydroxyanthranilate, which is converted to 2-amino-3-carboxymuconate semialdehyde (not shown) by 3-hydroxyanthranilate dioxygenase. The semialdehyde undergoes a spontaneous condensation and rearrangement to form quinolate, which is converted to NaMN by quinolate phosphoribosyltransferase (Qprt). NaMN is then adenylylated by Nmnat1, Nmnat2 and Nmnat3, to form nicotinic acid adenine dinucleotide ($NaAD^+$), which is converted to NAD^+ by glutamine-dependent NAD^+ synthetase (Nadsyn1). NAD^+-consuming enzymes (Figure 3) break the bond between the Nam and ADP-ribosyl moieties. Nam, which is also provided in the diet, is salvaged by a Nam phosphoribosyltransferase termed PBEF to NMN, which is adenylylated to form NAD^+ by Nmnat1, Nmnat2 and Nmnat3. Na, which is provided in the diet and, potentially, by bacterial degradative pathways in vertebrates, is salvaged by Na phosphoribosyltransferase (Naprt) to form NaMN. NR, which occurs extracellularly in blood and milk and can be provided in the diet, is salvaged by nicotinamide riboside kinases (Nrk1 and Nrk2). Na and Nam are also converted to nicotinuric acid and *N*-methylnicotinamide elimination products (not shown).

Sirtuins

Sirtuins, so named because of their similarity to yeast silent information regulator 2 (Sir2), are enzymes that function primarily in reversing acetyl modifications of lysine on histones and other proteins [5]. Also termed type-III histone deacetylases (HDACs), or, more precisely, type-III protein lysine deacetylases, sirtuins bind two substrates: the first is a protein or peptide that contains an acetylated lysine, and the second is NAD^+ [13] (Figure 3). Sirtuins position the leaving acetyl group to attack the ribose C1 carbon of the ADP-ribose moiety of NAD^+, which produces acetylated ADP-ribose plus Nam and the deacetylated protein lysine [14]. The acetylated ADP-ribose rearranges to form a mixture of 2′ and 3′ acetyl-ADP-ribose [15].

Sir2 was first identified as a positive regulator of gene silencing at cryptic mating-type loci. It functions in complexes that remodel chromatin to repress transcription and recombination in a manner that depends on reversing acetyl modifications on histone H3 and histone H4. Sirtuins from archaea, bacteria, yeast, invertebrates and vertebrates deacetylate histone and non-histone targets to alter enzyme activity and protein-complex formation, and to activate and repress transcription (Reviewed in [5]).

The relationships between sirtuins and ART activities are intimate and complex. For example, a trypanosomal sirtuin possesses both ART and deacetylase activity [16], whereas murine Sirt6 seems to be an ART but not a deacetylase [17]. In addition, activation of the Sir2 ortholog

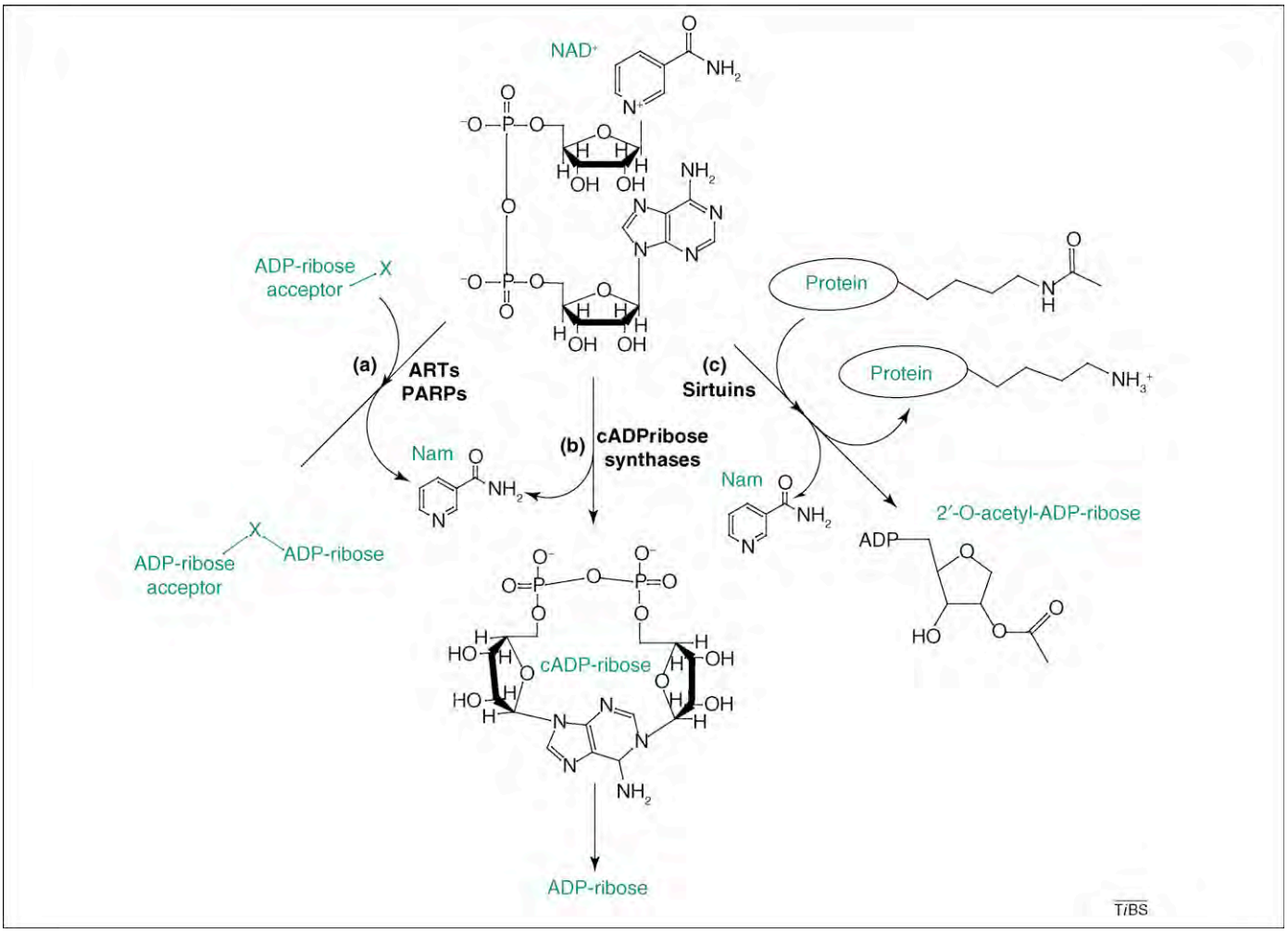

Figure 3. NAD^+ as a substrate for ADP-ribose transfer, cADP-ribose synthesis and protein lysine deacetylation. **(a)** ARTs and PARPs transfer ADP-ribose from NAD^+ as a protein modification with production of Nam. In the case of PARPs, the ADP-ribose acceptor, X, can also be ADP-ribose, forming poly(ADP-ribose). **(b)** cADP-ribose synthases cyclize the ADP-ribose moiety of NAD^+ with production of Nam. These enzymes also hydrolyze cADP-ribose. **(c)** Sirtuins use the ADP-ribose moiety of NAD^+ to accept the acetyl modification of a protein lysine, forming deacetylated protein plus Nam and, after acetyl-group rearrangement, a mixture of 2′ and 3′ O-acetylated ADP-ribose. Each NAD^+-consuming enzyme is inhibited by the Nam product.

Sirt1 is associated with reduction of PARP1 activity whereas deletion of Sirt1 increases the production of PAR [18]. Reciprocally, the cell death caused by activation of PARP1 in cardiac myocytes can be reduced by either administration of NAD^+ or increased NAD^+ biosynthesis, and the protective effect of NAD^+ biosynthesis depends largely on the presence of Sirt1 [19]. This constitutes direct evidence that therapy targeted to protect cellular NAD^+ is indicated by activation of PARP in heart failure.

Nam metabolism, and intracellular and extracellular NAD^+

A common theme among NAD^+ consumers is inhibition by Nam. ART, PARP [20], CD38 [21] and sirtuin [22] enzymes each contain a Nam-product site that can be occupied in the presence of substrates and enzyme intermediates. Thus, each enzyme can be inhibited by Nam, which effectively drives the formation of base-exchanged substrates. Because of this type of product inhibition, the salvage and/or elimination of Nam are crucial steps in NAD^+ metabolism.

Whereas Nam is salvaged to Na in fungi and many bacteria, the gene that encodes nicotinamidase is absent from vertebrate genomes and, thus, this route is not available to humans (except, potentially, in the gut where commensal bacteria might contribute to Nam salvage in the host). There is a human but not fungal gene encoding a Nam *N*-methyltransferase that converts Nam to *N*-methylnicotinamide *in vitro* [23]. In addition, humans express a homolog of the *H. influenza nadV* gene, which has Nam phosphoribosyltransferase activity [24] (Figure 2). Remarkably, this activity has been identified in a polypeptide named pre-B-cell colony-enhancing factor (PBEF), for which there are convincing reports of intracellular and extracellular localization. Intracellular PBEF increases NAD^+ concentrations and, as a consequence, has cell-protective benefits [19,24–27]. Extracellularly, PBEF has two known activities. First, the polypeptide synergizes with stem cell factor and interleukin 7 to promote the formation of pre-B-cell colonies [28]. Second, as an activity termed visfatin, PBEF is secreted by visceral fat, in order to bind the insulin receptor and mimic the effects of insulin [29]. The relationship between the enzymatic activity of PBEF and its extracellular activities has not been investigated. However, it is reasonable to suggest that PBEF functions, in part, by relieving Nam-mediated inhibition of an extracellular NAD^+-consuming enzyme

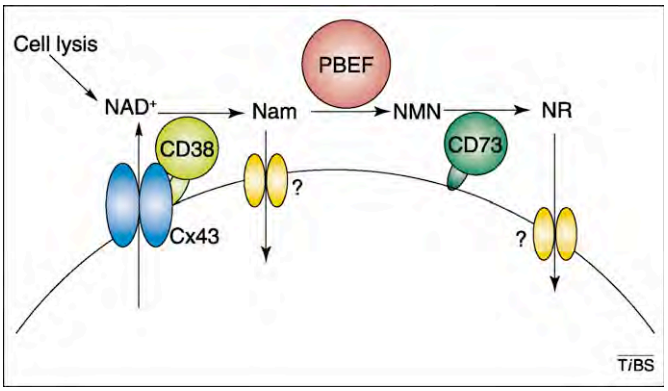

Figure 4. A potential extracellular NAD$^+$-cycle in vertebrates. Extracellular NAD$^+$ could be derived from ether cell lysis or, potentially, specific transport through Connexin 43 hemichannels. Extracellular cADP-ribose synthases, such as CD38, produce Nam from NAD$^+$. Nam might be converted to NMN by PBEF (Nam phosphoribosyltransferase) with subsequent dephosphorylation to NR by CD73. Nam and NR are thought to be imported by unidentified transporters.

and/or by participating in a NAD$^+$ biosynthetic cycle that is partially extracellular.

The source of NAD$^+$ for extracellular NAD$^+$ consumers such as ARTs and cADP-ribose synthase is a matter of interest. Although an obvious source of NAD$^+$ around sites of inflammation is cell lysis, there are strong indications that NAD$^+$ is transported via connexin 43 hemichannels, specifically to provide NAD$^+$ for the CD38 active site [30]. As shown in Figure 4, a potential extracellular NAD$^+$ biosynthetic cycle in vertebrates might be initiated by transport of NAD$^+$ by connexin 43 for consumption by CD38 to produce Nam and cADP-ribose. PBEF, with sufficient phosphoribosyl pyrophosphate (PRPP), might then convert Nam extracellularly to NMN [24]. In addition, CD73 – an ecto-enzyme that is homologous to nadN, the NMN nucleotidase of *H. influenza* [31] – might convert NMN to NR. Because *H. influenza* multiplies in vertebrate blood despite mutation of nadN [32], it is reasonable to surmise that NR circulates in vertebrate vascular systems and is taken up by cells that express a NR transporter.

NAD$^+$ synthesis in neuroprotection

Damage to nerve fibers leads to a series of molecular and cellular responses that are termed Wallerian degeneration or axonopathy. Axonopathy is a critical early event in distinct degenerative conditions including Alzheimer's disease (AD), Parkinson's disease and multiple sclerosis (MS), and it occurs in response to infections, alcoholism, acute chemotherapy-associated toxicity, diabetes and normal aging [33]. The Wallerian degeneration slow (*wld^s*) mouse is a spontaneous mutant that contains an autosomal dominant genetic alteration that confers resistance to nerve cell damage *ex vivo* and *in vivo*. The fusion protein encoded by *wld^s* contains the first 70 amino acids of ubiquitination factor Ufd2a and full-length Nmnat1, which is tandemly triplicated [34,35]. Overexpression of Nmnat1 blocks the axon degeneration induced by vincristine and transection in dorsal root ganglion (DRG) neurons [36,37]. It has also been shown that axonopathy is accompanied by depletion of NAD$^+$ and ATP, and that expression of *wld^s* protects neuronal NAD$^+$ levels [37].

Differences between the first two reports [36,37] of protection against axonopathy require reconciliation, especially in light of a putatively negative report [38] and subsequent clarifications of the protective value of NAD$^+$ synthesis in *ex vivo* [27] and *in vivo* [39] models of neurodegeneration. Milbrandt and co-workers have used lentiviral expression in DRG neurons to show that Nmnat1 protects against vincristine-induced axonopathy in an active-site dependent manner, and that bathing DRG neurons in 1 mM NAD$^+$ is also protective [36]. Based on RNAi-mediated knockdowns, they suggested that NAD$^+$-mediated protection depends on Sirt1 [36]. Independently, He and co-workers have corroborated protection by Nmnat1 and NAD$^+$, and provided evidence that exposure to vincristine and nerve transection lead to depletion of NAD$^+$. However, their study casts doubt on the role of Sirt1 as the key mediator of protection against axonopathy with the observation that embryonic *sirt1*−/− DRG neurons can be protected [37]. The report, which concludes that Nmnat1 does not substitute for the Wld^s fusion protein, actually confirms that lentiviral expression of Nmnat1 is protective, although possibly less so than full-length Wld^s [38]. This latter observation might be the result of a protein-stabilizing mechanism of the Ufd2a fragment. Although these investigators failed to produce a mouse transgenic for *nmnat1* that conferred a robust *wld^s* phenotype, their transgenes expressed Nmnat1 from the β-actin promoter [38] rather than the Ufd2a promoter, which is highly expressed in neurons [40].

Two more recent studies clarify the power, if not the precise mechanism, of NAD$^+$-mediated protection against neurodegeneration. The Milbrandt group developed lentiviral-expression systems for eight NAD$^+$ biosynthetic enzymes and examined the cellular localization and ability of these enzymes to protect mouse DRG axons from dying back after transection from neuronal cell bodies. Expression of Nam phosphoribosyltransferase and Na phosphoribosyltransferase genes protects, but only when neurons are cultured with Nam and Na, respectively, and neither Nam nor Na protects without overexpression of the corresponding biosynthetic gene. As in the earlier study, Nmnat1 protects without any remnant of Ufd2a but, in addition, a mutation that abolishes nuclear localization of Nmnat1 has no effect on protection, whereas expression of Nmnat3 either in the mitochondria (native) or nucleus (engineered) protects. These results indicate that neurons contain sufficient nicotinic acid mononucleotide (NaMN) or NMN for the increased expression of Nmnat to elevate NAD$^+$, and that increasing NAD$^+$ in the nucleus, cytoplasm or mitochondria protects against degeneration, which is ultimately a cytosolic process. Four compounds, NAD$^+$, NMN, NaMN and NR, protect without concomitant gene therapy. Although it is unclear how the non-drug-like phosphorylated compounds (NAD$^+$, NMN and NaMN) enter cells, and whether they are transported as nucleosides (NR and Na riboside), the data indicate that the Nrk pathway is primed to protect DRG neurons if the NR vitamin is supplemented. Indeed, the study shows that Nrk2 mRNA increases 20-fold in the 2 weeks following sciatic-nerve transection in rats [27].

A study in experimental autoimmune encephalomyelitis, a mouse model of MS, shows that the *wld^s* mutation has a

mild protective effect against development of neuromuscular deficits whereas Nam provides striking, dose-dependent delay and protection against the development of hind-limb weakness and paralysis. Indeed, Nam provides even greater protection to *wld*^{s} mice than to wild-type mice, probably because large doses of Nam render the Nmnat-biosynthetic step limiting [39]. In summary, the diseases and conditions that involve Wallerian degeneration (e.g. AD, chemotherapy-induced and diabetic-induced peripheral neuropathy, MS, and alcoholism) are collectively common and occur increasingly with advancing age. Thus, therapies that protect neuronal NAD^+ might prove to be quite powerful. However, the most effective compounds and formulations remain to be determined.

NAD^+ synthesis in candidiasis

Candida glabrata, the second leading cause of candidiasis, is a fungus with an interesting variation in NAD^+ metabolism. *Saccharomyces cerevisiae* NAD^+ metabolism differs from that of humans because the yeast lacks ARTs, PARPs and cADP-ribose synthases, and contains nicotinamidase (Pnc1) rather than PBEF. The *C. glabrata* genome is additionally missing genes for the *de novo* biosynthesis of NAD^+, such that it is a Na auxotroph [41]. Just as *S. cerevisiae* Sir2 represses transcription of sub-telomeric genes in an NAD^+-dependent manner [42], so *C. glabrata* Sir2 represses transcription of sub-telomeric *EPA1*, *EPA6* and *EPA7* genes, which encode adhesins that promote urinary-tract infection. Because *C. glabrata* cannot make NAD^+ *de novo*, low Na levels limit the function of Sir2, thereby derepressing adhesin genes and inducing a switch to adhere to host cells. As a consequence, increased dietary Na provides some protection against urinary tract infection in mice [41].

High-dose Na is a common, over-the-counter and prescription drug that increases high-density lipoprotein (HDL, otherwise known as 'good') cholesterol and reduces triglyceride levels [43] via an unknown mechanism. However, high-dose Na causes flushing via a receptor mechanism [44] that is unrelated to NAD^+ synthesis. Because patients with candidiasis might be particularly sensitive to flushing, we suggest that Nam and NR should be tested as anti-*C. glabrata* agents. The *C. glabrata* homologs of Pnc1 and Nrk1 are represented in National Center for Biotechnology Information (NCBI) databases (NCBI codes: CAG57733 and XP_448957, respectively). Nam might fail to support Sir2-dependent repression of adhesin genes because it is an inhibitor of Sir2 [45], which might result in adhesin gene derepression. Indeed, because there is no known route to produce Na in vertebrates, we suggest that *C. glabrata* is NAD^+-limited after depletion of NR, which is known to circulate based on the *Haemophilus* literature [32], and that the *C. glabrata* gene-expression switch might be either prevented or reversed by supplementation with NR.

NAD^+ synthesis in the regulation of aging

All fungi and animals that have been examined have characteristic rates of aging that depend on environmental conditions and yield mutations that confer either progeric or long-lived phenotypes. Calorie restriction (CR) is the most powerful intervention known to extend the lifespan of yeasts, worms, flies and mammals (Reviewed in [46]). CR increases lifespan and delays the onset of distinct debilitating diseases in different models. CR reduces carcinogenesis in mouse models, prevents kidney disease in rats, and forestalls diabetes and cardiovascular disease in monkeys. In addition, although there is no experimental proof that CR extends human lifespan, the hematological, hormonal and biochemical parameters of the eight people on a CR diet for almost two years in the Biosphere were similar to those of mice or monkeys on CR [47]. Although most humans would balk at CR diets that might leave us colder, smaller and lacking in sex drive, the longevity-promoting effects of CR are so profound in so many models that if we could understand the molecular basis of these effects, we might be able to develop tools to delay consequences of aging, and promote some of the cellular and physiological changes that occur in CR.

In yeast, the proximal cause of replicative senescence (failure of a mother cell to produce a daughter cell) of wild-type cells is the accumulation of extrachromosomal rDNA circles (ERCs) that are formed by recombination between tandemly arranged rRNA genes [48]. Thus, *sir2* mutants have shorter replicative life spans because Sir2 has a crucial role in repressing rDNA recombination [49].

In a landmark paper, Guarente and colleagues showed that CR extends replicative lifespan in yeast in a manner that depends on Sir2 and Npt1, the Na phosphoribosyltransferase [50]. The mechanisms by which CR promotes NAD^+-dependent activities of Sir2 might include increasing the NAD^+:NADH ratio [51], reducing inhibitory Nam [52], elevating NAD^+, and increasing levels of either Sir2 or specific Sir2–substrate complexes. Of the mechanisms that involve relief of inhibition, biochemical and cellular data suggest that Nam is a more effective inhibitor than NADH [22,53,54]. There are Sir2-independent mechanisms by which CR extends lifespan in yeast *fob1* mutants that do not accumulate ERCs [55]. The proximal causes of death in yeast *fob1* mutants and their interactions with CR are being pursued to identify additional targets that might be conserved in humans. There is also evidence that a Sir2-independent target of Nam limits the effects of CR [56], but much or all of this regulation might involve the paralogous sirtuin, Hst2 [57].

In worms and flies, increased gene dosage of the Sir2 ortholog extends lifespan [58,59] and, in flies, the beneficial effect of CR depends on dSir2 [59]. Hyperactivity, a physiological response to CR in vertebrates, depends on Sirt1 in mouse [60]. Because Sir2 has been conserved to alter gene expression in response to CR in metazoans, sirtuin activators are being developed as agents that might provide some of the benefits of CR. Resveratrol, a plant polyphenol that is enriched in red wine, was identified as an activator of human Sirt1 in a high-throughput screen [61]. Although activation by resveratrol depends on the identity of the Sirt1 substrate [62,63] and resveratrol has other targets in addition to Sirt1, multiple reports indicate that Sirt1 is one of the key targets of resveratrol [18,19,64]. Indeed, hard data now support the ability of high-dose resveratrol to increase the lifespan of worms and flies [65], and the health and vitality of overfed mice [66,67].

Although the data do not establish Sirt1 orthologs as the only mediators of the complex beneficial effects of resveratrol in vertebrates, increased mitochondrial biogenesis in liver [66] and muscle [67] can be explained by increased Sirt1-dependent deacetylation of the transcriptional coactivator, PGC-1α [68].

In the liver of mice fasted for 1 day, the levels of NAD^+ and Sirt1 are increased, which leads to Sirt1-dependent deacetylation of PGC-1α and consequent induction of gluconeogenic genes [68]. In a murine model of AD that overexpresses a human mutant amyloid β protein, CR increases levels of NAD^+ and Sirt1 and reduces Nam in the brain [69]. In this model, Sirt1 and NAD^+ reduce the production of amyloidogenic peptides and the resulting neuropathology [69]. Thus, although Sir2-dependent repression of the formation of ERCs is yeast-specific, there is broad conservation of CR, NAD^+ and sirtuin function. Moreover, the AD model indicates that specific NAD^+-boosting molecules might replace CR in treating specific diseases, which was a far from trivial assumption.

In cardiac and neuronal models, there are indications that some aspects of the protective effects of NAD^+ synthesis are mediated by sirtuins [19,69], but other effects might be sirtuin-independent [37]. In light of the localization of three human sirtuins to mitochondria, the control of mitochondrial acetyl-coA synthetase 2 by Sirt3 [70,71], and the connection between mitochondrial function and aging, a key area for future investigation to identify cell-protective and anti-aging targets of NAD^+ within mitochondria.

Na and plasma lipids

Finally, it is important to reinvestigate the mechanisms by which Na reduces levels of triglycerides and low-density lipoprotein cholesterol and elevates HDL cholesterol. It has long been assumed that the beneficial effects of Na on plasma lipids are mediated via a receptor rather than a vitamin mechanism because of the high dose required (100-fold higher than that required to prevent pellagra) and the failure of Nam to provide similar benefits [72]. Today, however, low HDL cholesterol and poor reverse cholesterol transport are regarded as a distinct molecular pathology and as risk factors for coronary heart disease [73] and AD [74]. Maintaining reverse cholesterol transport in the face of a distinct pathology might necessitate large doses of a vitamin, particularly because Na metabolism involves competition between synthesis and breakdown of NAD^+, production of nicotinuric acid, and metabolite excretion.

Although lack of a beneficial effect of Nam might be interpreted as evidence of a receptor-based mechanism, it is also consistent with a mechanism in which a sirtuin target is activated by NAD^+ and inhibited by high-dose Nam. Moreover, the Gpr109a receptor, which recognizes Na to the exclusion of Nam, mediates the flushing response [44], which is clearly an off-target effect. We suggest that in some individuals reverse cholesterol transport might be limited by a sirtuin-dependent deacetylation reaction such that high-dose Na and resveratrol both result in altered expression of apolipoproteins, transporters, receptors and/or enzymes that are involved in lipid metabolism. The ability to elevate NAD^+ with NR will enable the long-standing problem of the mechanism of action of NA in plasma-lipid homeostasis to be investigated.

Concluding remarks

The first century of NAD^+ research has been punctuated by multiple discoveries. Elucidation of the essential role of NAD^+ in glycolysis was followed by discoveries in human nutrition and coenzyme biosynthesis. In recent years, the role of NAD^+ in protein deacetylation has been discovered. NAD^+ precursors have been used to protect severed axons from degeneration, ameliorate neuromuscular deficits in a mouse model of MS and reduce the severity of candidiasis in a mouse model. Studies are needed to clarify the targets and mechanisms of NAD^+ function in these models, and to determine the safe, effective boundaries of nutritional and therapeutic interventions to replenish NAD^+ in humans.

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NAD Therapy! Too Good to be True?

Index

Foreword by Dr Abram Hoffer

I became interested in the pyridine nucleotide cycle, NADNADH in the early 1950's after we had demonstrated that vitamin B3, one of the main precursors of this system tripled the recovery rates of acute schizophrenic patients compared to a placebo. The pure vitamins are the natural precursors in the body of the pyridine nucleotide cycle. Either niacinamide or niacin yielded the same beneficial results. This conclusion was based upon the first prospective double blind randomized controlled therapeutic trials in psychiatry in world psychiatry, we completed between 1952 and 1960. But it was not possible to obtain any NAD to be used in therapeutic trials until around 1960 when I was given an NAD prepared in a medium designed to bypass the destructive processes in the stomach. In order to become familiar with its potential therapeutic effect I began to treat a small number of my patients at Royal University Hospital in Saskatoon. Some of these were already responding to larger doses of vitamin B3 and some had not yet been started on treatment. I gave them 1 gram capsules once daily. **To my astonishment and delight there were almost an immediate response and patients who would ordinarily take 3 to 6 months to shows an adequate response to vitamin B3 were responding on NAD in days and weeks.**

One of the more chronic patients was a patient I had transferred to my ward from a mental hospital where she had been treated for many years with no success. I did not think she would respond but after 7 days or so she was very much better and after a few weeks she was well enough to be discharged. The psychiatrist who had been treating her in the mental hospital saw her under my care and he was also very surprised. It appeared clear that NAD was doing something when properly prepared. But I could not continue the studies because the company that was providing it discontinued their studies. **I then went through a most terrible period because my supplies of NAD ran out and I had to deal with my patients who had done so well relapse back into their original disease. My patient we had discharged into the community had to be re-admitted, had to be returned to the mental hospital where she died several years later. She had not responded to vitamin B3 but had to NAD.**

A couple of half-hearted short term therapeutic trials were conducted in the United States using a different preparation which could not bypass the stomach and using chronic deteriorated patients of the type resident in mental hospitals in those days up to 30 years and more and these investigators saw no response. When I tried to use pure NAD given as a powder, I saw no response. Dr. N Kline at Rockland State Hospital in New York used our test, the HOD test for before and after evaluation I saw the scores before and after and there was a response but he ignored the results of that test. After that I was no longer able to obtain any NAD and continued with our vitamin B3 studies which eventually became known as orthomolecular psychiatry and medicine.

This new work with NAD Therapy is very exciting and I think is right on target. It is indeed an NAD Energy Deficiency (NED) because in the absence of this coenzyme cycle almost all the reactions in the body run down. Energy is indeed essential not only to drive our muscles but to digest our food, even to think and to feel. But we will have to rid ourselves of the old vitamin-as-prevention concept which was so useful in helping us isolate the synthesis of the vitamins. The old idea that each deficient vitamin causes one deficiency disease is rapidly being buried in the dust bin of medical history.

If one looks at pellagra, for example, the symptoms are so wide ranging and pervasive that it was a very difficult diagnosis to make until pure niacin became available. In the Southern United States of America where pellagra was endemic the test was to give their patients in their mental hospitals this new vitamin. If they recovered in a matter of weeks, they were diagnosed as pellagra. If they did not, they remained schizophrenic. A single metabolic error or deficiency can cause an amazing variety of conditions depending on many factors for which we have no explanation.

Multiplicity of symptoms and large differential diagnosis does not mean that the condition is not caused by a single deficiency and this has to be identified. The old paradigm is being replaced by the new one the vitamin-as-treatment paradigm. NED is pervasive around the world and will become much more prevalent.

I congratulate Theo Verwey and his colleagues for this remarkable advance in using this concept and in using a simple test, the ratio of pyruvate to lactate as a diagnostic measure, to indicate the dose, duration of treatment etc. I realize that he has made a very complete review of the literature. For instance, not many know about our 1960 studies with oral NAD.

When the clinical founded Energy Values based on the lactate and pyruvate blood tests and the NAD Therapy protocols outlined in the E-book ***NAD Therapy! Too Good to be True?*** are empirically confirmed there will be an enormous change in modern psychiatry. It will mark the retirement of the present psychiatric paradigm which can be best described as a system which uses' descriptive diagnostic terms which have no causal or treatment relevance.

The new system will depend upon laboratory tests to determine where the error in the metabolism of the body lies and will indicate which nutrients should be used to correct that error. Psychiatry has always been forced to deal with and to treat diseases for which there has been no known cause and for whom there has been no adequate treatment. Thus, in 1900 the differential diagnoses of the major psychoses included dementia praecox, scurvy, pellagra and tertiary syphilis of the brain. But as soon as the cause and the correct treatment were discovered, these diseases were removed from the field of psychiatry and taken over by general medicine. The finding that vitamin B3 cured pellagra eradicated this disease in most high technical societies. The same for scurvy. Penicillin removed the syphilis patients from psychiatric care. Dementia praecox remained and was renamed schizophrenia. This has still remained the province of the psychiatrists but with the work described in this book and so much other work shows that schizophrenia will also be taken over by the rest of medicine. The newer work on the important role on the essential fatty acids, omega three especially lead by Dr. David Horrobin, the work we did over so many years with the megavitamin approach make this prophecy a certainty.

Megavitamins are coming into their own. A recent report by DB Ames shows that the 50 genetic diseases that require megavitamin therapy comprise only a small proportion of the total that will eventually be recognized and properly treated. Diagnosis will become more secure not only to indicate the presence of absence of schizophrenia but to indicate what the treatment ought to be.

The recent topical niacin test for schizophrenia developed by Dr. David Horrobin will clear up the confusion between the psychoses and the other psychoses but in the end the use of laboratory markers may remove the need for the clinical diagnosis. Thus we found that the urine test for krytopyrole, further developed by Dr. CC Pfeiffer, selected those patients with uniform biochemistry and improved response to treatment no matter what they were called clinically.

Psychological diagnosis may become a pleasant diversion but will eventually be of little interest in the same way that serologic test for syphilis is much more important than the extensive clinical descriptions of this disease in vogue before these tests were developed. I have given a lot of attention to the schizophrenias because I think this condition presents us with a very good example of what will happen with all of the NED conditions. And the NADNADH system, plays a major role in the genesis and in the treatment of schizophrenia.

For these reasons I consider the information in the E-book: ***NAD Therapy! Too Good to be True?*** so valuable and important and I fully expect to see the corroboration of this work world wide once it becomes known to the medical profession and even more when the general public of sick people and their families hear about it.

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Victoria, British Columbia
April 2002

Introduction

In 1994, approximately 3000 prescriptions for fluoxetine hydrochloride (Prozac) were written for infants aged younger than one year, this alarming statistic was cited in an article in the Journal of the American Medical Association, (Vol. 283 No. 8, February 23, 2000). Approximately 10 per cent of all babies are born with a maternally inherited NAD Energy Deficiency (NED) which they themselves can not yet verbalized in understandable terms to their caregivers. Some of these energy deficient babies will be diagnosed as depressed and end up using antidepressants before their first birthday. Fortunately for these babies there are two simple and non invasive blood tests that will show us their metabolic energy levels. The costs of these two blood tests are only R192.00, but it will save thousands of rands in treatment and unmeasurable pain, despair and premature death. "Depressed newborns had higher umbilical lactate levels than vigorous newborns irrespective of the method of delivery. Umbilical cord blood levels of lactate, base deficit, and pH were measured in 452 liveborn infants. In vigorous newborns, the mean umbilical arterial and venous concentrations of lactate were lowest with elective cesarean section, higher with cesarean section performed during labor, and highest with vaginal delivery."[723]

Some of these NAD energy deficient babies will grow up and run in to inexplicable problems as adults, others will never reach the age of three years. "At that stage I... I felt I was working under immense pressure. I was so tired and I had no energy. I had been married for a few months, my second marriage, and I wasn't feeling too well at that stage. I did have a few patients who had problems, or whom I noticed were always coming back for their Pethidine injections. They were allegedly suffering from migraine, but they clearly only came for the Pethidine. One day I just injected myself with one of these vials"[32]. (Dr Jaques Botha, medical doctor in treatment as a Nutrimalaika patient for his prescription drug abuse).

In Alkogen's therapy rooms, patients, of all walks of life and age groups, reveal that they are even too exhausted to pray and feel that nothing will help. Some are even too tired to express this or to accept the redeeming love of God. Others attempt in vain to make it through another day by using self-medication in the form of prohibited or undesirable chemical substances or unhealthy eating habits. Some indulge in socially inexplicable behaviour in order to feel human for a brief while. The entire process is complicated further because their beloved and significant others often do not understand their weariness of life, or can no longer put up with it. We have often labelled many of them with professional stereotypes, like depressive, alcoholic, eating disordered, hyperactive, drug-dependent, delinquent, co-dependent, chronic fatigued and many others. Few of those who provide support understand that these persons might simply lack the metabolic energy to continue. Because there is no existing concept, we can refer to them as the unfortunate persons who suffer from NED. As will become evident in the later chapters, NED can be defined as the physical state that develops when the body does not have enough coenzyme 1 (NAD) molecules and accompanying energy metabolic cofactors to generate enough metabolic energy on cellular level to maintain the body in a constant state of health.

- "Nicotinamide adenine dinucleotide (NAD), is an energy "currency" of the cell, all cellular life requires it and there is a concomitant pantheon of proteins that interact with it".[762]

NED exerts a negative effect on man as a whole and therefore ought to be dealt within a multiprofessional manner. This ebook therefore specifically aims to provide deeper insight into the latest information on the body's biochemical functioning in respect of metabolic energy. We often care for the body passively, by depending on medical science to maintain it, by reframing our diseases on a psychological level or by praying and hoping for miracle cures on a spiritual level. Scientific knowledge in the biochemical field has also not yet been recorded in SELF-HELP diaries and reading material that are easily accessible, as is the case with spiritual and psychological issues. This statement merely points out that relevant and therapeutical information on the subject of biochemistry is not readily available to the public. This ebook is an attempt to, in particular, discuss the importance of NAD Therapy as a safe and natural generator of cellular energy in the treatment of NED.

The goal in writing this ebook is to provide a clear and simple account of the key ideas of NAD Therapy and its therapeutic application in NAD Energy Deficiency related syndromes (NEDRS). Although we wanted NAD Therapy to be accessible to readers in all of the related disciplines, we could not cover all of these perspectives in detail. NAD Therapy simply starts with the normalising of the cellular energy metabolic production on mitochondrial level, resulting in an energenetic person ready for appropriate medical or psychiatric interventions, psychotherapy, pastoral counselling or any other applicable form of therapy. We also chose not to produce a rigorous formal treatment approach. We did not reach for the highest possible level of scientific integration of the various seemingly unrelated concepts. We tried to choose a level of detail that points the therapeutic inclined in the right directions without distracting from the simplicity and potential generality of the underlying ideas.

We first came to focus on what can be referred to as NAD Therapy in late 1988. As you may be aware, many of the chronic ailments that human beings suffer from, tend to take root in an energy metabolic deficient cellular environment. For instance: "As the biological techniques for measuring mitochondrial function have become increasingly refined since the 70s, more than a hundred diseases have been identified as having a mitochondrial basis. Although these overt mitochondrial diseases affect only a small percentage of our population, we wonder to what degree subtle "subclinical" mitochondrial impairment may be involved in more common complaints. Are overt mitochondrial diseases just the "tip of the iceberg" of a much larger and as-yet-unidentified metabolic deficiency? The vast majority (90%) of the energy needs of the human body are met by mitochondrial oxidative phosphorylation. Oxidative phosphorylation is a highly refined and efficient system for producing the prodigious amounts of energy that are required to maintain the structure and function of the body, and regulate body temperature in warm blooded animals. Oxidative phosphorylation takes place entirely in mitochondria (tiny cellular organelles that closely resemble bacteria in both size and structure)."[82]

When cells are exposed to a NAD deficient environment, their structure change or they simply die and are disposed of by the body. "It is postulated that a decrease in nicotinamide adenine dinucleotide (NAD) concentration has a primary association with carcinogenesis. The following observations are presented as evidence:

1. NAD and adenosine triphosphate (ATP) concentrations are lower in cancer cells;

2. chemical carcinogens and radiation can cause a lowering of NAD concentration in precancerous cells:
3. biosynthesis of NAD in Ehrlich ascites tumor cells is altered; and
4. NAD is involved in regulating deoxyribonucleic acid (DNA) synthesis.

The lowering of NAD concentration would lead to the expression of oncogene and/or virogene according to the protovirus hypothesis, and the cellular characteristics of cancer cells can also be explained through the lowering of cellular NAD."[48]

One of the most important aspects to note about NAD Therapy is the sheer breadth of its application. It is useful and valuable for so many different symptoms and health issues. A good way to understand NAD Therapy is to consider two of the examples and possible applications that have guided its development. These two examples share features that are so basic that they are easy to overlook.

"Because insulin was discovered in l922 and niacin in l937, no one realized the importance of NAD deficiency in diabetes, even though a small group headed by Tom Spies in l939 published their study of low NAD levels in diabetics. But a lapse of niacin research during and after World War II gave the pharmaceutical companies a voice of unquestioned authority over the new practicing clinicians who had no real experience with niacin deficiency cases and had not lived through events of the Pellagra years in the South, indeed did not recognize the symptoms of pellagra. I discuss this disease in my recent publication on the NAD Deficiency Diseases, wherein I describe the subclinical pellagras (Cleary 1986), and their response to the administration of niacin. The reason antidiabetic agents work is that they mimic the action of NAD which is very low in diabetes, causing a release of insulin from the beta cells, but they do not restore function of the mitochondrial Krebs cycle as NAD does, they do not cure this problem.[639]"

"Vit B3 treatment took time - often months - before it produced benefits. It was most effective with early schizophrenics - those treated within a year after onset. In cases of longer duration, it sometimes helped when combined with other treatment (sic), including electroshock. Then, late in 1965, Dr. Hoffer began to work with a new chemical, NAD, a derivative of nicotinic acid. Produced as an experimental drug, it seemed to do everything the vitamin did - but in days. Early in 1966, at a New York medical meeting, after three months of trials with NAD, Dr. Hoffer made a preliminary report. Of 17 patients treated, 13 had shown dramatic improvement. A woman hospitalized for eight years seemed almost completely recovered three days after NAD treatment began. It seemed to Dr. Hoffer that NAD was the active form of nicotinic acid; that in normal circumstances, the body converted nicotinic acid from food into NAD but that in the schizophrenic the conversion couldn't take place, with the result that large amounts of adrenaline were turned into adrenochrome. There will be further studies to clarify the NAD question.[640]"

It is important to note the latest research findings regarding niacin and nicotinamide. It appears that most of the therapeutical benefits ascribe to these compounds are actually only possible by means of its conversion to NAD in the cells. For example:

- "The beneficial effects of nicotinamide for the treatment of HIV infection appear to be linked to cellular utilization of NAD. Nicotinamide appears to be void of any cell-free reverse-transcriptase inhibition or virucidal activities. However, several

cell-associated observations link HIV, nicotinamide, and NAD. HIV-infected cells demonstrate an increase in the ADP ribosylation of proteins, a phenomenon in which NAD is used as the ADP-ribose donator to covalently modify proteins. As a general feature, nicotinamide inhibits ADP ribosylation reactions. Protein ADP ribosylation can occur in the nucleus, in the cytoplasm, and on the cell surface of lymphocytes. PARP is a nuclear enzyme that catalyzes the formation of ADP-ribosepolymers that attach to multiple different proteins. The activity of PARP is critical to the integration of foreign DNA, including proviral DNA; inhibition or absence of this enzyme interrupts the HIV life cycle. Along with poly-ADP ribosylation, monoribosylation steps also involve proteins in cells, including the ADP ribosylation of both HIV Tat protein and cellular defence. The antimicrobial action of nicotinamide might also work through the modulation of certain histone deactylase reactions (i.e.,Sir2 proteins) that use NAD in the silencing of chromosomal DNA".[767]

The role of NAD in the therapeutic functions of other medications also becomes available with latest research: "We recently developed a class of novel antitumor agents that elicit a potent growth-inhibitory response in many tumor cells cultured in vitro. WK175, a member of this class, was chosen as a model compound that showed strong in vitro efficacy. WK175 interferes with the intracellular steady-state level of NAD(+), resulting in a decreased cellular NAD(+) concentration. We found that WK175 induces apoptotic cell death without any DNA-damaging effect... These results imply that decreased NAD(+) concentration initiates the apoptotic cascade, resulting in the antitumor effect of WK175."[772]

The pioneering work of the world renowned Dr. Hoffer with NAD and its precursors, as recorded in various books and articles, was the main cornerstone in the development of NED and NAD Therapy. He is deservedly recognized as one of the five individuals who pioneered the new medicine for the 21st century. "Once again, the synthesis of a new idea that incorporated biochemical genetic individuality, nutritional modulation of gene expression, and functional physiology resulted in a leap forward into the field of biologically based psychiatry. These five individuals pioneered the new medicine for the 21st century. The recognition that our genes do not determine our disease, but instruct us regarding the optimal environment for health represents a major shift in medical thinking. The acceptance of this model within the medical paradigm is no longer in question. It is just a question of how long it will take for this model to be fully integrated within the standard practice of medicine. The contributions of Archibald Garrod, Linus Pauling, Roger Williams, Hans Selye, and Abram Hoffer have created a force of change that cannot be held back, because truth is its own vector".[651]

Many concepts, dealt with briefly in this ebook, are relatively new and those who require more information should refer to this ebook's bibliography. For instance: "Fifty years ago, in the early days of biology, so little was known about the cell that all of the proteins outside of its nucleus were grouped into one big "cytoplasmic soup." Now, as the list of known cellular ingredients continues to expand beyond the capacity of any recipe card, two Rockefeller University scientists are taking a step back to ask whether there might be a better way to organize the current thinking about a particularly important class of proteins inherent to all living cells".[793] The aim of this ebook is not to provide a comprehensive review of each theme addressed, but only brief and introductory notes and guidelines are provided to stimulate the reader's own research. This is unavoidable,

since the literature on NAD and other energy metabolic related concepts consist of thousands of scientific articles, which one person cannot assimilate meaningfully, during the course of a lifetime. Therefore only a selection is presented, to stimulate further research.

Energy Requirements for The Journey of Life from the Womb to the Tomb

All of the billions of people, except a few who ever walked this earth, started life as a single set of DNA in an egg fertilized by a sperm. The DNA in each cell does not weigh more than one six-millionth of one-millionth of a gram. It is difficult to comprehend that this little speck of DNA (kept intact by sufficient cellular NAD, also known as coenzyme 1) was capable of starting a process, which led to our fingernails and toenails, our eyebrows and eyelashes and our range of functioning organs, including the hundred billion cells in the brain.[729] "Nicotinamide adenine dinucleotide (NAD), an energy "currency" of the cell, all cellular life requires it and there is a concomitant pantheon of proteins that interact with it".[762]

2.1 OUR BODY: THE HOST OF LIFE

Irrespective of whether one is old or young, male or female, black or white, holy or sinful, prostitute or nun, pope or punk, all of us share this one common denominator of a physical body, which is the host of human life. During our life, our bodies constitute us. We need a body to be able to complete this earthly part of our life. None of our achievements, ideas, failures and emotions would be possible without our bodies. We travel through life, while we actually remain completely ignorant about how our bodies function, thereby missing out on an entire dimension of our existence.

One of the most horrible evidence of this ignorance of the body and its functions is the high incidence of many unwanted and teenage pregnancies. During 1999 in the USA alone, 8 720 legal abortions were carried out on 14 year old girls; 88 420 in the age group 15 to 17; 152 520 in the age group 18 to 19 and 422 550 in women aged 20 to 24 years old.[724] A total of 672 210 lives were legally ended in the USA during 1999 by no choice of their own. The abortion figure for the world during 1999 is 26 million legal abortions and 20 million illegal abortions. This means that 126 027 new lives were aborted every day during 1999.[728]

Every healthy baby that is fortunate enough to see the light of day represents three kilograms of potential. Its little body is a collection of various chemicals, namely approximately 10 per cent protein, 10 per cent fat, 1 per cent sugar and 75 per cent water. Their composition is orchestrated by the 100 000 genes, which the baby inherited by means of the 23 pairs of chromosomes from its parents.[729] In order to build our bodies, approximately 74 of the 114 chemical elements are grouped into certain genetically-related chemical compounds. Chemical elements are the basic building blocks, like oxygen, hydrogen, phosphate, carbon, nitrogen, gold, iron, zinc and iodine, amongst others. We obtain these chemical elements from the food, air and water that we take in. Experts estimate that an adult's body is composed of approximately R 23.00's worth of chemical elements, mostly a few buckets of water. The final product, the living body, is however priceless. These genetic instructions determined and organize our entire physical life. And what a life it will be! For the 10% of babies who are born NAD deficient, the major cause of NAD Energy Deficiency (NED), this life can be one long nightmare. Some NED babies will not even make it to the age of two years.

Each healthy young one, who shows up in the developing world, can expect to live for approximately 72 years if it is a boy and 78 years if it is a girl. This little bundle, which is

helpless and dependant at this stage and if we assume it is a girl, her body will transform and convert itself many times during these three-quarters of a century and the resultant will be dependent on the metabolic energy available. From when she is a baby and changes into a young child, an adult and ultimately into the grey years and death, she will needs lots of NAD energy to beat a continuous series of challenges and have to adapt to them. Her body will need NAD energy and nutrients to grow, until it contains ten-thousand billion cells, which will almost all undergo a constant cycle of death and renewal.[729] For each of these growing and renewal processes, from each individual cell to the whole body, constantly needs sufficient ATP generated by NAD from food to maintain quality of life. Babies with NED will have problems with NAD energy production due to their genetic predisposition and will not live a healthy life. During her life she will:

- Talk for up to ten years.
- Breathed 41 million times and inhaled about 173 million litres of air.
- Walk 22 000 kilometres.
- Drive for one year in a car.
- Sleep for 22 years.
- Be paid for nine years of work after at least changing her career three times.
- Talk for two-and-a-half years on the telephone.
- Fall in love twice, have sex more than 3 000 times and kiss for two weeks.
- Grow 28m fingernails, 950km of hair and 2m of hair in her nose.
- Discard 19 kg of dead skin.
- Spend five years eating and drinking.
- Renew her skeleton 11 times.
- Renew the inner lining of her stomach 32 448 times.
- To successfully complete and enjoy all of the above, her body will have to manufacture about 1140 tons of ATP using 950 tons of NAD to reach the average age of 78 years.

Thanks to modern science, we are today able to look inside ourselves on cellular level, in a way in which no previous generation could do it. For instance, the importance of the mitochondria and its role in NED in families are more highlighted in research since the 70's. Genetic and chronic NED is transferred from the mother to her children and are already present at the time of conception. The manifestation of NED will vary from each of her children, for example the eldest can suffer from asthma (energy block = 47) since age two; the second child, a brilliant doctor only developed Alzheimer's disease (energy block = 71) in his sixties and the third and last daughter's NED showed up at age 30 because she could not have children of her own due to fertility problems (energy block = 62). All of this could be assessed just after birth by two simple blood tests (the biochemical indicators of NED): the lactate and pyruvate tests and the lactate/pyruvate ratio. NED can be successfully addressed by NAD therapy and the nutriceutical supplements involved. NED can also be ignored, but this does not change anything to the destruction, to which it leads. Genuine caring couples planning their new families will already attend to their planned child's NAD energy needs even from before conception. Even before they plan the kid's room they will ensure a proper sperm, ovum and womb for this precious new life.

The story of the human body is spelled out over millions of years and this story is also retold and improved on by each of us during our life. We live our bodies, but nevertheless we are not as intimately acquainted with it as we could be. This is, for all

living creatures, in a way the greatest story, which has ever been told. It starts with those two cells - the largest one in the human body and one of the smallest, namely an ovum and a spermatozoon, an egg and a sperm cell. The unborn child is a human being, just as you and I are, from the moment of, or just following the moment of, conception when the two cells unite. Regarding the constituting ovum and the sperm the resultant baby will has no choice, but to accept its genetic code as the blueprint for his life.[729] So much then for choosing again.

2.2 CONCEPTION: THE START OF THE JOURNEY

For 38 weeks two individuals are linked to each other, while the one is developing inside the other one. The amount of NAD energy (ATP, mainly generated from food particles and NAD in the mitochondria of each cell) available to both the developing child and mother will too a great extent determine the quality of life for each. The mother is nevertheless, almost like the father, actually merely a bystander, irrespective of how close the physical linkage between her and her unborn baby is. The child, to whom she gives life, is not part of her, the way that a blossom is part of a plant's bole. It is a separate human being, a stranger irrespective of how close the physical link is between her and her unborn baby. The developing child is genetically as different from her as any of his brothers and sisters are different from each other.[729]

THE OVUM: The ovum, the egg, stores all the necessary material to initiate the growth of the embryo. It contains ribosomes, about 50,000 species of mRNA, tRNA, and morphogenetic factors, yolk proteins and the cell nucleus. The ovum (oocyte) is viable for only 48 hrs following ovulation, during which it moves along the ovarian tube where it may be fertilized. During oocyte maturation, lactate and pyruvate are the sources of energy.[721] The egg had been formed before the woman's birth and waits twenty, thirty, forty or more years before it is prepared and released for fertilization. The ovum contains mitochondria each with its own set of DNA. This number of mitochondria is fixed per ovum and is transferred to the embryo. "Levels of lactate, pyruvate, oxy- and carbohaemoglobin were shown to change regularly during women's menstrual cycle reflecting changes in metabolism in respect to forming and destroying of the ovum".[690]

THE SPERM: "Capacitation is a complex series of molecular events that occurs in sperm after epididymal maturation and confers on sperm the ability to fertilize an egg. In most cases, capacitation media contain energy substrates, such as pyruvate, lactate and glucose, a cholesterol acceptor (usually serum albumin), NaHCO(3), Ca(2+), low K(+), and physiological Na(+) concentrations".[689] Out of perhaps 200-400 million sperm cells which are poured out, there are only one-hundred survivors left in the race by the time when they will have reached the egg. It after all requires thousands of rowing movements with the tadpole tail, to move a sperm one centimetre forward. "Low osmolarity, low lactate concentrations or the protein content may be responsible for the loss of sperm motility".[720]

As soon as the first sperm and the egg cell meet each other, the outer membrane of the two merge and chemical changes in the egg quickly prevent more sperms from entering it. Only the sperm's head penetrates the egg cell and the tail and its mitochondria drops off the sperm’s head and is lost. When the sperm cell is inside the egg, it releases a chemical signal which activates the egg. The sperm's head is then drawn towards the core of the egg and their genetic material merges. This is the moment of conception,

when the genetic composition of a new individual is created. The DNA from the father's sperm combines with DNA from the mother's ova. If the fertilization (uniting of the two cells) does not take place, both cells will die. The cells are from human beings, but are not human beings. The embryo is already genetically male or female, and a completely unique individual. Will he have his father's blue eyes and his mother's wide feet? The blueprint for all of these inherited traits is established at this time. It is a unique human being, for none like it ever existed before, and none quite like it will ever exist again. It is a real person, just as real as you and I. Genetically; it is totally different from the body of the father or the mother. Organically, it is independent, programmed from within, growing in an orderly manner, moving toward further maturity.[729]

"It was known that immediately after an egg and sperm fuse, a wave of calcium ions sweeps through the cell, triggering fertilisation. But scientists have spent the last decade trying to discover what triggered this calcium release. Tony Lai, of the University of Wales College of Medicine, tackled the problem by taking a candidate enzyme, PLC-zeta, and injecting it into unfertilised eggs. He immediately saw the wave of calcium sweep through the cell. The egg cell then began to divide and grow as if it had been fertilised. "It's only when you get to the blastocyst stage that the embryo stops growing," says Lai "It's at this stage that you require the male genes to kick in. You need the full genetic complement after this."[776]

The mother is completely unaware of all of these things which occur inside of her, but as soon as this has taken place she is hosting her child. Or one should rather say that another human being is creating himself, while he is using the mother like a parasite. A human being's development can in no way be compared to, for example, the assembling of a car. Although needing the protective environment of his mother's body, this living being is completely independent in its functions from the very beginning of his or her life, and at only ten days of age takes over complete physiologic control of certain functions within the mother's body. One example of this is that the unborn child stops his or her mother's menstrual periods.[729]

All of us were once an infant - that kept growing into an adult. The only difference is nutrition and time. Nothing else has been added. You are a continuum person. You began when the two cells united within your mother or in a test tube. Since then you grew until you reached adulthood. You are now more developed than when you were in your mother, but you were all there, back then.

The fertilized ovum begins growing by dividing into two cells. One of these cells will form the embryo's body and internal organs. The other cell will form the external system that the embryo will need to survive in the womb; the amniotic sac and chorion (the blood vessels that will later make up the placenta). First the fertilized egg divides approximately every 12 hours. It divides first into 2 cells, then 4, 8, 16, 32, 64 and so on. As a result there is soon a huge quantity, more than a million cells, after only twenty divisions. The dividing cells form three layers, much like a cake with a filling in the centre. The outer layer will in time form the skin, as well as nails, hair, lenses of the eye, salivary glands and all nervous tissue, including the brain. The central layer will create muscles, bones, cartilage, veins and kidneys. The inner layer will produce the gullet, stomach and intestines, as well as the liver, pancreas, bladder and the lining of each lung. The heart also starts as a group of cells underneath the brain. How this instruction is given exclusively to this group of cells is a mystery. It indeed remains a secret, the

same way that a large part of the development of the embryo still remains a mystery.[729] From this it is more than clear that irrespective who you are, you simply started out as two cells merging as one and multiplying into the billons of cells who you are today. Ignore the maintenance of your cells and you will certainly pay a dear price on cellular level.

"Since mitochondria were established to carry their own functional genome, a new mechanism of genetic nonmendelian inheritance, maternal inheritance, was discovered**.** All the mitochondria in the newly formed zygote are derived from the ovum (i.e., maternally derived). Mitochondrial DNA is more vulnerable to mutations in the oxidizing environment of mitochondria; its repair mechanisms are poor compared to nuclear DNA. Mutations in mitochondria accumulate in cells until a threshold is reached. Eventually, the proportion of mutant mitochondria exceeds wild type, resulting in the manifestation of impaired cell function."[722] Since the 70s, more than a hundred diseases have been identified as having a mitochondrial basis. .. The vast majority (90%) of the energy needs of the human body are met by mitochondrial oxidative phosphorylation. Oxidative phosphorylation takes place entirely in mitochondria (tiny cellular organelles that closely resemble bacteria in both size and structure)."[82] "Pyridine nucleotides *(NAD, NADH, NADP etc.)* are mostly stored within mitochondria where they are involved in different functions ranging from energy metabolism to cellular signalling".[687]

"Mitochondria play a central role in both programmed cell death (apoptosis) and the morphological changes indicative of cell death caused by enzymatic degradation (necrosis), through the opening of the mitochondrial permeability transition pore (MPTP). Subsequent mitochondrial permeability transition pore closure allows ATP levels to be maintained, ensuring that cell death remains apoptotic rather than necrotic. The cells of most tissues have a finite lifetime with a few cells dying at any one time and being replaced by new cells. Such cell death is known as programmed cell death (apoptosis) and is strictly controlled. A particularly dramatic example of apoptosis is seen in tissue remodelling during embryo development. Apoptosis also occurs following a moderate insult, insufficient to kill the cell outright but enough to cause significant cell damage. (e.g. A short period of hypoxia or exposure to low doses of a chemical toxin). In contrast, if the initial damage to a cell is too severe, the precisely regulated process of apoptosis is not possible and cell death occurs by necrosis .The cell and its organelles swell and the plasma membrane ruptures with the loss of intracellular contents into the surrounding medium. This attracts neutrophils which cause an inflammatory response and secondary damage to the tissue. In many cancers it is an impairment of apoptosis that leads to unrestrained cell proliferation and an insensitivity to chemotherapeutic agents. Clinically it would be desirable to inhibit cell death in the former situations and stimulate it in the latter. In recent years it has become apparent that mitochondria play a critical role in the mechanism of both apoptotic and necrotic cell death, in addition to their widely recognized function in the provision of ATP to sustain function".[798]

FIRST WEEK: Between 6 to 9 days the embryo implants in his or her mother's uterus. "Implantation of the fertilized ovum into the endometrium is the most difficult process of early pregnancy. Even among perfectly fertile couples, as many as one third of all pregnancies are lost due to deficient implantation. Implantation and formation of placenta is the major determinant of fetal growth and development".[721, 734] "During implantation, extravillous trophoblasts breech uterine vessels that are embedded in a decidual cell matrix. Through this invasive process the embryo gains requisite access to

the maternal blood supply, while risking exposure to high circulating glucocorticoid levels. Thus, the expression of 11 beta-HSD (whose catalytic activity is NADP(+)-dependent, and NAD(+)-dependent) by the decidual cell layer may be essential in regulating cortisol exposure of the developing embryo prior to placentation".[741]

2.3 LIFE IN THE WOMB: THE FIRST LEG OF THE JOURNEY

Life in the womb is generally depicted as being a time of peacefulness and serenity, but the reality is a little different. "The body of the mother responds to pregnancy by a weight gain (12 kg in the average). This increase appears in the second and third trimester of the pregnancy. This increase involves the growth of the uterus from 50 g to 1000 g and the growth of the fetus and fetal membranes. The breasts grow by 1 kg. About 1.5 kg of extra body fat and increased volume of the extracellular fluid and blood contribute as well. The volume of blood increases by about 30%. The basal metabolic rate increases by about 15%. The cardiac output increases by about 30 - 40% above normal. Placental circulation involves about 625 ml of blood per minute.[719] All of this needs lots of NAD energy for both her and her newly developing baby.

"Prostaglandins E2 and F2 alpha regulate a number of physiological functions in reproductive tissues, and concentrations of these bioactive modulators increase during pregnancy. Corresponding to the increase in circulating levels of prostaglandins during pregnancy is an increase in enzymes that metabolize these agents. Three prostaglandin-metabolizing enzymes induced during pregnancy are NAD(+)-dependent 15-hydroxyprostaglandin dehydrogenase (PGDH), NADPH-dependent carbonyl reductase, and cytochrome P450-dependent prostaglandin omega- or 20-hydroxylase."[650]

TWO WEEKS: The embryo's heart is beating. Throughout his or her development, the embryo's body is fully functional, though the organs are still developing and incomplete. The embryo has a separate brain divided in three segments; the forebrain, midbrain, and hindbrain and spine. The placenta is forming. Limb buds, the beginnings of arms and legs, are forming.[734] "NAD is a very specific component, an essential component of your body. If you do not have it, none of your systems functions and this includes your brain. If you don't have NAD, you die; it's as simple as that."[65] "NAD-dependent methylenetetrahydrofolate dehydrogenase-methenyltetrahydrofolate cyclohydrolase (NMDMC) catalyzes the interconversion of 5,10-methylenetetrahydrofolate and 10-formyltetrahydrofolate in mitochondria of mammalian cells, but its metabolic role is not yet clear. Its expression in embryonic tissues but not in most adult tissues as well as its stringent transcriptional regulation led us to postulate that it may play a role in embryonic development. To investigate the metabolic role of NMDMC, we used a knockout approach to delete the nmdmc gene in mice. Heterozygous mice appear healthy, but homozygous NMDMC knockout mice die in utero".[766]

FOUR WEEKS: Circulation to and from the placenta begins. The placenta is a very special, amazing organ that connects the mother's circulatory system with the embryos. The placenta filters oxygen out of the mother's blood into the baby's. It also gathers nutrition for the embryo. And lastly, the placenta sifts waste out of the embryo's blood. Soon the embryos own kidneys will begin to function, and share this work with the placenta. The embryo has hands with ridges that will grow into fingers, and two-segmented arms. The embryo has feet, thighs, and calves. Internal organs are growing.

The tongue, oesophagus and stomach are well developed, as are the kidneys. The embryo's liver, gall bladder, and pancreas have been developing for several days. Lungs begin to develop. The thyroid and other glands are forming. The embryo's face and sensory organs are forming. He or she has eyes, including a retina that already has colour, as well as ears, a nose, and mouth. Reproductive organs are beginning to form.[734, 735]

FIVE WEEKS: The brain divides into more specialized segments. The telencephalon is the primitive cerebrum, the 'thinking' part of the brain and is responsible for sensory perception, memory, learning, and conscious thought. The diencephalon develops into the thalamus and the hypothalamus, the 'feeling' part of the brain serving as a relay station between the senses and the brain. The hypothalamus produces basic drives and emotions such as hunger, thirst, pleasure, and fear. The cerebellum, medulla, and pons are responsible for unconscious physical processes like blood circulation or breathing, as well as reflexes, muscle coordination and movement. The embryo has a palate, completely with tiny tooth buds. His or her face is nearly finished forming and looks reasonably human, though lacking the muscles needed for facial expressions like smiling or frowning. The embryo begins to move.[734]

SIX WEEKS: The embryo looks like a baby in miniature, though his or her head is still very large compared to the rest of the body, because the brain is growing so quickly. "L-myo-inositol-1-phosphate synthase (EC 5.5.1.4) from mammalian fetal and adult brain differ considerably with respect to their stability towards different temperatures between 25-65 degrees C. This property has been found to be associated with the presence of the synthase co-factor, NAD, bound to the enzyme protein. The lower thermal stability of the fetal enzyme increases in presence of added NAD (0.8 mM) whereas the higher thermal stability of the adult brain enzyme declines when NAD is specifically removed from the enzyme".[795] The embryo has distinct fingers. All the embryo's organs and organ systems have been developed, though they are still immature and need time to finish growing. Several organ systems, including the circulatory system (heart) and nervous system (brain) are already functioning. The embryo has distinct toes.[734, 736]

EIGHT WEEKS: The unborn baby is now called a 'fetus', because he or she has finished with the process of creating and only growing and developing of his whole body is left. Eyelids begin to form.[734, 736] "As long as fetal oxygen reserves are not depleted, fetal metabolic functions will continue aerobically, even though fetal hypoxemia is present. As O2 reserves are exhausted in some tissues, fetal hypoxemia will be associated with tissue hypoxia, the net result of which will be anaerobic metabolism, lactic acidosis, and tissue death. Whether a fetus is adequately oxygenated or not is a function of the quantity of oxygen reserve available. A fetus with a substantial oxygen reserve can compensate fully for most interference in its oxygen supply and can maintain oxidative metabolism under a variety of conditions. In contrast, a fetus with minimal oxygen reserves will not tolerate even the mildest degree of O2 deficiency without developing tissue hypoxia or even death in utero."[724]

9 TO 10 WEEKS: The fetus touches his or her own face and sucks his or her thumb, and makes breathing and swallowing motions. The sense of smell begins to develop. The fetus urinates and experiences hiccups. He or she is moving almost constantly, and can step, kick, somersault, stretch, and move his or her arms. At the end of the ninth week, the critical developmental phase will have passed. The rest of the pregnancy is

characterized by a rapid increase in size and further growth and differentiation between organs and tissues.[735, 736]

11 TO 13 WEEKS: At about twelve weeks it will already have turned into a little acrobat, who rolls from the back to the front, while it tumbles through the fluid and waves with its little arms and legs as if it wants to explore its environment. Even the facial muscles are exercised with little frowns and movements of the lips. The fetus's bone marrow begins to produce white blood cells. The fetus's external reproductive organs are visibly male or female. The inner parts of the ear are formed, and the fetus may be able to hear. The bones become hard, like in adults bones, whereas they had previously been soft. "We propose a role of extracellular NAD(+) in bone homeostatic control".[771] The sense of taste develops.[734, 736]

14 WEEKS: Fetuses display individual personality. The fetus can experience pleasure and happiness or displeasure and fear. Fetuses at this age are also startled, and their heart rates increased, by loud unpleasant noises. The mother, may first feel her baby kicking. He or she is finally strong.[736]

15 TO 16 WEEKS: The fetus's nerves are being coated with a fatty substance called myelin. Myelin makes faster nerve transmissions possible and insulates the nerves so that impulses can be sent over longer distances. The fetus has fingerprints.

19 WEEKS: This is the youngest that any baby has been born and survived. Babies born this young may have problems with infections, since their immune systems are still immature, and may have trouble breathing. In mothers "the second half of the normal pregnancy was characterized by an increase in activity of hexokinase, in content of 2,3-DPG, ADP, by a distinct decrease in ATP, NAD and the ratio ATP/ADP".[739]

24 WEEKS: This is the age at which the laws in most consider a baby "viable", or able to survive outside the womb.

30 WEEKS: "At thirty weeks of gestation, there are 6 million ova in the ovary of the female fetus; at birth, there are one million of them; 300,000 to 400,000 are present at the onset of puberty, but only 400 follicles develop sufficiently to expel the ovum. After menopause, there are no follicles present."[721]

38 WEEKS: This is the age at which a baby should, ideally, be born. At 38 weeks the baby's lungs are fully functional and his or her immune system is ready for the outside world.

Its phenomenal rise over a period of nine months, from a bunch of little cells to a well-developed baby, is over. There is more growth in the first part of life than in the last part of it. The human body has completed 90% of his or her growth at the time of birth. Only 10% occurs between birth and adulthood. None after that. The fetal brain gives the birth signal. Also, it is believed that the fetal brain activates the synthesis of estrogens, which increase uterine contractility.[721] It is ready to commence on the first significant and dangerous journey, which it will ever undertake. The second journey will only be dangerous for some of us, although the departure is caused by death.

2.4 BIRTH: CROSSING THE FIRST BRIDGE

All of us have already undertaken it, fortunately only once. It was the time, when you decided that the time had arrived to exchange the snug watery world of your mother's womb for the greater world outside of it. You had to get out of there, but your greatest obstacle was the size of your head. The tension was enormous and overwhelming. Eventually everything was over and you slipped out. You gasped for breath. Your lungs expanded. Suddenly they were filled with air. You screamed, probably. Someone cut your umbilical cord, which had been your life line. The noise was terrible.[729]

You had just completed the most significant journey of your life. You were born and were merely one of the nine human beings born every second of the day. A baby's first breath requires a huge amount of strength, to overcome the surface tension, which had kept the lungs closed when they had been filled with fluid. The lungs contain chemicals, to relieve the surface tension and to prevent the lungs from collapsing, when the first breath is exhaled. These chemicals are produced deep into the pregnancy and this creates problems for babies, who are born prematurely. Undeveloped lungs are often the critical factor, which limits very premature babies' chance of survival.[729]

"Sudden Infant Death Syndrome (SIDS) has been also linked to exposure to ambient carbon monoxide... Fetal hypoxia caused by exposure to carbon monoxide could be a factor contributing to SIDS deaths." [769] "Blood glucose, pyruvate and lactate were examined during hospitalization of 13 cases of acute carbon monoxide poisoning developing from short (less than or equal to 1.5 h) or long (10-14 h) exposure. CO intoxication resulted in increased blood levels of all carbohydrate metabolites studied. Increased levels of pyruvate and lactate were much more pronounced and lasted for a longer time following long, compared with short, CO exposure despite similar blood COHb level (about 40% at the beginning of hospitalization). The results showed difference in biochemical effect of short and long single exposure to CO that could not be detected by the measurement of COHb".[296] "Infant patients with "cerebral lactic acidosis" show neurological symptoms, elevated levels of lactate in CSF, little or no systemic acidosis and levels of lactate in blood so slightly elevated that they would be overlooked. Lactate elevation confined to CSF and brain has been described in biotinidase deficiency and in some mitochondriopathies."[727]

"There is a need for metabolic screening facilities in developing countries. A battery of four simple tests namely arterial blood gases, blood ammonia, urinary ketones and blood lactate in tertiary health care centers is advocated".[727] "The purpose of the study was differential diagnosis of lactic acidosis in 44 children aged from 2 weeks to 4 years. In all of them the lactate level in repeated determinations exceeded 27 mg/100 ml. From the point of view of clinical manifestations the children were divided into three groups: 26 with hepatomegaly and hypoglycaemia (I), 6 with ataxia and retardation of somatic development (II), 12 with mental retardation and muscular hypotonia (III).[714] "We have therefore determined fetal and maternal lactate concentrations and acid-base status under various conditions in 589 women at the end of gestation and during labor. The results show that metabolic acidosis develops in all fetuses because of increased production of lactic acidosis is primarily of fetal origin."[721] "Umbilical cord blood levels of lactate, base deficit, and pH were measured in 452 liveborn infants. In vigorous newborns, the mean umbilical arterial and venous concentrations of lactate were lowest

with elective cesarean section, higher with cesarean section performed during labor, and highest with vaginal delivery. This suggests a rise in the fetal lactate level in response to labor. Depressed newborns had higher umbilical lactate levels than vigorous newborns irrespective of the method of delivery"[723] Global surveys conservatively estimate the occurrence of inherited metabolic disorders in the range of three to four per thousand live born infants. Macrocephaly and microcephaly are common. Approximately 5% of children are either macro- or microcephalic.

Another danger, which the newly born must beat, is control of temperature. Foetuses in the womb do not have such concerns, because they can enjoy their mothers' warmth. After birth babies are however seldom capable to even do something simple, like shivering, which is important for adults to produce warmth. There are however brown deposits of fat around the baby's neck, shoulders, breastbone and spine. When he gets cold, his little body starts to burn the fat in an unique metabolic process, which releases a lot of heat and metabolic energy.[729]

Then there is the baby's appetite. It is enormous in proportion to its body weight. During the earliest days it can eat 3 per cent of its weight, but it increases rapidly to more than 10 per cent. Around the tenth day, the baby will already, with a lot a slurping and sucking, have consumed the same amount of milk as its body weight. Around this time it will gain approximately twenty grams in weight every day, or about one gram for every twenty grams which it consumes. If an adult consumed similar percentage of his body weight, he would have to process seven or more kilograms per day.[729] Your baby eats so much because he needs lots of NAD energy to sleep and grow. "You no sooner fall into a deep sleep when you're awakened by the only member of your family who seems to be getting enough rest: your baby! If you're feeling a bit frazzled and exhausted by your baby's erratic sleep patterns, you're not alone. According to Dr Richard Ferber, author of Solve Your Child's Sleep Problems, newborn babies typically sleep about sixteen or seventeen hours per day, but rarely for more than a few hours at a time".[757]

Rates of pediatric injuries by 3-month intervals for children 0 to 3 years of age: "There were a total of 23,173 injuries; 636 resulted in death. The overall annual rate for children aged 0 to 3 years was 371/100,000. Children aged 15 to 17 months had the highest overall injury rate before age 15 years. For children 0 to 12 months of age, there was a different leading cause of specific injury for each 3-month period: other falls from height (0-2 months), battering (3-5 months), falls from furniture (6-8 months), and non airway foreign body (9-11 months). Hot liquid and vapour injuries were the leading specific causes for children 12 to 17 months. Poisoning by medication was the leading specific cause of injury for all age groups from 18 to 35 months and exceeded poisoning by other substances. Pedestrian injury was the leading specific cause of injury for all age groups from 36 to 47 months. Fall from furniture has the highest rates of specific causes of falls from age 3 to 47 months."[743] Even worse than this is: the so-called medically unexplained chronic fatigue in childhood which may cause considerable disability and is substantially familial.[740] Chronic fatigue amongst schoolchildren must be differentiated from psychosomatic disorders and absenteeism[119]. The average energy block of children and adults suffering from chronic fatigue is 74.

"Most children develop a clear-cut sense of whether they are boys or girls at a young age. This sense of being "a boy" or "a girl" is called gender identity, a term that came into the medical literature in the 1950s. For most children this develops somewhere

between 18 and 30 months of age. After gender identity is formed, gender stability develops. Gender identity is not the same as gender, which is commonly used to mean the biologic identity. For most people, gender identity matches with biologic gender, but there is condition called gender identity disorder (GID) in which biologic gender is not the same as the gender identity of the person. This is a rare disorder but one that lead to a lot of heartache and turmoil for both the affected child and his parents."[759] Adolescents and adults with gender identity problems have an average energy block of 66.

Learning a language is a survival mechanism for the baby and in this regard the child has a phenomenal capacity to acquire language during its first six years. Thereafter it will never be easy again, to learn how to speak a language; schoolchildren will attest to this. Research indicates, that people who learn a language when they are older use another part of the brain, than when the baby does it for the first time.[729]

At the same time when a language is being acquired, social skills are developed. At the most basic level the child must become aware that he is an individual, who differs from all other people and things. As all parents know and realize to an ever-increasing extent over the years, a child's growing up consists of much more than learning skills, the ability to stand straight, learning words, drawing circles, becoming stronger and more clever. It consists of developing a unique person, someone who realizes that he is an individual. There is however a small hurdle, which must be traversed. Puberty and the accompanying period of adolescence are the rockiest part, which remains on the road to adulthood.[729]

2.5 PUBERTY: OUR BIOLOGICAL DESTINATION

We often suffer from the misconception that we are in one way or the other in control of our bodies. It is however, the least true with regard to the physical aspect, our biological composition which controls us. This is seldom as obvious as during the tempestuous years of puberty. "Although more than 82% of the 104 pregnant teens (age between 13 and 18) were aware of where to get birth control, they demonstrated no deep understanding of the menstrual cycle and its relationship to intercourse and only 11% used effective contraception. Of the birth control non-users 74% of the girls reported they did not want to get pregnant. In spite of unprotected coitus, most girls were surprised at conception."[752]

Puberty is not only a time of confusion for adolescents, but also a time which continues to confuse scientists. The exact causes and the reason why it happens at that stage of life remain a mystery.[729] We know that the nervous system and hormones are involved, but social and psychological factors and nutrition also play a part. The changes in these years during which maturing occurs are normally spread over four years and can quite normally start at any time between the age of eight and thirteen years in girls and nine and fourteen years in boys.[729]

In a normal group of children there can therefore be pubertal children, who range in age from eight to eighteen. This means that some underwent all of their pubertal changes before others of the same age have even started with it. This leads to great unhappiness amongst those, who feel that they matured prematurely, too late, or simply because they are different from their friends. Since girls start changing approximately eighteen months

before boys, girls can be bigger, stronger and physically more advanced than their male classmates. This can also lead to emotional tension.[729]

Like most processes in the body, the commencement of puberty is brought about by the brain. The hypothalamus, a small structure with the size of a grape's pit in the center of the brain, starts to secrete large quantities of hormones. They, in turn, stimulate the pituitary gland, which is also located in the brain, to produce two hormones, which are known as LH and FSH. First they are released during the night, in regular deliveries, while the child is sleeping. As puberty progresses, more of it is secreted, until the adult pattern has been reached, which will prevail throughout life.[729]

LH and FSH are identical in boys and girls and in men and women. The effect of it on the targeted tissues is different however. In boys LH binds with specific groups of cells and this stimulates them, to increase their production of testosterone. It is interesting that production of testosterone also depends on the hormone prolactin, which is better known for its stimulation of milk secretion in women. This very male hormone is the key to sexual maturing. It increases the size of the genitals, develops the structures which produce sperms, stimulates the growth of hair in the face, on the chest and in the pubic region, increases muscle mass and bone density, lets the larynx or voice box expand and arouses the sexual drive.[729]

In girls and women the hypophysis secretes its hormones in a monthly pattern. FSH, which is the abbreviation of follicle-stimulating hormone, lets egg follicles ripen in the ovary. It stimulates the ovaries to produce estrogen, which is the key to puberty in girls, even before ovulation begins. Estrogen causes the depositing of fat on the breasts, buttocks and thighs. It has a special effect on the pelvic bones; it flattens and widens the legs.[729]

Estrogen receptors in the skin make the skin soft and smooth, while the male skin in contrast responds to testosterone by becoming thicker and stronger. LH controls the levels of the other female hormone, progesterone, which plays a determining role in the menstrual cycle.[729]

If there is not enough NAD for these processes it can cause a lot of problems for the incumbants. NAD deficiency can lead to insufficient NAD for the production of the male hormone, i.e. testosterone, and the female luteinisation hormone. It could, in the case of men, be the explanation for the feminisation syndrome (loss of beard, enlarged breasts and low sex-drive) and the masculinisation syndrome in women (menstrual problems, increased beard-growth and deeper voice)[125].

This is puberty. It is not the same as adolescence, although it forms part thereof. Adolescent characteristics, like increase in size, weight, strength and intelligence, are merely proportional changes. When puberty commences, our children who are perfectly adapted up to a point, are nevertheless not capable of carrying out the instruction to be fertile and multiply.[729]

By the time when puberty has been completed, we shall already have traversed the last hill and we shall be looking at the peak of the mountain, for which all of the previous physical developments in us prepared us. We shall still have to learn a lot, but biologically we have already reached our destination. Physically, mentally and socially

we can occupy our position as independent members of the human race. And, if we choose so now, we can transfer the genes, which formed us, to the next generation.[729]

In a study about defloration "82.3% report "love" as their main motive, 12.5% report to have done it "out of curiosity" and only in 7.2% it happened "by chance". Only 36.4% were prepared psychologically for the act of defloration. In 42% the coitus occurred at parties and 43.7% in the evenings.[753] Overall, 91% of the 2933 sexually active female respondents indicated that their first intercourse was voluntary. 76% of women 13 years or younger at first intercourse, compared with 90% of those 19-24 years old, characterized their first intercourse as voluntary.[754] The truth is not embedded in this statistics regarding our postpubertal body which belong to us, but who easily renders its biochemical control to our opposite sex partner. So rather don't play house before you married and ready for parenthood.

2.6 ADULTHOOD: OUR PSYCHOLOGICAL DESTINATION?

As a species, we performed extremely well. Homo sapiens is not particularly strong, nor particularly fast, agile or well-adapted to the cold or heat. The billions of human beings on this planet however occupy a larger part of the earth's land area than any other species. Our 1.4 kg of nerve tissue, the intellectual seat of our species, is obviously by far the most difficult part of our body to comprehend. We do not know why it is so large and how it happens, that it is so clever. In one way or the other its billions of cells and its millions of connections are operating in such a way that we not only call ourselves homo sapiens, which means wise man, but some indeed earn this special name.

It is mankind's grey matter energized by NAD, in conjunction with an agile hand and the ability to talk, which in any case require a good brain, which made this form of life the most comfort-oriented, most widely distributed, most intelligent, most extroverted, most creative and potentially the most devastating earthly species, which has ever existed.[729] Derivatives of niacin, mainly in the form of NAD and NADP coenzymes, are found abundantly in brain tissue. In the case of niacin deficiency, the brain's supply of NAD declines sharply and the functioning of the brain is disturbed; malfunctioning of the brain (dementia) is indeed one of the primary characteristics of pellagra. If the NAD deficiency lasts for an extended period, permanent brain damage develops[144].

Our brain is probably the host of our spirit and definitely the seat of our soul. "A team of neuroscientists from the University of California at San Diego said the most intriguing explanation is that the seizure causes an over stimulation of the nerves in a part of the brain dubbed the "God module". "There may be dedicated neural machinery in the temporal lobes concerned with religion. This may have evolved to impose order and stability on society," the team reported at a conference last week. The results indicate that whether a person believes in a religion or even in God may depend on how enhanced is this part of the brain's electrical circuitry, the scientists said. If the research is correct and a "God module" exists, then it might suggest that individuals who are atheists could have a differently configured neural circuit. A spokesman for Richard Harries, the Bishop of Oxford, said whether there is a "God module" is a question for scientists, not theologians. "It would not be surprising if God had created us with a physical facility for belief," he said."[726] Nobody have to be a slave of his/her NAD deficient body/brain or of its physical drives. By using the available knowledge you can

manage your body and taking care of it, then your body becomes your wonderful host and friend.

During adulthood most people marry and start a new generation. We teach our children to wait for this time in life so that they can choose their spouse with wisdom and love. Reality shows that our body do the choosing in most cases, it is called assortative mating. The finding in this study of an increased prevalence of psychiatric disorder in the first-degree relatives of the ill spouses would support the hypothesis of assortative mating, that there is a tendency for individuals with a predisposition to psychiatric illness to marry, rather than the existence of a marital interaction which causes an increased concordance for psychiatric illness.[755] "Our results indicate that assortative mating is common among parents of extremely obese children and adolescents... We interpret our results as being consistent with the hypothesis that an increased rate of assortative mating has contributed to the recent rise in obesity rates in several countries."[756]

Marriage partners choose each other through assortative mating, due to similar NAD energy levels. Someone, who is addicted to religion (energy block = 62) and with a mission in life to save her husband's soul, will therefore for example marry an alcoholic (energy block = 66), someone who needs NAD energy more than so-called love. All of this is not visible on the external level at the time of marriage, but this will only become apparent after several years of marriage. So much then for let your heart speak in choosing the mother of your children. NED can be ignored, but it does not change anything to the destruction, to which it definitely leads.

Due to their ignorance of their bodies and the possible role of NED some so-called adults have just enough energy to conceive a child and enjoy the act, but do not have enough energy to provide a safe, healthy and loving environment for the child to develop and grow up. Various excuses will be provided for not taking care of their young ones. "Throughout the world, an unknown number of children, most likely in the millions, are kept in orphanages and other non-penal institutions. Many of these children are kept in grossly substandard facilities and provided with inhumane care; many are left to die. Ironically, those responsible for nurturing and providing for the children they take into their care often physically and sexually abuse the children, and subject them to other cruel and degrading treatment. Even in institutions that are clean and provide adequate food, staff often neglect children, leaving them to lie alone in cribs or small beds with no stimulation, play, or adult attention." Even worse than this is the many children whose NED are ignored by their parents in the best of households.

2.7 AGING: THE LAST LEG OF THE JOURNEY

Each one of us, who lives today, is the product of successful reproduction. Our parents succeeded in reproducing us, their parents were successful in reproducing them and in this way one can trace the story of success back to the beginning.[729]

While we are moving through the early stages of life, our bodies change and develop to deal with the challenges of each new age. What happens then? Sooner or later each one of us realizes that we aged. The road gradually goes downhill, after we have reached the peak of physical performance. We become less competent in virtually every aspect, particularly during the last leg of our journey.[729]

Our physical appearance changes. We shall probably become shorter, more crooked, stiffer, grey, more bald, more wrinkled, have a drier, thinner and discoloured skin, with a double chin or a pointy chin, a different voice, bad hearing, poor eyesight, varicose veins, ineffective memory, larger earlobes and a broader, longer nose. Science has not yet presented a universally acceptable theory about ageing, but with our ever-increasing knowledge about molecular biology it is not surprising that research is concentrated on the internal functioning of cells. It can help to answer one of the most difficult questions about ageing.[729] Nutritional deficiencies are prevalent in the elderly, particularly among the frail, institutionalized, or impoverished. Muscle dysfunction is linked to inadequate intake of energy and protein, providing evidence for defects in morphology, physiology, and function.

We know that most tissues in the body are constantly coming and going. New differentiated cells can be produced during adult life in either of two ways: they can form by the simple duplication of existing differentiated cells, which divide to give pairs of daughter cells of the same type; or they can be generated from relatively undifferentiated stem cells. Rates of renewal vary from one tissue to another. The lining of the intestine is replaced every three days, red blood cells are replaced every 120 days, the skin is constantly discarding dead cells while new ones are being pushed to the surface, even your skeleton will replace all of its cells every seven years. There are few things in our body, which are older than ten years.[729] Even in a slowly renewing tissue, a small but persistent imbalance between the rate of cell production and the rate of cell death will lead to disaster. If 2% of the hepatocytes in a human divided each week but only 1% died, the liver would grow to exceed the weight of the rest of the body within 8 years. Homeostatic mechanisms must operate to adjust the rate of cell proliferation and/or the rate of cell death in order to keep the organ at its standard size. Menopause in Females: At the age of 40 or 50 years or later, the menstrual cycles usually become irregular and ovulation fails to appear (anovulatory cycles). The reason for it is the disappearance of the ova from the ovaries. All were either released or degenerate. When the cycles cease, menopause takes place. The loss of estrogen then causes: thinning of the vaginal epithelium; decreased vaginal secretion; decreased breast mass; hot flushes, night sweats and vaginal dryness; often heart disease; osteoporosis, decreased bone mass; psychic sensation of dyspnea; aging skin; irritability; fatigue; anxiety; mental deterioration and some loss of memory and sometimes psychotic states.[719]

Why do we therefore not always look and function, as if we are very young? Why do our earthly bodies not live forever? Each cell contains the body's complete genetical code in the DNA, which is stored in its core, and these DNA controls the cell's actions and reactions. In chemical terms, DNA is a huge, extremely complex molecule. The DNA must nevertheless create a perfect copy of itself, every time when the cell splits. Problems arise, when this does not happen.[729] One of the main reasons for DNA failure is NAD deficiency. NAD plays a major role in repairing DNA[44, 156, 196].

Damage due to free radicals and accumulating faults in the DNA are however not the complete story of ageing. A mighty factor is simple the lack of NAD energy to lessen the wear, due to continual affrontations, which bombard our bodies externally as well as internally. Polluting substances, toxins, natural radiation, viruses, bacteria and the ultraviolet light from the sun are attacking us all from the external environment, while our cells must fight internally against dangerous waste products and the hormonal consequences of physical and psychological tension.[729]

Since the body is such a complex and intimately integrated entity, degeneration in one system also makes its consequences felt elsewhere. The ear degenerates. Balance degenerates in its wake. Since vision also deteriorated, the chances of accidents are much greater. Bones break more easily when the person falls and bedriddenness have more permanent consequences on the muscular system, balance and strength of bones. What starts as subtle changes leads over the years to weakness and brittleness in adults, who once upon a time were healthy, reduced ability of most physiological systems and an ever increasing vulnerability to diseases and death?[729]

2.8 DEATH: OUR SPIRITUAL DESTINATION?

Death does not come suddenly, but gets the better of us while we are becoming ever more susceptible to it. After forty the rate of death doubles with every eight years with which the age advances, until all of us are ultimately caught by it. All of us know that that is our fate, but why is it like that?. Even if one becomes one-hundred years of age, you merely lived 5 214 weeks. Throughout the world hundreds of people die each second. Death is not a rare event, but it is the only event where NAD energy plays virtually no role. We nevertheless live from day to day and devote too little attention to the departure from earthly life, which awaits all of us.[729] This departure takes place, when the spirit leaves the body and soul, until they are re-united again in the hereafter. Put briefly, one can say that the body's billions of cells are held together by the spirit and the body returns to dust, after the spirit has departed from it.

We consider death to be an accident, which affects people here and there, but not as an omnipotent conqueror. By leading a healthy life, we enhance our quality of life. It however does not ensure longevity as is abundantly claimed by the owners of various nutritional supplements. Until recently, most people died at home. The family, often including the children, gathered around the deathbed, watched the death and discussed issues. In today's developed world, most people die in hospitals and in other institutions.[729]

Nowadays we do not see much of this finality and unfortunately many lost the religious anchors, on which previous generations could depend on so well. More than ever before death is still the great unknown entity to many people. If death comes suddenly, a completely healthy body can within moments become transformed to a state in which it cannot continue to live. Most deaths however come slowly, with a gradual collapse of the bodily systems.[729]

The last gasps of breath when death finally arrives are often accompanied by a rasping sound, which is referred to as the death rattle. It is caused by spasms in the muscles of the vocal cords. Immediately before death there is often a brief period, which is referred to as the agonal phase (derived from the Greek word agon, which means struggle). The muscles might, because of acid in the blood, start to jerk spasmodically and sometimes there is a brief jerking or swelling in the chest or shoulders.[729]

The battle against death is scary to people who witness it, but the dying person is usually too ill to be aware of it. As soon as death occurs, the eyeballs expand when the muscles which control the iris give up control for the last time. Sometimes the eye sheds a last tear, which is referred to as the lacrima mortis.[729]

Decomposition can be observed after approximately 48 hours in a moderate climate, or sooner if it is warm. It manifests itself initially as a green discoloration on the abdomen, which darkens to purple and then black. The early stages of decomposition are caused by digestive enzymes in the intestine. The body literally starts to digest itself from inside. Intestinal bacteria rapidly take control and the physical body is destroyed.[729]

Our bodies are built from atoms, which have already existed since the beginning of the universe. It is a fundamental law of physics that matter cannot be made or destroyed. The same atoms, which formed our planet, are absorbed in food, air and water to form our bodies for a short period and when we die, they are returned so that they are absorbed elsewhere. They are taken up in the food chain as nutrients for plants and small animals, which live in soil.

The Goal of NAD Therapy: Normal Energy Metabolic Processes for Optimal Wellbeing

A lot of myths exist about energy for living and about what it actually is. By dissecting everything into its smaller components one will eventually end up with nothing. This is the wonder of life, that only God could have created everything from nothing. The NAD energy required by our bodies is not mysterious vibration but is applicable chemical compounds changing from one form to another, and during the change, NAD energy is released that can be used for all human activities. Just as a motor car cannot run on potatoes, our bodies cannot function on the vibrations of music or whatever. The nett result is: if the required chemical compounds are not present no appropriate NAD energy can be released for utilisation by our bodies' cells, irrespective of other vibrations or resonances that could still be available. Prof Hans Krebs received the Nobel prize for medicine and physiology in 1953 for describing the cell's energy metabolic cycle and all the chemical compounds involved.

No behaviour is possible without the body, during the earthly part of one's life. All human activity (irrespective of whether it occurs on purpose, instinctively, knowingly or unknowingly), except dying, requires NAD energy to take place, to be suppressed, maintained or controlled. If the body has enough NAD energy in a usable form at its disposal, it can perform activities like eating, laughing, mourning, obedience, sleeping, praying, deciding, learning, playing, contemplation, conversion, attending church, concentration, cellular replacement, breathing, digestion, dreaming, sport, working, sex, temperature regulation and millions of other functions. The greater the amount of usable NAD energy and available quantity thereof, the higher the quality of life and functioning. The brain, for example, uses ten times more NAD energy than any other organ and has a very limited supply of NAD energy, which has to be replenished continuously. The bodies of NED sufferers do not on their own produce enough NAD energy, to be able to perform all of these activities and this makes their bodies unstable.

"Energy metabolism is defined as the sum of complex and integrated chemical reactions by which the body derives energy from the environment and maintains the proper functioning of all biologic processes. The final common pathway for all these processes is the complete oxidation of carbohydrates and fats and partial oxidation of proteins to carbon dioxide and water. These processes occur primarily in the mitochondria and are coupled to the biochemical reactions of the tricarboxylic acid cycle (better known as the Krebs cycle)".[547]

"At the cellular level, energy is used to make new proteins, to bring nutrients into a cell and expel cellular wastes, to repair damaged DNA, to synthesize neurotransmitters, etc. At the organ level, the heart uses energy to pump blood, the kidneys use energy to filter wastes while recycling precious nutrients, the brain uses energy to conduct electrical nerve impulses, the lungs use energy to take in oxygen and expel carbon dioxide and so on. At the level of the whole person, we use energy to walk, run, talk, chop wood, lift objects, work a computer keyboard, ad infinitum. The energy source for all these levels is the same - it is the bio-energy molecule ATP (adenosine triphosphate) the "universal energy currency of the cell"[567].

Energy cannot be created or destroyed, it can only be converted from one form into another. This rule also applies to the generation of energy in the human body. The energy, that is stored in food, must be released or produced in the body, by means of particular chemical reactions referred to as metabolism. Dietary carbohydrate from which humans gain energy enters the body in complex forms. The major source of dietary carbohydrate for humans is starch from consumed plant material. This is supplemented with a small amount of glycogen from animal tissue, disaccharides such as sucrose from products containing refined sugar and lactose in milk[544].

3.1 FROM FOOD TO METABOLIC ENERGY

"Food is of no use to our body until we have allowed the cells of our body to convert the food energy (organic energy) into chemical energy through respiration. Cell respiration is when organic material (the food we eat) is converted into chemical energy within the cells to provide the energy we use to perform our everyday activities. Chemical energy is stored within the bonds between carbon and hydrogen. Every time a bond is broken energy is released due to the exothermic reaction that takes place, that is, energy is given to the body. Glucose is a good energy store because of the six carbon-hydrogen bonds. However, the main source of energy is one that is produced within our body. It is the universal energy carrier, ATP, formally known as adenosine triphosphate"[546].

Digestion is a complex process. The cells that line the digestive tract secrete into the lumen of the gut a variety of substances, such as hydrochloric acid and digestive enzymes, to break down food molecules into simpler nutrients. The cells absorb these nutrients from the gut lumen, process them, and then release them into the blood for utilization by other cells of the body. All of these activities are adjusted according to the composition of the food consumed and the levels of metabolites in the circulation.

The first step in the metabolism of digestible carbohydrate is the conversion of the higher polymers to simpler, soluble forms that can be transported across the intestinal wall and delivered to the tissues. The breakdown of sugars begins in the mouth. Saliva is slightly acidic and contains lingual amylase that begins the digestion of carbohydrates. Once the food has arrived in the stomach, acid hydrolysis contributes to its degradation; specific gastric proteases and lipases aid this process for proteins and fats, respectively. The mixture of gastric secretions, saliva, and food, known collectively as chyme, moves to the small intestine. The resultant glucose and other simple carbohydrates are transported across the intestinal wall to the hepatic portal vein and then to parenchymal liver cells and other tissues. There they are converted to fatty acids, amino acids, and glycogen, or else oxidized by the various catabolic pathways of cells[544]. Most of these pathways are in the mitochondria, whose outer membrane forms an aqueous channel through which proteins up to 10,000 daltons can pass and go into the intermembrane space.[742] The average person's body contains enough glycogen to provide energy for 6-12 hours. In contrast to this, it contains enough fat to provide energy for up to 40 days[149]. An adult man produces enough heat every day during the metabolism of energy, to boil almost 40l of water[209].

Energy is also required to enable these digestive and metabolic processes. Between 5% and 10% of the energy that is available in the body is required for metabolising food. Various factors play a role in the generation, storage and utilisation of energy, and

include the body's surface-area, age, gender, thyroid hormones, dopamine, serotonin, adrenaline, body temperature and women's menstrual cycle[143].

3.2 MAJOR PATHWAYS OF ENERGY METABOLISM

Glucose is oxidised by all tissues to synthesise ATP. The first pathway which begins the complete oxidation of glucose is called glycolysis. The normal pathways are briefly described[320, 545]:

3.2.1 Glycolysis

Glycolysis (the breakdown of glucose to pyruvate and lactate, occurs in the cell cytoplasm): Glucose + 2 ATP + 4 ADP + 2 NAD -> 2 Pyruvate + 2 ADP + 4 ATP + 2 NADH + energy. Oxidation of glucose is known as glycolysis. Glucose is oxidized to either lactate or pyruvate. Under aerobic conditions, the dominant product in most tissues is pyruvate and the pathway is known as aerobic glycolysis. When oxygen is depleted, as for instance during prolonged vigorous exercise, the dominant glycolytic product in many tissues is lactate and the process is known as anaerobic glycolysis. "These studies demonstrate that orderly glycolysis in the erythrocyte is regulated by the NAD-to-NADH ratio and also provide a method that makes possible the in vitro study of erythrocyte glycolysis."[235]

The conversion of pyruvate to lactate, under anaerobic conditions, provides the cell with a mechanism for the oxidation of NADH (produced during the G3PDH reaction) to NAD which occurs during the LDH catalyzed reaction. This reduction is required since NAD is a necessary substrate for G3PDH, without which glycolysis will cease. Normally, during aerobic glycolysis the electrons of cytoplasmic NADH are transferred to mitochondrial carriers of the oxidative phosphorylation pathway generating a continuous pool of cytoplasmic NAD.[546, 733]

3.2.2 Gluconeogenesis

Gluconeogenesis is the biosynthesis of new glucose, (i.e. not glucose from glycogen). The production of glucose from other metabolites is necessary for use as a fuel source by the brain, testes, erythrocytes and kidney medulla since glucose is the sole energy source for these organs. Under fasting conditions, gluconeogenesis supplies almost all of the body's glucose to the brain as energy from ketone bodies which are converted to acetyl-CoA. Synthesis of glucose from three and four carbon precursors is essentially a reversal of glycolysis. The three reactions of glycolysis that proceed with a large negative free energy change are bypassed during gluconeogenesis by using different enzymes. Lactate is a predominate source of carbon atoms for glucose synthesis by gluconeogenesis.[730, 733]

3.2.3 The Pyruvate Dehydrogenase Complex

The pyruvate dehydrogenase complex (which oxidizes pyruvate to enter the citric acid cycle, operates only under aerobic conditions): Pyruvate + NAD + Coenzyme A -> CO2 + acetyl-CoA + NADH + energy. Cofactors required for pyruvate dehydrogenase include five different coenzymes namely: thiamine pyrophosphate (TPP) from thiamin; flavine

adenine dinucleotide (FAD) from riboflavin; Coenzyme-A (CoA), from pantothenate; nicotinamide adenine dinucleotide (NAD), from vitamin niacin and alpha-lipoic acid.[544]

3.2.4 The Citric Acid Cycle (Krebs Cycle)

The citric acid cycle (which completes the oxidation of carbohydrates and other substrates to carbon dioxide, occurs in mitochondria of cells): Acetyl-CoA + 3 NAD + FAD + ADP -> 2 CO2 + Coenzyme A + 3 NADH + FADH2 + ATP. Regulation of the TCA cycle, like that of glycolysis, occurs at both the level of entry of substrates into the cycle as well as at the key reactions of the cycle. Fuel enters the TCA cycle primarily as acetyl-CoA. The generation of acetyl-CoA from carbohydrates is, therefore, a major control point of the cycle. This is the reaction catalyzed by the PDH complex. The PDH complex is inhibited by acetyl-CoA and NADH and activated by non-acetylated CoA (CoASH) and NAD. Since three reactions of the TCA cycle as well as PDH utilize NAD as cofactor it is not difficult to understand why the cellular ratio of NAD/NADH has a major impact on the flux of carbon through the TCA cycle.[737]

3.2.5 Electron Transport and Oxidative Phosphorylation

Mitochondrial oxidative phosphorylation in vivo is dependent on the degree of reduction of the intramitochondrial reducing power ([NADH]/[NAD], cytoplasmic energy state ([ATP]/[ADP][Pi]) and intracellular oxygen pressure. Electron transport and oxidative phosphorylation (occurs in membranes of mitochondria in cells only under aerobic conditions). Nutritional implications and chemical structures are NAD and FAD. While the large quantity of NADH resulting from TCA cycle activity can be used for reductive biosynthesis, the reducing potential of mitochondrial NADH is most often used to supply the energy for ATP synthesis via oxidative phosphorylation. Oxidation of NADH with phosphorylation of ADP to form ATP are processes supported by the mitochondrial electron transport assembly and ATP synthase, which are integral protein complexes of the inner mitochondrial membrane. Oxidative phosphorylation traps this energy as the high-energy phosphate of ATP. In order for oxidative phosphorylation to proceed, two principal conditions must be met. First, the inner mitochondrial membrane must be physically intact so that protons can only re-enter the mitochondrion by a process coupled to ATP synthesis. Second, a high concentration of protons must be developed on the outside of the inner membrane.[731, 742] "A prolonged decrease in ATP levels underlies a number of neurodegenerative disorders. Defects in oxidative phosphorylation are associated with a number of neurodegenerative disorders."[748]

"The precise relationship between mitochondrial DNA mutations, impairment of oxidative phosphorylation and clinical phenotypes is not well understood. The prevailing view is that defects in ATP generating capacity due to mitochondrial DNA defect leads to energy failure, cellular dysfunction and eventually cell death in the affected tissues."[765]

3.2.6 The Pentose Phosphate Pathway

The pentose phosphate pathway (an alternate pathway for glucose oxidation). The pentose phosphate pathway is primarily an anabolic pathway to generate reducing equivalents, in the form of NADPH, for reductive biosynthesis reactions within cells, to provide the cell with ribose-5-phosphate (R5P) for the synthesis of the nucleotides and nucleic acids and to metabolize dietary pentose sugars derived from the digestion of

nucleic acids as well as to rearrange the carbon skeletons of dietary carbohydrates into glycolytic/gluconeogenic intermediates.[738]

3.2.7 Beta-Oxidation of Fatty Acids

Beta-oxidation of fatty acids (occurs in mitochondria of cells, only under aerobic conditions): Chemical structures and nutritional implications are coenzyme A (CoA), from pantothenic acid; flavin adenine dinucleotide (FAD), from riboflavin (vitamin B2) and nicotinamide adenine dinucleotide (NAD), from niacin. Fatty acid oxidation is reduced as this process requires NAD as a cofactor. Glycogenolysis is the breakdown of glycogen to glucose.[732]

3.3 ENERGY FACTORIES: THE MITOCHONDRIA

The mitochondria are essentially the body's power plants. All mitochondria are inherited from our mothers via the ovum, with virtually no mitochondria coming from our fathers, because the sperm head that penetrates the ovum in fertilization does not contain any mitochondria[548, 549]. If a number of the mitochondria in the ovum are defective, problems may arise as they divide and the infant is formed. If the defective mitochondria are in the muscles, the muscles may be weak due to poor energy production. This is true for all the body's organs including the brain[549]. Depending on where a metabolic block is in an inborn error of metabolism, we can try to provide energy from foodstuff that does not need that particular defective metabolic pathway[550]. "Pyridine nucleotides (NAD etc) are mostly stored within mitochondria where they are involved in different functions ranging from energy metabolism to cellular signalling. Here we discuss the mechanisms of mitochondrial NAD(+) metabolism and release that may contribute to the crucial roles played by these organelles as triggers or amplifiers of physiological and pathological events".[687]

The mitochondria are small structures which are present in all cells. The quantity of mitochondria varies amongst the different types of cells. Liver cells, for example, contain many more mitochondria than sperm cells[129]. The energy that is generated, is apportioned for use in cellular activity, for storage as chemical compounds that are rich in energy (like ATP and NAD derivatives), and the remainder is released as heat[39]. The primary "objective" of the energy metabolism is the manufacturing of ATP (about 50kg per day in the average human being) thereby providing the power for all cellular activities[370].

Ninety per cent of the body's energy is provided by the mitochondria's process of oxidative phosphorilisation. It is an extremely effective system for providing sufficient energy, to maintain the body's structure and functioning, and for regulating the body's temperature. The process consists of two metabolic processes that are closely linked to each other, i.e. the citric-acid cycle and the electron-transfer chain. In complex I of the electron-transfer chain, NAD to NADH is involved; in the citric-acid cycle three NAD to NADH compounds are involved[82]. The citric-acid cycle cannot function without the availability of NAD and NADP. Slight deviations in the activity of the mitochondria can lead to weakness, fatigue and cognitive problems[51, 68].

Mitochondria have a crucial role both in energy production and the viability of the cell and recently mitochondria have been implicated in programmed cell death (apoptosis).

Although much smaller than the nuclear genome, MtDNA is equally important. MtDNA defects and the resulting mitochondrial dysfunction are important contributors to human degenerative diseases, ageing and cancer[356]. Mitochondria play a pivotal role in cellular metabolism and in energy production in particular. Defects in structure or function of mitochondria, mainly involving the oxidative phosphorylation, mitochondrial biogenesis and other metabolic pathways, have been shown to be associated with a wide spectrum of clinical phenotypes. The ubiquitous nature of mitochondria and their unique genetic features contribute to the clinical, biochemical and genetic heterogeneity of mitochondrial diseases[357, 361].

The Krebs or citric acid cycle is the final common pathway of food components, and is also the source of basic structural or anabolic molecules that feed and support organ maintenance and neurological function. This fundamental pathway of energy flow is critical for all organ systems. Conversions of the Krebs cycle intermediates are under the control of enzymes that often require vitamin-derived cofactors and minerals for their function. Mild inborn errors of energy metabolism which may be compatible with survival at least into young adulthood, but not with normal development of mental and neurological functions, have been associated with the abnormal spilling of the Krebs cycle's intermediates[532].

3.4 ENERGY SYSTEMS USED DURING EXERCISE

The Cori cycle operates during exercise, when aerobic metabolism in muscle cannot keep up with energy needs. Glucose synthesized in liver and transported to muscle and blood. A highly exercising muscle generates a lot of NADH from glycolysis but without oxygen there is no way to regenerate NAD from the NADH (need NAD!). Lactic acidosis can and would result from insufficient oxygen (an increase in lactic acid and decrease in blood pH). So, the NADH is reoxidized by reduction of pyruvate to lactate by enzyme lactate dehydrogenase. Results in replenishment of NAD for glycolysis. Then the lactate formed in skeletal muscles during exercise is transported to the liver where it is used for gluconeogenesis. Lactate is transported through the bloodstream to the liver. Lactate is oxidized to pyruvate in the liver. Liver lactate dehydrogenase reconverts lactate to pyruvate since has high NAD/NADH ratio. Pyruvate is used to remake glucose by gluconeogenesis. Glucose is transported back to the muscles via the bloodstream.[733]

3.4.1 LESS THAN 10 SECONDS

The immediate energy system provides energy rapidly but for only a short period of time. It is used to fuel activities that last for about 10 or fewer seconds. For example weight lifting and picking up a bag of groceries. Components include existing cellular ATP stores and creatine phosphate (CP).[733]

3.4.2 10 SECONDS TO 2 MINUTES

The nonoxidative (anaerobic) energy system used at the start of an exercise session and for high intensity activities lasting for about 10 seconds to 2 minutes. Examples, 400 meter run or to dash up several flights of stairs. Creates ATP by breaking down glucose and glycogen. Does not require oxygen. Two key limiting factors (1) body's supply of glucose and glycogen is limited (2) nonoxidative system results in the production of lactic acid.[733]

3.4.3 LONGER THAN 2 MINUTES

The oxidative (aerobic) energy system requires oxygen to generate ATP. The aerobic production of energy does not produce any toxic waste products and so is the preferred system for prolonged exercise. Used during physical activity that lasts longer than 2 minutes (e.g. distance running, hiking ATP production takes place in cellular structures called mitochondria. Can use carbohydrates (glucose and glycogen) or fats to produces ATP. The actual fuel source depends on: intensity and duration of the activity as well as the fitness status of the individual.[733]

3.4.4 LONGER THAN 70-92 MINUTES

In general, carbohydrate use increases with increasing intensity and falls with increasing duration of an activity. Fats are used for lower intensity exercise. Glycogen stores are finite, and inevitably become depleted during long continuous exercise lasting in excess of 70-92 minutes (the more intensive the exercise, the quicker the glycogen is depleted). This applies not only to endurance events, such as marathon running but also to intermittent exercise sports such as soccer and rugby. When glycogen stores have been used up, the muscles attempt to cover their energy needs from fat metabolism. Unfortunately, because fat cannot supply energy at as rapid a rate as carbohydrate, the competitor is forced to slow down or reduce his/her rate of work to the level at which energy expenditure and energy synthesis are matched. This situation is made worse by the fact that when glycogen stores in the muscles are used up, blood glucose (hypoglycemia) reduces the supply of glucose to the brain, contributing to the feeling of exhaustion and causing a decrease in technique and the ability to make correct decisions.[733]

3.4.5 RECOVERY AFTER EXHAUSTIVE EXERCISE

Choice of diet has a dramatic effect on glycogen recovery following exhaustive exercise. A diet consisting mainly of protein and fat results in very little recovery of muscle glycogen even after 5 days! On the other hand a high carbohydrate diet provides faster restoration of muscle glycogen. Even though, however, complete recovery of glycogen stores takes about 2 days. During a prolonged exercise session, carbohydrates are the predominant fuel at the start of a workout, but fat utilizations (aerobic) increases over time. Carbohydrate metabolism is an energy system that does not depend on oxygen, but is only available for a short period of time as it rapidly causes fatigue. One of the reasons for this fatigue is the accumulation of lactic acid which quickly reduces the ability of the muscles to contract effectively. Lactic acid in the muscles can cause discomfort both during and after exercise, and total recovery will not occur until the excess lactic acid produced during exercise has been fully degraded. [733]

NAD Energy Deficiency(NED): The Focus of NAD Therapy

Research indicates that 10% of the world's population is suffering from NED, mostly manifesting as chronic fatigue syndrome (CFS), substance abuse, depression, stress, anxiety and various other chronic illnesses. NED is a spectrum disorder, which is initially difficult to understand. Grandmother might, for example, be suffering from NED masked as obesity, her son's workaholism masked his NED and her granddaughter might be a drug addict. The daughter-in-law is a religious addict, who never misses any prayer meeting. All of them wonder where the granddaughter could pick up this dirty and sinful habit. All four of these seemingly unrelated conditions are masks of NED, which are only revealed on different levels and in different ways. This e-book will clearly demonstrate the golden thread of NED that exists amongst these various "unrelated disorders" and the effective role of NAD Therapy in the treatment thereof.

NAD Energy Deficiency (NED) differs from energy deficiency that is defined as the lack of food and in its worst state is called famine. **NED is the cellular energy metabolic state, irrespective of the amount of food available or consumed, that develops and persists when there is not enough molecules of NAD and the other energy metabolic cofactors or energy factories (mitochondria) to convert the organic energy in food to chemical energy for use in the cells, tissues and organs.** NED is insufficient chemical energy for life and must not be confused with the spiritual or psychological exhaustion, which often accompanies it or is confused with it. There are several definitions and descriptions of physical energy and they lead to confusion on the part of most people. Parents, for example, incorrectly think that a hyperactive child (kinetic energy) possesses too much physical energy, when he merely has to little energy (chemical) to lead a controlled life. Before the organic energy in food can be carried into the body's cells it must first be converted by means of several steps, like digestion and metabolic processes, so that it can then be released as chemical energy in the cells. Such released energy in cells only then becomes available, so that conscious and subconscious activities (kinetic energy) can take place on the physical, psychological and spiritual level. Research indicated, that 90% of our physical energy must be made available from the biochemical processes in the cells. Some people experience problems with the metabolic processes, even though enough nutritional particles are available due to a lack of sufficient mitochondria for the final conversion of nutritional particles to an adequate amount of chemical energy cannot be made available. Such conditions are referred to as NED, in order to distinguish them from chronic fatigue, which is merely one form of NED.

4.1 THE COURSE OF NED

Genetic NED is already present at birth in some babies and symptoms vary greatly. The symptoms and signs depend on where and which organs are affected by NED, and vary from person to person. In most cases of NED, it manifests itself in children in the form of changes in sleeping patterns, academic stress, problems with concentration, hyperactivity, behavioural problems and academical underachievement. After puberty sexual problems might arise and problems start developing with regard to relationships. In another group of persons with NED, it can only be highlighted after a job has been accepted in low productivity, workaholism and high degree of absence are displayed. In elder persons and the aged NED can hide behind masks like Alzheimer or Parkinson's

disease. The NED masks of the youth years such as enuresis and academic stress can be exchanged in later years for masks of alcoholism or toxic relationships. In brief, it means that NED can become visible as a result of non-execution or over-execution of any activity, which requires energy for the execution thereof.

4.2 NED IS A SPECTRUM DISORDER

Fatigue is a prominent disabling symptom in a variety of medical and neurologic disorders[268]. The familiar example of how white light viewed through a prism, splits into the colours of a rainbow is a good analogy of what is meant. NED can be viewed as a form of a spectrum disorder. In other words, one common cause (NED) can cause, maintain or contribute to a variety of disorders. All cells, tissues, organs and systems in our bodies need energy to function optimally. An NED can cause, depending on the cell location, various symptoms and disorders ranging from cell death to death itself.

4.3 THE MOST COMMON CONDITION IN THE 21st CENTURY

Dr Ali predicts in a group discussion of professionals, that chronic fatigue (which can be viewed as a form of NED) will probably be the most common condition in the 21st century, for which treatment will be sought3. Dr Gentile provided the following criteria during the same discussion, as an indication of chronic fatigue[88]:

- Exhaustion, which lasts for more than six months, without any diagnosed cause.
- No diagnosed physical cause of illness, that would provide an explanation.
- Sleeping disorders and no revitalisation on waking.
- Low tolerance of stress that is often associated with exhaustion and a vague sense of discomfort a few days after having participated in sport or strenuous physical activity.

Another well-known example that can also serve as an example of what is meant by NED, is the blocking of the recycling of nicotinamide adenine dinucleotide (NAD) by acetaldehyde. Restricting NAD recycling can lead to symptoms like problems with memory, irritability, problems with concentration, depression, apathy, low intellectual energy, increased anxiety and panic, increased craving for alcohol, sugar and nicotine, decreased sex drive and increased premenstrual tension[214].

4.4 METABOLIC INDICATORS OF NED

"The researcher must account for and reflect on innumerable variables. The clinician must choose key variables and act"[455]. Treatment differs from research in so much that it must be based on sound research findings and that it must be feasible and affordable. There are various methods to measure energy metabolic deficiencies in research, but only a few are affordable and feasible to be used in daily practice. Treatment is also based on the most cost effective methods to obtain results in the alleviation of patients' suffering. The metabolic indicators of NED (lactate and pyruvate blood tests) that are reviewed in this publication meet the requirements of affordability, feasibility and general accessibility for most practitioners.

4.5 NED INHERITED, ACQUIRED AND INDUCED

"Recent advances in our understanding of the structure and function of the mitochondria have led to the recognition that inherited and acquired mitochondrial dysfunction may be responsible for diseases affecting the liver and other organ systems. Secondary mitochondrial hepatopathies are conditions in which the mitochondria are major targets during liver injury from another cause, such as metal overload, certain drugs and toxins, alcoholic liver injury, and conditions of oxidant stress. Treatment of these disorders is currently empirical, involving agents that may improve the redox status of mitochondria, promote electron flow, or act as mitochondrial antioxidants"[535].

Many acquired conditions including infections, severe catabolic states, tissue anoxia, severe dehydration and poisoning can lead to hyperlactacidaemia. All these causes should be ruled out before considering inborn errors of metabolism[436]. "Lactic acidosis is associated with both inherited and acquired metabolic diseases. Lactic acid metabolism in the presence of altered gluconeogenesis, anaerobic glycolysis, and acid-base balance is a major factor in many disorders. Inborn metabolic errors accompanied by derangement of metabolic pathways of glucose, pyruvate, amino acids, and organic acids and toxic and systemic conditions that promote tissue hypoxia or mitochondrial injury result in lactic acidosis. In the presence of acquired disorders, treatment is directed initially toward modification or cure of the primary condition and then toward eliminating acidosis and other metabolic complications. Specific therapy is available for some inborn errors of metabolism"[536]. The rare congenital lactic acidosis is a consequence of enzyme defects. The acquired form is relatively common in critically ill patients[537].

4.5.1 Genetic NED (Irreversible & Chronic)

- "Primary disorders of energy metabolism are those in which the primary insult affects the cellular machinery required for energy metabolism. A typical example would be a defect in a gene coding for a mitochondrial protein.[320]
- "All mitochondrial DNA in a cell is derived from the unfertilized ovum (sperm have virtually no mitochondria), and hence all characteristics encoded by the mitochondrial DNA are maternally inherited[641]". "Pyridine nucleotides are mostly stored within mitochondria where they are involved in different functions ranging from energy metabolism to cellular signalling. Here we discuss the mechanisms of mitochondrial NAD(+) metabolism and release that may contribute to the crucial roles played by these organelles as triggers or amplifiers of physiological and pathological events".[687]
- "Mitochondrial diseases are a group of disorders characterized by morphological or functional defects of the mitochondria, the organelles producing most of our cellular energy. As the only extranuclear site carrying genetic information, the mitochondria add an important chapter into the inheritance patterns of genetic diseases. Mitochondrial DNA (mtDNA) is exclusively maternally inherited in humans, but a mitochondrial disorder may follow either maternal or Mendelian inheritance, depending on the site of the primary gene defect.[359]

4.5.2 Acquired NED (Irreversible & Chronic)

- "Secondary disorders are those in which the derangements of energy metabolism are presumably secondary to some other insult but may still be important for the cellular pathophysiology".[320]"

- A number of acquired conditions including infections, severe catabolic states, tissue anoxia, severe dehydration and poisoning can give rise to hyperlactacidaemia. All these causes should be ruled out before considering inborn errors of metabolism".[436]

4.5.3 Induced NED (Reversible & Temporary)

- "The ratio of lactate/pyruvate was elevated in both sexes after the 25% fat-calorie period".[542]
- We have reported a case of lactic acidosis induced by ingestion of sustained-release nicotinic acid".[314]
- "Several tumour-therapeutic drugs reduce NAD and NADH levels, thereby inhibiting glycolytic energy production."[631]
- "In the case of hypoxia, or other causes of inhibition of the electron transport chain, NADH accumulates and the supply of NAD is depleted. This pushes the balance between pyruvate and lactate dramatically in favour of lactate further exacerbating its production in these circumstances. This change also occurs with alcohol abuse with alcohol dehydrogenase depleting NAD and producing NADH.[642]"

4.6 CHRONIC NATURE OF NED

Research shows that NED is most often genetic and chronic in nature and, if it is not treated effectively, continuously and appropriately, it will have a progressive and destructive course. Like chronic diseases, NED is characterized by sociomedical and psychological characteristics. NED must therefore be managed continuously from a multiprofessional approach. There are no "quick-fix" solutions in the short-term, because although it is treatable it is not curable. NED shares the characteristics of chronic diseases which can be summarized as follows[134]:

- The condition is, or seems to be, irreversible.
- Patients with chronic diseases place a great demand on the available healthcare resources.
- Chronic conditions are often treatable, but not curable.
- The multidimensional nature of chronic diseases often demands major adjustments to the lifestyle of the patient and his family.
- In contrast to patients with acute diseases, which are treated in particular by medical and nursing staff, patients with chronic diseases are more generally treated by their family and resources in their community.
- Chronic diseases often rob patients of their familiar and identity-related roles, and demand that they must develop an alternative lifestyle.
- Many chronic diseases in the long term require incorporation of and adaptation to special regimes of treatment.

4.7 GENDER AND NED

The rate of fatigue among women has been reported to be higher than among men. Life events such as childbirth, menopause, and socially imposed roles may confer unique vulnerability[272]. Chronic fatigue was the primary and most commonly mentioned health concern by 153 women participating in one study. Fatigue was ranked first by 27.5%

women and as one of the top 10 complaints by 80.4% women. They ascribed their fatigue to a combination of home and work activities (63.4%), poor sleep (38.2%), lack of time for themselves (34.1%), lack of exercise (32.5%), financial worries (28.5%), relationship problems (22.0%), emotional causes (17.9%), taking care of ill or frail family members (13.8%), lack of social or individual support (9.8%), poor physical health (8.9%), working in home or child care (3.3%), or gender bias/harassment (2.4%)[271].

4.8 PLEAS FOR ENERGY

"I finally reached the point where I felt that everything was too much for me. I felt as if I were no longer able to deal with even the smallest things. I had a flat in the city and lived alone. I reached the stage where I would come home from work in the evenings and simply close the door behind me. I didn't talk to anyone. I didn't go out or visit friends. By eight in the evening I was already in bed, waking up only at seven the next morning, barely in time to go to work. I experienced a complete withdrawal from society... People either feel okay or they don't. I never felt okay. I was extremely depressed and I basically felt that there is nothing worth living for. When I came to Nutrimalaika, I was considering suicide on a daily basis. It was the one thing I thought of all the time, more so than anything else"[247].

These pleas for physical energy to be able to go on with a meaningful life, are echoed by thousands of patients every day in consulting rooms. Due to various reasons few people really understand the actual role of energy, and specifically the chemical energy processes in our bodies. Despite the teaching of biology to millions of children and students, most patients think of energy as something mystical and out of reach of ordinary man. They view the restoration of energy, by applicable supplementation, as unthinkable and too simple a remedy for a long-lasting and debilitating problem affecting their whole being. This and other reasons keep them tied down in their destructive state of continuous suffering.

Although becoming tired is normal, staying tired for prolonged periods is abnormal as is to be chronically and untimeously plagued by NED. Most people revitalise their physical energy by means of nutrition, rest and sleep. There is however a group of people (including children even at birth) that experience severe problems in revitalising their energy levels through these natural means. If the body has a sufficient and regular supply of energy in an accessible and usable form at its disposal, it can perform activities, like eating, regulating temperature, sleeping, praying, laughing, grieving, working, cellular life and making love.

All human activities except dying, on all levels of being, require physical energy to be performed. If too little or irregular physical energy is available, due to any of a variety of possible factors, various bridging mechanisms (i.e. substances and or behaviour) are used to cope with the NED. Some of these bridging mechanisms can develop into full-blown disorders. To discuss the disorders associated with NED for clarification purposes, one can broadly refer to them as NEDRS. The concept "NED" serves only as an umbrella description and is not a diagnostic entity in itself. It is only offered as a possible concept to facilitate comprehensive treatment and understanding.

4.9 COPING MECHANISMS WITH NED

Coping strategies with NED include energy conservation, energy restoring efforts, enhancing resistance to fatigue, and temperature control[320]. It is a natural phenomenon to immediately and subconsciously revert to one or other form of recovery when we experience problems. At Nutrimalaika it is observed that people, unaware of their underlying NED, desperately try to manage their NED by adopting one or more of the following coping mechanisms:

Active coping styles: this can be viewed as an active approach (restoring energy) to deal with the underlying NED. These persons respond very well to the treatment approach discussed in this book.

- Using chemical substances and behaviour (legal, illegal and natural) to increase their energy levels, or to suppress the symptoms of NED. Examples of this are substance dependency, obesity, bulimia, workaholism, insomnia, sex or love addiction and the abuse of certain prescribed drugs.
- Attempting to address and deal with the trigger, by means of therapy and counselling. The prerequisite for achieving success with this process, is that sufficient energy must be available to facilitate change. The patient can draw the wrong conclusion, that neither counselling nor therapy works. An example of this is the "revolving door syndrome" where patients constantly change therapists and treatment regimes.
- Attempting to increase stamina, in other words, an attempt is made to accomplish more with the little energy that is available. Examples of this are excessive exercising and exercise dependency.

Passive coping styles: this can be viewed as a passive approach (conserving energy) to deal with the underlying problem. These persons initially experience problems to comply with the treatment approach outlined in this book. However, when their energy levels stabilises they too benefit from treatment to become actively involved in treatment.

- Reducing activities that require energy, or adapting to low energy levels. Examples of this are lower productivity, depression, chronic fatigue syndrome, sexual anorexia and excessive sleeping.
- Using inappropriate energy to deal with energy related problems on another dimension of being. For example using only spiritual interventions (waiting or relying on miracles alone) to alleviate physical problems for which effective treatment exists.
- Substituting one form of coping mechanism with another and wrongly believing that the underlying NED is effectively dealt with. Various treatment approaches set "positive" addictions (e.g. lifelong support groups) as the treatment goal for chronic disorders.
- Living only on one dimension of being and neglecting or ignoring the existence of the other dimensions of being and refraining from being a fully integrated human being. Religious addiction and co-dependency are possible examples of this coping mechanism.

4.10 PATIENTS' VIEWS OF NED

If we as therapists listen carefully to what our patients are saying, we will be able to hear these energy deficiencies and also the pain and shame revealed to us. To illustrate this point the following abstracts from published interviews, with patients treated for various disorders, are provided.

"Very tired, completely exhausted. I could not concentrate. By noon I was completely exhausted. I could not sleep at night - I was too tired to sleep. You are too tired to lift your arms. I think I had other symptoms like pain in the legs and in my lower back. I don't know what caused them... I didn't have any energy. When a piece of paper landed on my desk, I felt like tearing it up, whereas in the past, I found it very rewarding to create order. I am very meticulous. Things have to be done in a certain way, filed in a certain way, and balanced in the same way. It started getting to me. I didn't have the energy or the drive to do all these things. I struggled to do things that used to be easy. It was a matter of "I cannot work one minute longer". By twelve o' clock my work day was over. I tried to hide it from my management team"[181].

"You start to neglect your relationship with God and with your family. You don't rest properly. Finally I realised that I was such a devoted minister that I almost destroyed myself, simply because I kept on giving of myself. I kept on giving, and did not receive anything in return from God or my family. It is a vicious cycle. I realised that there was a certain day in the week that I didn't have much to do. I considered it my "day off". I would drink quite heavily to drown the tiredness, the desperation, the depression, because I didn't have the energy, or inner strength left, for I had given my all for other people. I had nothing left, I ended up a frustrated person, angry with everybody, and drinking was all that was left to do"[35].

"My marriage ended in divorce about 13 years ago. I received custody of the children. My life virtually fell apart. I couldn't get my life together and became depressed. About eight years ago I started seeing the psychologist. Before the time I kept thinking there had to be more to life than what I was experiencing at that stage. Nothing made me happy. I didn't know what happiness meant and I didn't know myself. All I knew was that God had to have something better in mind for me. That was when I went for help, and the psychologist and I have come a long way since"[127].

"I always had a hard time at school. I never took part in physical activities such as football, and that definitely had an effect. You know, when you take part in a sport where you exert yourself physically with other people, you make friends more easily. Not being able to keep up, affects many areas of your life ... for one thing it is very difficult to concentrate. A lack of energy affects everything you do. You just do less. Even your state of mind is affected. What I mean is that you may feel down when there is absolutely no reason to feel that way. The more energy you have, the more you give, the better you feel, the more you can do. I mean, the experience you had ... you are what you have achieved. It gives you a chance to experience things"[60].

"My family did not see me for almost four years, because of my involvement with her. She could not socialise and talk to people. So we both became withdrawn. I lost my friends. Then it was only she and I. Then I felt I could not take it any more. This was after I got divorced from her. A deadly tired feeling came over me. I did not want to live

anymore. I did not want to work anymore. I did not want anything. Nothing in life could cheer me up anymore"[255].

4.11 THE PAIN AND SHAME OF NED

NED (expressed as fatigue) is a common symptom reported by patients. For both professionals and patients, discussions related to the subject of fatigue are frustrating and unsatisfying, because of differences in expectations, a narrow focus in therapeutic approach or solutions and management[269]. In the process to unravel the mysterious cause of alcoholism, the important role of sufficient energy for effective living in general was noticed by the author. Patients generally describe NED, irrespective of the presenting disorder, as fatigue, tiredness, weariness, depression, lack of physical energy, failure to cope, powerless, exhaustion, stress, feeling strained, feeling empty, helplessness, feeling drained and various other symptoms and signs.

"In addition to arising from multiple etiologies, fatigue is also multidimensional in its manifestation and impact. Its effect on the quality of life of the patient is comparable to that of pain. Experienced by most patients as an extremely frustrating state of chronic energy depletion, it leads to loss of productivity which can reduce self-esteem. As a subtle and chronic symptom, it also places people at risk for being questioned about the authenticity of their complaints, particularly during the post-treatment, disease-free survival period. Patients themselves are reluctant to complain of fatigue, perhaps because they believe little can be done about it"[569].

Research shows that 77% of subjects with chronic fatigue syndrome (CFS), the lack of energy for sensible living, were called "psychological cases" by one or more of the physicians consulted. Most of these CFS sufferers were experiencing problems with stigmatization as expressed by estrangement (95%), attribution of CFS to psychological causes by others (77%), using an educational disclosure coping strategy (77%) and had to be secretive about their symptoms (39%)[267]. This stigmatization is not limited to CFS alone but applies to all other forms of NED.

4.12 PSYCHOLOGICAL INDICATORS OF NED

NED has a negative or inhibitory effect on the psychological functioning of the sufferer. Objective psychometric testing with the 16 Personality Factor Test (16PF SA92) indicates that the following five personality factors are most often found amongst NED-sufferers.

4.12.1 Ego Strength: Immature (C-)

Approximately 56% of NED sufferers will probably be irritated rapidly by people and issues and are dissatisfied with their earthly existence and family. They become frustrated quickly and are often overwhelmed by the limitations in their life. They feel inadequate to deal with the demands of life. They are unpredictable with regard to their interests and attitudes. They become upset easily, avoid their duties and tend to leave projects in a state of non-completion. They are prone to worry about issues and are comfortable to interact with others in a confrontational manner. Their lack of energy makes it difficult for them, to complete their daily tasks successfully. They also find it difficult to utilise their egostrength and are therefore very dependant on other for

assistance and guidance. They often experience problems with handling emotion, frustration and impulses, or with finding a realistic outlet for it. At times they are overwhelmed by it and this leads to emotional outbursts and other immature actions. They brag about the many projects, which they complete at work and for others, but the most important project, namely the quality of their life, remains undealt with.

4.12.2 Impulsivity: Serious (F-)

They set themselves difficult targets and react with hostility, if these targets are not achieved. They are quiet, introspective, pessimistic and obsessed with correctness. They are able to engross themselves in boring work and often become very upset by change and unexpected events. They often suffer from symptoms, like headache, phobias, worrying, depression and/or nightmares. They are perceived by others, as very serious persons. This factor was found amongst 46% of persons, who suffer from NED. This characteristic of NED sufferers, makes it practically impossible for them to accommodate humour, which on its own can be a healing function.

4.12.3 Insecurity: Worrying (O+)

They tend to belittle themselves and prefer to be broody over everything. They are emotionally very sensitive and easily become worried and scared. They are subjected to feelings of inferiority and inadequacy. They often feel excessively exhausted, avoid stimulation and tend to be emotionally unstable. They normally exhibit an excessive level of morality and commitment to duty, which causes them a lot of anxiety. They experience their serious feelings of guilt as a vague internal conflict, which they cannot control easily. This factor was found, amongst 46% of persons, who suffer from NED.

4.12.4 Tension: Driven (Q4+)

They are tense and irritable persons, who become upset easily by small issues. They are excessively tense and restless. Furthermore, they are very impatient and easily lose their temper. Irrespective of how exhausted they feel, they still experience an obligation to do things. They feel dissatisfied with themselves, because none of their numerous projects are completed successfully. They experience intense feelings of rejection and suffer from a lot of sexual frustration. As a result of the above-mentioned characteristics, they tend to exhibit anxiety-related disorders. Their psychological energy is often inadequate for dealing with situations and this leads to great anxiety and irrational concerns. This factor was found amongst 41% of persons, who suffer from NED.

4.12.5 Boldness: Restrained (H-)

The person is usually very shy, suffers from an unusually poor self-concept and experiences problems expressing himself. The person avoids careers requiring intimate interpersonal contact and prefers to have one or two intimate friends. Frequently he displays a pronounced and prolonged reaction to threats and trepidation. His greater sense of duty, dedication to work and regard for authority leads to panic-stricken reactivity. In the presence of the opposite sex he is very inhibited and quiet. His withdrawn nature and hostile privacy are often the result of previous experience of human contact being exhaustive.

4.13 HUMAN FUNCTIONING AND NED

The well-known psychologist, Maslow, had already compiled his hierarchical model of needs many years ago. We can extend it, by linking it to energy. Maslow's postulated integrated model of needs will be considered as a basis to illustrate human functioning. It represents a good example of the various needs that humans experience and that require sufficient energy to be met and maintained. As can be seen clearly in the following table, it also integrates all three the dimensions of being, i.e. spirit, soul and body.

Furthermore, one can suggest the possibility that the energy, required to satisfy the need meaningfully, increases in proportion to the level of the need. In other words the progress to the next level requires a certain amount of energy to achieve satisfaction. All human activity and needs require energy to be performed or not to be performed. No behaviour is possible, without the body. One cannot walk or sit without a body, nor can one speak, think, pray or subscribe to religious faith without a body. According to this model we would require the most energy to reach and maintain the transcendental level. Furthermore if there is a decrease in energy it follows that the person will revert to a lower level of functioning. Although this is merely an idea which warrants further investigation, it is daily observed in practice.

4.14 HIERARCHY OF NEEDS ACCORDING TO MASLOW[108]

According to Maslow, transcendence is the highest need, which can be satisfied, and it can only be satisfied satisfactorily if the other seven needs are satisfied. Transcendence is the ability of a person, to succeed in spite of limited ability and unfavourable circumstances, and to help others to achieve self-fulfilment. If someone's energy level declines, it firstly exerts a negative influence on one's transcendental need, then on self-actualisation, thereafter on the aesthetic needs then the cognitive needs, then respect, then love and intimacy, then safety and security and lastly the physiological needs of e.g. nutrition, sleep, sex etc. In other words, persons who suffer from serious NED function mostly on the bodily level

Various researchers emphasise the central and vital role of NAD in most processes of life[136, 191]. Dr Davis stresses the importance of NAD, as follows: "NAD is important for energy. If you have too little NAD, many of your enzymatic reactions fail to function and then you cannot produce the energy. You cannot produce ATP. NAD supplements must also be added to the minimum maintenance. NAD is a very specific component, an essential component of your body. If you do not have it, none of your systems functions, and this includes your brain. If you don't have NAD, you die; it's as simple as that. You will never have no NAD. You will always have a little NAD, because your electron-transfer chain possesses areas in which energy is generated, the electrons take in NAD and release it. In this way, it causes the functioning of the electron-transfer chain. This is why I say, that NAD is not a nutritional supplement. NAD is an essential and highly specialised component of the body, which requires it to function"[65]. Despite the fact that most of us have learned about NAD at school while studying biology, it remains relatively unknown as a nutriceutical energy metabolic supplement especially for NED.

5.1 BIOSYNTHESIS OF NAD

NAD is a co-enzyme that is mainly absorbed from food or produced naturally in the body from certain nutritional elements, by means of various biochemical processes[105, 259] . "Most niacin in food is in the form of NAD or NADP. Niacin is absorbed in the small intestine, mostly in the form of NAD or NADP"[369]. NAD is mainly obtained from the NAD that is present in food[38]. NAD can be produced in the liver, in particular, under the control of the hormones that are secreted by the adrenal glands[259]. Nicotinamide is an important precursor of NAD, under physiological conditions[151]. Tryptophan is another important precursor of NAD and the body obtains a large proportion of NAD from this source. In the case of human nutrition, 60 mg tryptophan is the equivalent of 1 mg niacin[64].

"NAD is synthesized in red cell from nicotinic acid and PRPP through the formation of nicotinate mononucleotide and desamido-NAD. Synthesis of one mole of NAD requires two moles of ATP. NADP comes from NAD phosphorylation by NAD-kinase (EC.2.7.1.23). NAD and NADP analysis on a population with ATP level ranging from 800 to 2500 nmoles/ml red cells showed a close correlation between ATP and pyridine cofactors. Moreover, NADP level appeared to be dependent of the redox-state of NADP/NADPH couple. Subjects with low NADPH (G-6-PD) deficient red cells, (Hb Koln) showed lower NADtot/NADP tot ratio, suggesting a NAD-kinase equilibrium shift toward NADP related to lower levels of the negative effector NADPH."[796] "Nicotinamide mononucleotide adenylyl transferase (NMNAT) is an essential enzyme in all organisms, because it catalyzes a key step of NAD synthesis. However, little is known about the structure and regulation of this enzyme... NMNAT appears to be a substrate of nuclear kinases and contains at least three potential phosphorylation sites".[786]

5.2 BIOCHEMICAL FUNCTIONS OF NAD

NAD was the first co-enzyme to be identified in 1905 by Harden and Young[138]. NAD has more than 100 functions in the human metabolism. Even the activity of the citric-acid cycle, which is found in most cells, becomes restricted in the lack of NAD and NADP[154]. The body constantly requires NAD and if the NAD level becomes too low, the need for it

is activated in the primitive part of the brain. This biochemical action cannot be controlled by the mind or changed by willpower. Alcohol and the metabolites, which it creates, suppress this need for NAD. Excessive exercising and the associated secretion of endorphins also suppress the need for NAD[51].

5.2.1 Metabolic Detoxification of Chemical Substances

NAD has already been used successfully since 1939, for the short-term treatment of alcoholism[51]. O'Halleren was however the acknowledged leader in treating various types of substance dependencies with the aid of NAD supplements. He used NAD to treat alcohol-, heroin-, cocaine-, morphine-, meperidine-, codeine-, amphetamine-, barbiturate- and sedative dependents[166]. NAD does not have the same side-effects as nicotinic acid at high dosages, like serious flushing and the release of histamine[211].

The intracellular metabolism of alcohol, and possibly also of other chemical substances, requires NAD or derivatives thereof, in order to take place. Ninety per cent of alcohol is absorbed almost immediately in the body's cells; the remaining 10% is discharged mainly in the urine. Acetaldehyde is the first metabolite of various chemical substances, including alcohol, that is produced[26, 133, 166, 173, 176, 227, 249]. Acetaldehyde is also formed during stress. Acetaldehyde is used as a preservative in certain dairy products[214]. The last step in the metabolic detoxification process occurs in the citric-acid cycle, where three NADs are involved in the process. This cycle is also responsible for the conversion of proteins, carbohydrates and fats into ATP. This is a purely biochemical autonomic reaction, and neither the person's will or any other form of control can be exercised over it. The biochemical reactions can be simplified as follows:

Chemical Substance + NAD -> Acetaldehyde + NAD -> Acetate + CoA -> Acetyl-CoA +3NAD(H) -> ATP + H2O + CO2 + Heat

Ethanol toxicity is closely related to its metabolism in the liver. The elevated NADH/NAD ratio (i.e. NAD deficiency) results in alterations of the intermediary metabolism of lipids, carbohydrates, proteins, purines, hormones and porphyrins. This shift in metabolic pathways results in hyperlactacidaemia, lactacidosis, ketosis and hyperuricaemia. Furthermore, excess NADH can results in free radical production[491, 492, 493].

The NADH that builds up, e.g. during e.g. alcohol metabolism, will drive pyruvate to lactate which can lead to acidosis. The pyruvate is now not available for gluconeogenesis and if, as is common in serious alcoholism, the patient is not eating properly, hypoglycemia can result. The high NADH/NAD ratio will affect other processes such as b-oxidation. One clinical manifestation is liver disorders associated with alcoholism: fatty liver, alcoholic hepatitis and, sometimes, cirrhosis. The burden on oxidizing systems also leads to increased use of the P450 or microsomal oxidizing system which can have important effects on steroid metabolism and other processes involving this system[491, 492, 493].

5.2.2 Repairing DNA

NAD and niacin (a precursor of NAD), play an important role in defending cells against DNA damage by genotoxic particles. Research shows that niacin supplementation, particularly for persons who initially have lower levels, improves the level of NAD in

blood and lymphocytes[99]. NAD plays a major role in repairing DNA[44, 156, 196]. Research shows that damage to DNA can possibly stimulate the biosynthesis of NAD and that the repair of DNA can be increased and accelerated in cells with increased levels of NAD[112]. Cytotoxic substances reduce the intracellular levels of NAD and can lead to the death of cells. DNA strand breakage decreased proportionately to NAD concentrations over time in lymphocytes exposed to oxygen radicals[367]. The results suggest a general correlation between DNA damage and acute lowering of cellular NAD pools[377, 564].

"Rejoining of DNA single-strand breaks generated by treatment of plasmids with gamma-rays, neocarzinostatin, or bleomycin was catalyzed inefficiently by human cell extracts. The reaction was strongly promoted by the addition of NAD+, which was employed for rapid and transient synthesis of poly(ADP-ribose)... NAD(+)-promoted DNA repair by soluble cell extracts also occurred with alkylated DNA as substrate and was suppressed by 3-aminobenzamide. A similar stimulatory effect by NAD+ was observed for repair of ultraviolet-irradiated DNA, and this could be ascribed to the presence of pyrimidine hydrates as minor radiation-induced DNA lesions".[788]

5.2.3 Generating Energy

During one of our dietician's lectures in Nutritional Biochemistry at Pretoria University, an individual's theoretical daily need for NAD, assuming that none is recycled, was calculated. The calculation showed, that the average person's body contains approximately 16 grammes of NAD and that it had to be recycled 2 160 times during every 24 hours through the body. Had the body lacked the ability to recycle NAD successfully, 35,91 kg of NAD (approximately 72 000 containers of NutriNAD, or 7,2 million MultiNAD or MalaikaNAD capsules) would have to be taken every day, in order to supplement it. NAD plays an important role in the production of ATP (the basic energy molecule) in the body.

NAD and NADP, which are pyridine nucleotides, are rated as being amongst the important high energy compounds in the biochemistry of organisms[138]. The reduction of NAD plays an important part in the citric-acid cycle and contributes to the production of 22 molecules of ATP from one molecule of glucose[38]. NAD and its derivatives NADH, NADP and NADPH have regulatory functions in the generation of triose phosphates and pyruvate from glucose[607]. NAD is reduced to NADH in the metabolism of glucose. The hydrogen molecule is obtained from the metabolism of fats, carbohydrates and proteins. The activated NADH plays a part in several critical bodily functions, amongst others, in the continued production of ATP, which is the basic energy compound in the body[45]. NAD plays an important role in the release of energy from carbohydrates, fats and proteins[137]. In the absence of oxygen, pyruvate must be converted to lactate to regenerate NAD from NADH in the cytoplasm. In the presence of oxygen, the mitochondria can reoxidize cytosolic NADH by an indirect process, involving the mitochondrial "shuttle systems"[348].

5.2.4 Improving Immunity

Phagocytes use NADPH as a source of energy, to destroy pathogens. The NAD(P)H, that is available, is also used to protect the body against free radicals and to, in this way, prevent illnesses and damage. High dosages of ascorbic acid can supplement the activity of the NAD(P)H, which is only available to a limited extent[45]. Research on the

effect of the Epstein-Barr virus on lymphocytes, indicates that the cultivated cells' levels of NAD were lower. The addition of NAD restored the levels within two hours. The study also discusses the effect of NAD on the mitochondrial metabolism and the relationship between NAD and the activity of complex I in cultured human cells[194].

5.2.5 Improving Brain Functions

The brain is metabolically speaking one of the most active organs in the body and consumes approximately 20% of all energy generated[21, 350]. Its weight-to-energy ratio is ten times more than that of most other organs. The brain does not really have any reserves of energy, in the true sense of the word, and must therefore be supplied continuously with energy by the body. The brain, as a whole, consumes approximately 4 x 10^{21} molecules of ATP per minute and this increases during REM sleeping. During the first ten years of a child's life, the brain consumes up to twice as much energy as during adulthood[212]. When pyruvate oxidation is impaired, glycolysis will run faster than normal to try to make up for deficient ATP production. This will cause more production of lactate. The brain relies on oxidation of glucose as an energy source and has a limited ability to oxidize fatty acids. In cases of severe energy depletion mental retardation is not surprising[348]. NAD plays an important part in the production of ATP in cells[38].

Derivatives of niacin, mainly in the form of NAD and NADP coenzymes, are found abundantly in brain tissue. In the case of niacin deficiency, the brain's supply of NAD declines sharply and the functioning of the brain is disturbed; malfunctioning of the brain (dementia) is indeed one of the primary characteristics of pellagra. If the NAD deficiency lasts for an extended period, permanent brain damage develops[144].

Scientists have discussed the possible use of NAD for the treatment of neurodegeneration[155] and the improvement of brain functions. NADH plays a role in the synthesis of the neurotransmitters, i.e. noradrenaline and dopamine, which are important for maintaining a positive state of mind[42]. South African research on NAD, that was conducted for the manufacturer, also confirms the normalising effect of NAD on the neurotransmitters, i.e. dopamine, adrenaline and noradrenaline. NAD probably plays a role in the production of serotonin and other neurotransmitters in the brain[214].

5.2.6 Normalizing Cell Functions

"The corepressor CtBP (carboxyl-terminal binding protein) is involved in transcriptional pathways important for development, cell cycle regulation, and transformation. We demonstrate that CtBP binding to cellular and viral transcriptional repressors is regulated by the nicotinamide adenine dinucleotides NAD+ and NADH".[779]

"NAD is the substrate of a novel chromatin-associated enzyme-ADP-ribosyl transferase (ADPRT). In this study, the cell-cycle dependent change in cellular NAD content was observed in a line of human amnion FL cells. It was found that the cellular NAD content of FL cells was highest in G1 and lowest in S/G2-G2. 3AB, a potent ADPRT inhibitor, can inhibit the cell cycle dependent change in cellular NAD content and also inhibit DNA synthesis in the S phase and extend the S phase. The results indicate that ADP-ribosylation may be involved in DNA replication and cell cycle progression. It was also found that the DNA-damaging agents, MNNG, MMS and 4NQO could lower cellular NAD content in a dose-dependent way".[780]

"Hepatocytes were found to be remarkably resistant to suicidal NAD+ depletion due to consumption for chromatin-associated poly(ADP-ribose) biosynthesis, which normally follows infliction of DNA damage in mammalian cells... This differential behaviour, demonstrable also with other carcinogens, can be attributed to the different NAD+ biosynthetic capacities of these cells".[781]

"Marked depletion of intracellular NAD+ prior to toxicity and a protection against toxicity associated with maintenance of NAD+ suggest a possible role for the maintenance of intracellular NAD+ in cellular integrity." [782]

"Many cellular enzymes use NAD+ as coenzyme or substrate, depending on the nature of the enzymatic reaction. Under certain conditions the cellular NAD+ concentration may become rate-limiting for such enzymes. For instance, when eucaryotic cells are exposed to high concentrations of DNA-damaging agents, the resulting DNA strand breaks may stimulate the nuclear enzyme poly(ADP-ribose) polymerase (PARP) to such an extent that the cellular pool of NAD+, which is the substrate for this enzyme, is severely depleted, possibly leading to acute cell death".[783]

"When mouse leukemia cells are treated with gamma-radiation or neocarzinostatin the intracellular NAD and ATP levels fall rapidly. We have shown that the ATP response is a consequence of the decreased NAD level. We suggest that this low NAD level results in decreased glycolytic activity and that there is a subsequent accumulation of phosphorylated sugars associated with the fall in ATP. Under these extreme conditions, therefore, the NAD level probably regulates the rate of glycolysis in cells which are utilising a rapidly metabolisable sugar as their energy source".[784]

"Ionizing- and ultraviolet-radiation cause cell damage or death by directly altering DNA and protein structures and by production of reactive oxygen species (ROS) and reactive carbonyl species (RCS). These processes disrupt cellular energy metabolism at multiple levels. The formation of DNA strand breaks activates signalling pathways that consume NAD, which can lead to the depletion of cellular ATP. Poly(ADP)-ribose polymerase (PARP-1) is the enzyme responsible for much of the NAD degradation following DNA damage, although numerous other PARPs have been discovered recently that await functional characterization. Studies on mouse epidermis in vivo and on human cells in culture have shown that UV-B radiation provokes the transient degradation of NAD and the synthesis of ADP-ribose polymers by PARP-1... Identifying approaches to optimize these responses while maintaining the energy status of cells is likely to be very important in minimizing the deleterious effects of solar radiation on skin".[785]

"Peroxynitrite and hydroxyl radicals are potent initiators of DNA single strand breakage, which is an obligatory stimulus for the activation of the nuclear enzyme poly(ADP-ribose)synthetase (PARS). Rapid activation of PARS depletes the intracellular concentration of its substrate, NAD+, slowing the rate of glycolysis, electron transport and ATP formation. This process can result in acute cell dysfunction and cell necrosis. Accordingly, inhibitors of PARS protect against cell death under these conditions. In addition to the direct cytotoxic pathway regulated by DNA injury and PARS activation, PARS also appears to modulate the course of inflammation by regulating the expression of a number of genes... In vivo data demonstrate that inhibition of PARS protects against various forms of inflammation, including zymosan or endotoxin induced multiple organ failure, arthritis, allergic encephalomyelitis, and diabetic islet cell destruction".[787]

"Recent studies point to the naturally occurring molecules in expression of radiation damage and in protection. DNA repair was shown to be one of the parameters that can be modified to attain improved protection. The need for a natural compound that can enhance DNA repair in order to improve cellular protection focused our attention on nicotinamide (NA). The effects of addition of NA, a precursor for NAD+ synthesis, on the DNA repair capacity following gamma and ultraviolet irradiations were studied in several repair-proficient and repair-deficient cell lines. The addition of low concentrations of NA (less than 3 mM) resulted in increased repair synthesis in the repair-proficient cells. Addition to repair-deficient cells resulted in decreased repair synthesis. Cells which repair damage from one type of radiation, and not from another, responded accordingly to the presence of NA. However, addition of high concentrations of NA to repair-proficient cells resulted in decreased repair synthesis. Thus, nicotinamide can improve the repair capacity in a concentration-dependent manner, but it clearly requires the existence of functional repair processes."[789]

"An intimate relationship exists between DNA single-strand breaks, NAD metabolism, and cell viability in quiescent human lymphocytes. Under steady-state conditions, resting lymphocytes continually break and rejoin DNA. The balanced DNA excision-repair process is accompanied by a proportional consumption of NAD for poly(ADP-ribose) synthesis. However, lymphocytes have a limited capacity to resynthesize NAD from nicotinamide. An increase in DNA strand break formation in lymphocytes, or a block in DNA repair, accelerates poly(ADP-ribose) formation and may induce lethal NAD and ATP depletion".[790]

"These data indicate for the first time hormonal modulation of NADase resulting in two signals: (1) enhancement of NAD+ which may explain the increase in ADP ribosylation and activation of cholera-toxin substrates leading to facilitation of protein secretion; (2) suppression of cell cADP-ribose and consequently intracellular Ca2+ which may explain the melatonin-induced inhibition of protein secretion".[791]

"Extracellular NAD is degraded to pyridine and purine metabolites by different types of surface-located enzymes which are expressed differently on the plasma membrane of various human cells and tissues... ATP was found to be the main labelled intracellular product of exogenous NAD catabolism; ADP, AMP, inosine and adenosine were also detected but in small quantities... These results confirm that adenosine is the NAD hydrolysis product incorporated by cells and further metabolized to ATP, and that adenosine transport is partially ATP dependent".[792]

5.3 NAD(H) IN FOOD

Free nicotinic acid (vit B3) and nicotinamide (active form) are present in nature in only small amounts. Nicotinic acid is mainly bound to macromolecules in plants, while nicotinamide is usually a component of NADP (coenzyme form) in the animal world. Nicotinic acid can be formed in humans from the metabolism of dietary tryptophan. Important sources of preformed niacin include beef, pork, wheat flour, maize (corn) flour, eggs and cows' milk. Human milk contains a higher concentration of niacin than cows' milk. In unprepared foods, niacin is present mainly in the form of the cellular pyridine nucleotides NAD (coenzyme 1)and NADP.

Raw food contains the amounts of NADH detailed in the following table. Cooked food contains much less NADH because some of the NADH is lost during the preparation[23]. The NAD co-enzyme continuously varies between the NAD or NADH compound in the body[68, 83, 105]. Other derivatives of NAD are NADP and NADPH[138]. For the sake of completeness, the figures have been converted to show the quantity of food required to be taken to match the NAD used in one NutriNAD capsule.

RAW FOOD EQUIVALENT FOR EACH NUTRINAD CAPSULE

- 10kg of raw red meat
- 12.5kg of poultry
- 14.3kg of fish
- 25kg of yeast
- 250kg of potatoes
- 500kg of grain

5.4 STORAGE OF NAD IN CELLS

"Pyridine nucleotides are mostly stored within mitochondria where they are involved in different functions ranging from energy metabolism to cellular signalling. Here we discuss the mechanisms of mitochondrial NAD metabolism and release that may contribute to the crucial roles played by these organelles as triggers or amplifiers of physiological and pathological events".[687] There are two pools of NAD in most cells. One is the inner mitochondrial pool and the other is the cytoplasmic pool. "Tissue levels of NAD appear to be regulated primarily by the concentration of extracellular nicotinamide, which in turn is controlled by the liver in a hormone-sensitive manner. Hepatic regulation involves the conversion of excess serum nicotinamide to 'Storage NAD' and inactive excretory products, and the replenishment of serum nicotinamide by the hydrolysis of 'Storage NAD.' Tryptophan and nicotinic acid contribute to 'Storage NAD,' and thus are additional sources of nicotinamide[627]."

5.5 POSSIBLE CAUSES OF INDUCED NAD DEFICIENCY

It appears from literature that several factors can lead to NAD deficiencies. Genetics, nutrition, chemical substances and certain diseases possibly play a part[51]. Mitochondrial disorders could be a cause[68]. Nutrient dependency, ageing and nutrient deficiencies are possible causes[105]. Malfunctioning of the liver and adrenal glands might play a role[259]. NAD possibly cannot be recycled properly. The contributing potential of digestive problems can be added to this[214]. In the case of certain disorders, for example an overactive thyroid gland, too much energy is released as heat and it is stored inadequately[68].

NAD deficiencies are probably also induced or aggravated by the following chemical substances:

- biopsy-proven zidovudine myopathy resulted in a high lactate:pyruvate ratio[538].
- patients on valproic acid had reduced lactate and lactate:pyruvate ratios[539].
- elevated lactate in white matter and the possible response to antioxidants suggests mitochondrial dysfunction in progressive spongiform leukoencephalopathy following inhalation of heated heroin vapor[540].

- lactic acidosis is induced by ingestion of sustained-release nicotinic acid[542].
- the mean plasma lactate concentration was elevated in 42 patients poisoned with paracetamol[543].
- parvovirus infection was accompanied by rapid depletion of intracellular NAD stores[565].
- NAD synthesis is decreased significantly in thalassemic red blood cells[566].
- The ratio of lactate to pyruvate was elevated in both sexes after a 40-day period of a 25% fat-calorie restricted diet. The lactate and pyruvate decreased significantly only in males (pyruvate greater than lactate) but not in females[314].
- DNA-damaging agents N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), methyl-methanesulphonate (MMS) and 4-nitroquinoline-N-oxide (4NQO) could stimulate ADP-ribosyl transferase (ADPRT) activity and reduce the cellular NAD content in a dose-dependent way[564].
- Several tumor-therapeutic drugs reduce NAD and NADH levels, thereby inhibiting glycolytic energy production[631].

5.6 THERAPEUTIC CHARACTERISTICS OF NAD

"Nicotinamide mononucleotide adenylyltransferase (NMNAT), a member of the nucleotidyltransferase alpha/beta-phosphodiesterases superfamily, catalyzes a universal step (NMN + ATP = NAD + PP(i)) in NAD biosynthesis. Localized within the nucleus, the activity of the human enzyme is greatly altered in tumor cells, rendering it a promising target for cancer chemotherapy."[778] NAD-deficiency disorders include conditions like anorexia nervosa, substance dependency, early diabetes, heart problems, hypertension and various behavioural disorders. NAD deficiencies can develop as a result of diets that lead to lower NAD levels. Approximately 10% of people suffer from a serious and possibly chronic lack of NAD, which can often also be of a genetic nature[51]. Therapy with NAD precursors like nicotinamide might have remedial effects on possible biochemical abnormalities, thereby retarding progression of diabetic microangiopathy[607]. "NAD and NADH are converted into each other in numerous different metabolic activities. In some metabolic reactions it is NAD which is the needed catalyst, with NADH a useful by-product, in other reactions the situation is reversed[638]".

5.6.1 Patents for NAD Therapy

NAD was patented in 1964, for the treatment of drug dependency. It was registered in 1966, for the treatment of alcoholism. The patent for the use of NAD supplementation in the treatment of ileus and shock was awarded in 1967. The patent for use in the treatment of schizophrenia was also approved during the same year. Shortly thereafter, the patent for the use of NAD in the treatment of arthritis was also approved. A patent is registered which generates NAD or nicotinamide adenine dinucleotide phosphate (NADP) in the body[344].

5.6.2 Determining NAD Levels

NAD is present in all body cells and it is clinically not easy to measure it. Researchers found in their experiments, that the absolute conversion-speed of NAD is 78 000 molecules per second per cell and that it has a half-life of between 48 and 78 minutes[186]. NAD's half-life in the brain is approximately 3-4 days and in the liver approximately 10 hours[64]. High-pressure fluid-chromatography measurements can be used to measure

levels of NAD. The measuring method can be replicated easily and is a reliable method for measuring levels of NAD in human blood[195, 197]. Standard blood-tests, which provide an indication of NAD levels, consist of the lactate and pyruvate, ß-hydroxybutyrate and acetoacetate measurements[138]. The latter two measurements indicate the mitochondrial levels of NAD/NADH and this is a useful measurement for determining possible defects in the citric-acid cycle. In the presence of NAD or NADP 15-18% of the cortisol was converted to cortisone: no other products could be detected[443].

"A significant decline of cellular energy after aerobic performance was detected with both approaches to a similar extent ($P<0.01$). However, the extracellular NADH metabolisation assay (ENMA) is more convenient to perform than the determination of intracellular ATP/ADP. Due to its easy and versatile handling, a huge array of possible applications like monitoring the training efficiency of athletes, the fitness of senior citizens or the recovery from disease may be envisioned."[775]

5.6.3 Duration and Effect of NAD Therapy

NAD is not a drug and it takes a while before its effect can be consciously experienced. Most people become aware of an increase in energy after four or six weeks' supplements. It is furthermore also important to bear in mind, that NAD Therapy only provides energy for dealing with problems and cannot solve problems on its own. It provides the energy that is necessary to be able to identify and deal with the psychological and mental problems, which contribute or are due to low levels of energy.

Clinicians found during their treatment of a patient with MELAS, that the supplements' effect could be observed in the level of erythrocytes, after 6 weeks' treatment. The blood level of lactate to pyruvate declined by 50% within 3 days and its urine level declined within two weeks. Clinical improvement and reduction of scarring in the brain, as determined by MRI scans, occurred within a month[140].

"Alkylating agents cause a marked depletion of cellular NAD+ levels by activating nuclear ADP-ribosyl transferase (ADPRT), which utilizes NAD+ as a substrate in the synthesis of poly(ADP-ribose). As a consequence of NAD+ depletion, it is possible that cellular ATP pools could be depleted. Because of this, exogenously supplied NAD+ had been proposed as a way to counteract some of the effects of an alkylator. We found that exogenously supplied NAD+ significantly increased intracellular levels of NAD+."[777]

5.6.4 Safety of NAD Therapy

NAD Therapy has been used intravenously in South Africa since 1974 and, according to the manufacturer, no side-effects have yet been reported by clinicians. More than 15 000 NAD supplements (500 mg per drip) have been administered intravenously at Nutrimalaika since 1989, to more than 6 000 patients, who ranged in age from as young as 9 - 90. Furthermore, no race-, gender- or age-related contra-indications were encountered. Since 1995 many patients have used 50mg of NAD orally dissolved in 340ml of carbonated sodawater. This has now become the norm because almost all of the 6 000 patients at Nutrimalaika and those of the 120+ participating private practitioners have changed to the 50mg NutriNAD capsules specifically formulated for such use.

The following information is based on results from research, that was provided by the manufacturer of the intravenous form of NAD. The same quality of NAD is also used in the MultiNAD capsules. The lethality dosage (LD50) of NAD is as follows:

- 1 360mg/kg IV - mouse
- 3 500mg/kg IM - mouse
- 2 610-3 050mg/kg IM - rat
- 1 780mg/kg IM rabbit
- 2 900mg/kg IM dog
- 2 900mg/kg IV dog

Results of acute toxicity do not indicate any pathological changes in mice, rabbits, rats or dogs. Results of chronic toxicity after 52 weeks, during which NAD of up to 300 mg/kg was administered intramuscularly to rats every day, indicate no toxicity that can be attributed to NAD. Haematological evaluations, blood-chemical measurements and histopathological examinations of the heart, liver, kidneys, spleen, gonad, adrenal glands, thyroid and pituitary gland did not yield any significant changes. The same research indicates no significant changes during reproduction and gestation in rats. The NAD infusion is terminated on all patients during pregnancy, irrespective of these findings. During pregnancy only the capsules are continued with.

5.6.5 Stability of NAD Therapy

The NAD in the NutriNAD, MalaikaNAD and in the MultiNAD capsules consists of the same form of NAD. NAD is a powder, that ranges in colour from white to pale yellow. The NAD vials have an expiry date of two years after manufacturing, when stored in a refrigerator. If the NAD is in any solution, it will remain stable in a refrigerator for at least a week. All NAD preparations must therefore preferably be in powder form and must be stored in a refrigerator or cool place. A Canadian company recently changed their bottles to read NAD instead of NADH. NAD, known as Coenzyme 1, plays an important role in energy production. The company, felt that NADH was less stable as a supplement than NAD[638].

5.6.6 Alternative Names for NAD

NAD is also referred to in literature as diphosphopyridine nucleotide (DPN), nadide, adenine-D-ribose-phosphate-phosphate, cozymase, coenzyme 1, D-ribose-nicotinamide, vitamin PP and enzopride.

5.6.7 NAD Therapy and Interaction with Other Medication

No contra-interaction with any other medication, like antidepressants, neuroleptics or other medications, was reported with the use of the NAD containing capsules. It was however found, that the dosages of some medications (antihypertensives, insulin, medication for cholesterol, antidepressants, anxioliticums etc) have to be decreased in time. What however does happen, are that side-effects similar to an overdose of other medications, which are used at the same time, often come to the fore. Medication for blood pressure is an example of this. NAD stabilises the person's blood pressure and therefore the dosages of the medication for blood pressure must be adjusted accordingly, to prevent side-effects such as a too high or low blood pressure. What also

happens often, is that other symptoms and conditions, which were masked by the NED, become apparent to the NED sufferer, when the body becomes stabilised. It is then incorrectly referred to as side-effects of NAD Therapy.

5.6.8 Contra-indication for NAD Therapy

According to the manufacturer, no contra-indication has been reported since 1974 by any clinician, for the use of NAD. NAD must however be used with care in persons with Gilbert's disease, in whom it can cause serious abdominal pain[65].

5.7 HOMEOPATHY AND NAD THERAPY

Many of the medications, that are utilised in the practising of homeopathy, in the form of tablets and injections, contain NAD. The use of NAD Therapy is in line with the natural order, that is adhered to by disciplines which use natural healing. These medications are used to treat a large variety of conditions and particularly in homotoxicology. These medications have furthermore been used for many years.

5.8 POPULARITY OF NAD THERAPY

Although NAD Therapy were used in the treatment of alcoholism since 1939, patented in 1964 and the NAD vials officially registered in 1974 in South Africa it is still relatively unknown by treatment professionals. A possible explanation is that treatment professionals not working with substance dependency or those working with substance dependency from the moral treatment approach would probably be not aware of NAD Therapy and its energy related characteristics. NAD has been available as oral supplements in capsule form since 1997 in South Africa. An international researcher ascribes the relative unpopularity of NADH, also applicable to NAD therapy, to its high cost of around 10,000 dollars per kilogram[346]. Several laboratories around the world are currently involved in studies for the development of NAD analogues for therapeutical applications[92]. Although NAD is part of all nature and man since creation, NAD Therapy is relatively new. The chronological course of NAD reveals that it only picked up momentum since the ground breaking article of Prof Cleary in 1986.

- 1905 The coenzyme nicotinamide adenine dinucleotide (NAD) is identified
- 1939 NAD is first used for the treatment of alcoholism
- 1955 Dr Hoffer uses NAD for the treatment of schizophrenia
- 1961 Dr O'Halleren uses NAD-drips for the treatment of all chemical addictions
- 1970 The role of the mitochondria in various diseases are outlined
- 1974 The NAD-drips are registered and manufactured in South Africa for the treatment of acute and chronic alcoholism
- 1986 Prof Cleary writes the first article on NAD Deficiency Diseases
- 1989 Alkogen is founded for the outpatient treatment of all chemical addicts with NAD-drips In May 2004 the name is changed to Nutrimalaika.
- 1993 Mitochondrial DNA are identified as mainly maternally inherited
- 1994 Patients with a variety of disorders are treated at Alkogen with NAD-drips
- 1997 Alkogen Products manufactures the capsule MultiNAD and other nutritional supplements containing the metabolic energy cofactors
- 2000 The Afrikaans edition of this NAD Therapy e-book was published

- 2002 The first edition of this NAD Therapy e-book is published in which more than 100 disorders relating to NAD Deficiency are discussed
- 2003 Alkogen Products manufactures the capsule NutriNAD with 50mg pure NAD replacing the NAD-drips in the Alkogen Products treatment program
- 2003 Prof Cleary published the first international article on Alkogen's NAD Therapy
- 2003 Nutrimalaika, the nurses-led centres, is founded for the treatment of infants and children up to 12 years, old suffering from NED with MalaikaNAD (especially formulated for children) and NutriNAD supplements.

5.9 SPORT AND NAD THERAPY

"We previously reported that the blood NAD levels are decreased by severe exercise. College female students exercised moderately with bike-ergometers. The blood NAD levels elevated after moderate exercise. However, the blood NAD levels decreased after all-out exercise. The changes in whole blood tryptophan (a precursor of pyridine nucleotides) levels were similar to that in NAD. The glucose levels in whole blood and the non-esterified fatty acid levels in serum decreased according to exercising time." [774]

The Cori Cycle operates during exercise, when aerobic metabolism in muscle cannot keep up with energy needs. Glucose synthesized in liver and transported to muscle and blood. A highly exercising muscle generates a lot of NADH from glycolysis but without oxygen there is no way to regenerate NAD from the NADH (need NAD!). Lactic acidosis can and would result from insufficient oxygen (an increase in lactic acid and decrease in blood pH). So, the NADH is reoxidized by reduction of pyruvate to lactate by enzyme lactate dehydrogenase. Results in replenishment of NAD for glycolysis. Then the lactate formed in skeletal muscles during exercise is transported to the liver where it is used for gluconeogenesis. Lactate is transported through the bloodstream to the liver. Lactate is oxidized to pyruvate in the liver. Liver lactate dehydrogenase reconverts lactate to pyruvate since has high NAD/NADH ratio. Pyruvate is used to remake glucose by gluconeogenesis. Glucose is transported back to the muscles via the bloodstream. [733]

"This is mitochondrial medicine ... We can fix these blockage but they have to be understood by competent laboratory work and interpretation... There is nothing accidental or random... You go to the biochemical substrates and look at them instead of covering it up with drugs... A rational person will not oppose simple blood and urine studies for additional study of their case, especially when faced with the possibility of being on drugs the rest of their lives. A rational person will not feel threatened by this. When I approach physicians and talk to them, to partner with them to get the tests I want ordered for a patient, I rarely encounter resistance"[674].

Existing blood tests, which are internationally available and in use since 1925, are used and provide good indicators of a person's biochemical energy level. The two tests, which are used, are the lactate and pyruvate tests. The person's lactate and pyruvate are measured in venous blood by pathologists and the results are used to determine three energy values. The tests can also be conducted on arterial blood, cerebrospinal fluid and tissue biopsies from affected organs, to obtain more accurate results. The blood tests are generally available from most pathologists. Prior arrangement must however be made, to ensure that the required test tubes are available. The large range of normal values of the tests provides for 95% of the variation in the normal population. The chance that someone will present with NED, is therefore only 5%. Blood tests, which were conducted by independent pathologists for Nutrimalaika on more than 2 000 persons with one or the other form of NED or NEDRS, indicate that 87% exhibit a deviation in respect of one or more of the energy values. This finding is also reported in the more than 600 scientific articles, which were consulted.

"Concentrations of the energy-related substances lactate, pyruvate, glucose, and hypoxanthine were measured, and the lactate/pyruvate ratio was calculated".[280] "Lactate and Pyruvate: These two compounds provide useful insight to basic metabolic factors due to their position in the physical energy production process. Pyruvate is the anaerobic breakdown product of glucose. Its further conversion to acetyl-CoA requires the pyruvate dehydrogenase enzyme complex. Pyruvate dehydrogenase requires cofactors derived from thiamin, riboflavin, niacin, lipoic acid, and pantothenic acid for optimal function."[532] "Laboratory studied showed elevated levels of lactate and pyruvate in cerebrospinal fluid (CSF), without notable elevated levels in serum.[643]"

6.1 ENERGY VALUES DERIVED FROM THE BLOOD TESTS

The separate measurement of lactate and pyruvate, as well as the ratio between the two, provide a unique perspective of the energy metabolism, as well as several cues on how to improve the production of physical energy. In order to make it more comprehensible, it was transformed into three Energy Values each with a normal value at 100+. An energy value of 100 (borderline value) only means, that there is enough physical energy available for an ordinary day. Energy values higher than 100 means that the person has enough physical energy to engage in new projects or can handle daily demands more effectively. Most people shy away from new concepts and therefore it was decided, to refer to it as "energy values", because these are indicators of the NAD energy production. The debt of chemical energy is visible in cellular, tissue and organ damage and loss of quality of life over time.

Due to the general low physical energy levels of NED patients their blood are collected in a non fasting state, but the normal range for fasting values are used in the calculations of the Energy Values. Venous blood samples of more than 3 000 patients with NEDRS related complaints were collected at Nutrimalaika of which 87% clearly showed an NAD Energy Deficiency. Follow-up blood tests after 6 week of NAD supplementation showed an improvement in the average energy blocks of patients from 52 to 81. International research show that clinical improvement takes up to 12 weeks. Follow-up blood tests are now only done after 12 weeks of treatment. physical energy is visible in cellular, tissue and organ damage and loss of quality of life over time.

6.2 ENERGY VALUE I (Lactate to Pyruvate Ratio: Normal Range lower than10)239, 749

This value is an indication of the ratio between the measurements of lactate and pyruvate, and provides a reliable measurement of the NAD levels in the blood. The normal value is set at 100+ and values, which are lower than 100, indicate the possibility of an NAD deficiency. On their own, the two blood measurements might seem to be very good, but if they are viewed in relation to each other a more reliable indication of the real availability of physical energy becomes clear.

Formula for Energy Value I (Normal Value is 100+)

- Use both of the Pyruvate and Lactate values reflected on the blood test results
- Formula: (Pyruvate value x 1000) ÷ Lactate value

This formula is based on the following biochemical reaction that continually takes places in our bodies:

- **10 x Lactate = 1 x Pyruvate**

Energy Value I can be explained better, by comparing it to the concepts of financial assets and liabilities, and the relationship between the two, which is referred to as liquidity. Someone could be a millionaire if you look at his assets alone, but if his liabilities are taken into the equation and it greatly exceed his assets he is actually technical insolvent. Amongst the almost 3 000 patients, who were tested at Nutrimalaika, 53% deviated in respect of this value. Deficiencies on this value normalises with NAD supplements.

- "Measured enzymatically in blood or CSF as an index of impaired pyruvate metabolism due to defects of glucose oxidation (fed state) or gluconeogenesis (fasted). The ratio of lactate to pyruvate reflects the NAD/NADH ratio and is useful in distinguishing primary defects of pyruvate metabolism from defects of electron transport (or oxidation).[49]
- Lactate itself is a dead-end metabolite, metabolized only by lactate dehydrogenase. The extent and direction of that reaction is determined by the free [NAD]/[NADH][H+] ratio of cytoplasm with which lactate and pyruvate are in near-equilibrium. Pyruvate is a crossroads of most of the major degradative and synthetic pathways, but present in about one-tenth the amount of lactate. Information on the content of both lactate and its redox partner pyruvate is likely

to provide more information on the metabolic state of tissue than are measurements of lactate alone."[239]

- "The accumulation of intermediates reflects the increased lactate-to-pyruvate ratio; this leads to a secondary imbalance of the nicotinamide adenine dinucleotide-to-reduced nicotinamide adenine dinucleotide (NAD-to-NADH) ratio".[235]

6.2.1 Increased Lactate to Pyruvate Ratio

The lactate to pyruvate ratio proved to be the clinically most useful parameter in the evaluation and monitoring of mitochondrial diseases, showing higher sensitivity than lactate measurements only[293]. One study shows that lactate and pyruvate concentrations increase slightly at low levels of exercise without a change in lactate to pyruvate ratio until a threshold work rate at which lactate abruptly increases without pyruvate. The resulting increase in lactate to pyruvate ratio is progressive as work rate is stepped up and suddenly reverses when exercise stops[297]. A normal profile, even after stress and loading, does not rule out an inborn error of lactate to pyruvate oxidation[436].

6.2.2 NAD Deficiency

The coenzyme nicotinamide adenine dinucleotide (NAD) plays a fundamental part in many enzyme reactions involved in all cellular energy production[282]. NAD and its derivatives' NADH, NADP and NADPH have regulatory functions in the generation of triose phosphates and pyruvate from glucose[366]. "Measured enzymatically in blood or CSF as an index of impaired pyruvate metabolism due to defects of glucose oxidation (fed state) or gluconeogenesis (fasted). The ratio of lactate to pyruvate reflects the NAD/NADH ratio and is useful in distinguishing primary defects of pyruvate metabolism from defects of electron transport (or oxidation)[49]. A higher level of lactate to pyruvate is characteristic of NAD deficiency[265]. Low levels of physical energy in cells can play a role in the development of various diseases. Various factors can provide an explanation for low levels of energy in cells of which NAD deficiency is one of the major role players[51].

6.3 ENERGY VALUE II (Increased or Decreased Pyruvate Level: Normal Range 0.03 to 0.08)

As has already been explained, pyruvate must be converted by various co-factors into particles, which can be used by the energy factories. If too much pyruvate accumulates, which usually happens as a result of too few co-factors, or if too little is available, production of physical energy cannot occur to an adequate extent.

Formula for Energy Value II (Normal Value is 100+)

- Use only the Pyruvate value reflected on the blood test results
- If Pyruvate Value is between 0 to 0.048 then Pyruvate Value ÷ 0.0003
- If Pyruvate Value is 0.049 and greater then 8 ÷ Pyruvate Value

The metabolic basis for this formula can be oversimplified viewed as follows:

- **Pyruvate + NAD + CoA -> ATP + H**

2O + CO2

- **Pyruvate + NADH -> Lactate +NAD**

Deviations in respect of this value is like having money in the bank, but not being able to withdraw it for use. Amongst the approximate 2 000 patients, who have already been tested at Nutrimalaika, 54% showed deviations and 12% had borderline values. Research indicates, that various pathological conditions are in particular associated with increased levels of pyruvate. Low Energy Values II normalises with NAD and co-factor supplementation.

6.3.1 Increased Pyruvate Level

Increased blood pyruvate levels are reported in several disorders, including liver disease, congestive heart failure, diabetes mellitus, muscular dystrophy, thiamine deficiency, and various tumorous disorders[281]. Elevated levels of pyruvate may reflect a failure of the enzyme due to a functional need for cofactors derived from thiamin, riboflavin, niacin, lipoic acid, and pantothenic acid for optimal function. Levels of pyruvate in the tissues are further controlled by the biotin-containing protein, pyruvate carboxylase, which controls the first step in the reformation of glucose from pyruvate. Multiple forms of pyruvate carboxylase deficiency, some of which are biotin responsive, have been reported[278, 532].

6.3.2 Decreased Pyruvate Level

Low pyruvate levels indicate an accumulation of NADH and probably reflect severe mitochondrial dysfunction[279].

6.4 ENERGY VALUE III (Increased or Decreased Lactate Level: Normal Range 0.50 to 2.20)

This value indicates, that there is too much or too little lactate in the blood. The normal value is again set at 100+.

Formula for Energy Value III (Normal Value is 100+)

- Use only the Lactate value reflected on the blood test results
- If Lactate Value is between 0 to 1.00 then Lactate Value ÷ 0.005
- If Lactate Value is 1.01 and greater then 220 ÷ Lactate Value

This formula is based on the following biochemical reaction that continually takes places in our bodies:

Lactate + NAD -> Pyruvate + NADH

Lactate accumulates as a result of many factors, amongst others exhaustion as a result of activity or other causes. Too little lactate creates problems in respect of physical energy for the organs, which use it as a source of energy. Lactate + NAD is converted into Pyruvate + NADH. Research indicates that various pathological conditions are

associated in particular with increased levels of lactate. Amongst the approximately 2 000 patients, who were tested at Nutrimalaika, only 16% suffered from deviations in respect of this value. Low Energy Values III normalises with NAD and cofactor supplementation.

6.4.1 Increased Lactate Level

"Lactic acidosis in infants is a serious emergency. The vast majority of cases have an acquired cause. These include IV glucose given to a newborn; shock, even hypoxia, from different causes; infectious and parainfectious causes (e.g., sepsis even without shock, bacterial meningitis, urinary tract infection with the lactate-producing bacterium *Enterobacter cloacae,* Reye syndrome); poisoning by salicylates; seizures (seizures lead to increase in CNS lactic acid that results in increase in systemic lactic acid as in patients with bacterial meningitis); liver failure; and short gut syndrome."[750] Symptoms associated with inherited form of lactic acidosis is: episodic lactic acidosis from early infancy, failure to thrive, and hypotonia with or without features that may suggest specific defects.

Lactic acidosis is associated with both inherited and acquired metabolic diseases. Lactic acid metabolism in the presence of altered gluconeogenesis, anaerobic glycolysis, and acid-base balance is a major factor in many disorders. Lactic acid can be formed only from pyruvic acid; therefore, disorders that increase pyruvate concentration, enhance lactic acid formation, or reduce lactic acid degradation cause lactic acidosis. Inborn metabolic errors that are accompanied by derangement of metabolic pathways of glucose, pyruvate, amino acids, and organic acids as well as toxic and systemic conditions that promote tissue hypoxia or mitochondrial injury result in lactic acidosis.[536]

"Patients exhibiting a disorder of lactate metabolism suffer a high hospital mortality rate and are at risk for developing multiple organ failure. The mortality rate of critically ill patients with a blood lactate level greater than 5 mmol/L and an arterial pH less than 7.35 is 75% at 6 months."[751]

To date, no therapy specifically designed to lower arterial blood lactate levels has reduced mortality significantly[541]. Lactate accumulates when there is a block in the final oxidative phosphorylation stage of energy production. Such a block results in the inactivation of the Krebs cycle. Increased lactate is a common condition that can be caused by a variety of metabolic problems[532]. The ability of the mitochondria to oxidize substrates and generate energy is integral to normal homeostasis and to the ability of cells to survive in the face of impending energy failure. Lactic acidosis is a common and readily visible biochemical marker for mitochondrial dysfunction. Lactic acidosis represents only the most obvious example in which acquired or congenital abnormalities of mitochondrial energy generation contribute to the expression of a broad spectrum of clinical disorders[360].

Research findings suggest that elevated CSF lactate levels reflect the severity of metabolic impairment of the brain[301]. Disorders of the mitochondrial energy production can manifest in many tissues and may lead to various types of diseases. Since defects can occur on many sites of the oxidative phosphorylation system, molecular diagnosis can be difficult. Lactate measured in various body fluids is still the best selective screening parameter[503].

Acute lactic acidosis may actually present with no clinical symptoms or be manifest by a variety of non-specific symptoms such as fatigue, confusion, stupor, and coma. Respiratory collapse and shock may occur[632]. Numerous specific disorders affect oxidative metabolism. Lactate elevation frequently occurs and additional laboratory abnormalities often assist in focussing investigation. Diagnostic specificity may require, besides the blood and urine studies, tissue sampling, cerebral imaging, in vivo studies of tissue energetics, or molecular genetic analysis[363].

"However, either lactate overproduction or impaired elimination alone is insufficient to explain the development of lactic acidosis, because the liver has a large capacity to eliminate lactate via gluconeogenesis and oxidation, some patients with lactic acidosis have minimal or no liver metastasis, many with widespread liver metastasis or serious liver disease rarely develop lactic acidosis, the kidney is able to excrete about one third of lactic acid and, moreover, in one study, lactate overproduction by tumor cells was not demonstrated."[707]

"Infant patients with "cerebral lactic acidosis" show neurological symptoms, elevated levels of lactate in CSF, little or no systemic acidosis and levels of lactate in blood so slightly elevated that they would be overlooked. Lactate elevation confined to CSF and brain has been described in biotinidase deficiency and in some mitochondriopathies."[727]

6.4.2 Lactate Induced Sensitivity

Lactate infusion is currently the most universally studied of the pharmacological challenge tests in panic disorder. Analysis of lactate infusion studies to date suggests that patients susceptible to panic attacks are much more sensitive to lactate than are healthy controls or patients with other psychiatric disorders without panic attacks[311]. Sodium lactate infusions induce panic attacks in patients with panic disorder, but not in control groups. Late panickers had significantly elevated baseline cortisol levels[445]. Significant predictors of lactate-induced panic were prelactate infusion fear and the interaction of high cortisol levels and low hyperventilation levels[444]. Prolactin levels increased in all groups during lactate infusion. The elevated baseline prolactin for male panickers supports a relationship between prolactin and anticipatory anxiety[446]. Lactate-induced panic was associated with significant blood flow increases bilaterally in the temporal poles; bilaterally in insular cortex, claustrum, or lateral putamen; bilaterally in or near the superior colliculus; and in or near the left anterior cerebellar vermis[450].

6.4.3 Decreased Lactate Level

Decreased lactate is seen in people with very little physical activity. Highly trained athletes have such efficient conversion of lactate to pyruvate that they also display lower lactate levels[278].

6.5 THE ENERGY BLOCK: (Lowest Value of Energy Values I, II or III)

When looking at the energy blocks of the almost 2 000 patients, who have already been tested at Nutrimalaika, one sees that as many as 87% had problems with one or more of the energy values. A further 5% had borderline values of 100.

Energy Block (Normal Value is 100+)

- Lowest Value of Energy Value I, Energy Value II or Energy Value III

Elevations in lactate and pyruvate are markers for a variety of metabolic blocks[278]. Production of physical energy in cells consists of several biochemical processes. The cellular production of energy is possibly only as effective as indicated by the energy block, because the processes take place in interdependent cycles. The energy block indicates the lowest of the three energy values and what might be the reason for the chronic fatigue or the problem for which help is sought. It is, for example, like a watch which consists of several gears. If one of the gears malfunctions, it however affects the functioning of the entire watch negatively. When looking at the energy blocks of the almost 2 000 patients, who have already been tested at Nutrimalaika, one sees that as many as 87% had problems with one or more of the energy values. A further 5% had borderline values of 100

6.6 NOTES

These tests reflect the physical energy values in the venous blood. It is more accurate in arterial blood, cerebrospinal fluid and the effected tissue. In case of substance abuse or use of pain killers the physical energy values are falsely increased and more accurate values will be available after 6 weeks of use of supplementation. NAD supplementation only shows clinical improvement after 4-12 weeks of treatment. Repeat the blood tests after 12 weeks to determine the maintenance supplementation program.

Clinical Roots of NAD Therapy: Alkogen Treatment Centre

Alkogen Treatment Network was an officially registered private treatment network consisting of a multiprofessional group of private practitioners using NAD Therapy in treating NEDRS sufferers regardless of race, gender or age. Alkogen Treatment Network was the first centre in South Africa to use NAD Therapy on an outpatient basis to people suffering from NED. The oral nutritional supplements NutriNAD, MalaikaNAD, MultiNAD, EmCegene Forte, GeneClear and GeneSlim were specifically developed in collaboration with leading clinicians to facilitate NAD Therapy. These supplements are also exported to and prescribed and dispensed by international private practitioners. Alkogen Treatment Network had treated people from all over the globe but especially in South Africa. Many practitioners also referred patients for evaluation and programme formulation, and then continued with the treatment in collaboration with their local resources. As a result many practitioners and centres across the country collaborated with Alkogen Treatment Network in terms of treatment. Since 1989 - 2004 more than 7 000 patients and their relatives had been benefiting from their individualised treatment programmes at Alkogen Treatment Network.

- "The needs of people with chronic conditions are fundamentally different from those of other individuals. Chronic diseases are multidimensional, interdependent, disabling, interpersonal, and ongoing. Unfortunately, our current healthcare environment defies the logic of these characteristics. We are not multidimensional; we are highly specialized. We are not interdependent; we are highly fragmented. We focus more on disease than we do on disability. We frequently ignore the benefits of interpersonal relations. And we respond to the crisis of the moment, not to the ongoing nature of chronic conditions"[582].

At Alkogen Treatment Network the application of NAD Therapy was based on the results of recognised and accredited medical, psychological, nursing, pastoral and dietary evaluations supported by findings from research. Providing NAD Therapy within the centre ensures the availability of both the most advanced conventional treatment and care as well as accurate information and guidance with regard to NAD Therapy. This service allows the patient and the multiprofessional network of practitioners to focus not only on the patient's physical symptoms, but also on his or her overall quality of life. NAD Therapy ensures that most of the patients can be reintegrated successfully into their community, without expensive hospitalisation, examinations and medication. It actually entails more than treatment and is better seen as an energy management approach based on behavioural-genetic principals adhered to by both the practitioners and the patients.

- "Of the 503 respondents, 82 (16%) had considered utilizing alternative therapy for cancer after a diagnosis was made. Most respondents were moderately familiar with alternative therapy, such as nutrition therapy (59%), herbal therapy (63%), and acupuncture (62%). Only 6% of respondents actually saw a provider of alternative therapies; providers were most frequently nutritionists, counsellors, herbalists, and massage therapists. The user patient profile clearly indicates that usage is highest in patients with a diagnosis of at least 1 year. Seventy-five percent reported that they would prefer to receive a referral from their doctors, while 20% would prefer to use a telephone referral line. Two thirds of patients felt

that alternative care providers should be encouraged by the medical profession, and 85% indicated that alternative care should be offered at the cancer center as part of oncology treatment".[808]

7.1 ALKOGEN TREATMENT NETWORK AND THE MEDIA

Alkogen Treatment Network has featured in more than 60 national articles and radio interviews, and has even received coverage on a well-known Sunday evening current-affairs programme on an international TV channel. Two examples are printed here:

"The truth of the matter is that many of our most competent and gifted people drinks. And most of them drink because of a genetic (hereditary) biochemical predisposition in their brains, and as an attempt to escape from the nagging depressive and negative feelings (which the rest of us don't have!) that they experience... Alkogen Treatment Network is doing sterling work in this regard... thank God for the major breakthroughs in this important field!"[660]

"We trust that the Lord will bless you (Alkogen Treatment Network) and use you, especially in a country such as ours where people are sometimes hesitant to seek advice, because they believe that it is a disgrace... The Lord makes available people with the necessary training, expertise and skill, and you should not hesitate to contact these people (Alkogen Treatment Network)".[661]

7.2 THE BEHAVIOURAL-GENETIC APPROACH

Behavioural genetics, i.e. the science that studies the interaction between environmental factors and genetic factors, has already become well-established and the findings from research can no longer be ignored or denied. The findings are incorporated on all levels of treatment, for the patient's benefit. Up to 40% of the variation during metabolic resting, the thermal effect of food and the allocation of energy during a low or average level of exercising can be attributed to genetic characteristics[33]. Researchers found in their study of 216 identical twins and 144 non-identical twins, that genetic factors played a significant role in events during a lifetime, which cannot be linked to the person's will[20]. It is important to bear in mind, that the presence of heredity in respect of a characteristic does not mean that it cannot be modulated. Myopia is a good example of an inheritable characteristic, which can nevertheless be modulated. On the other hand, this means that a strong environmental component (for example parentage) cannot be changed easily[192].

7.3 GENERAL TREATMENT CONSIDERATIONS

Irrespective of the treatment discipline or approach there are a few general factors that are mutual to all disciplines. If neglected all treatment efforts will most probably be just superfluous and of no real benefit to the patient. Experience has shown that when teaching patients, healthcare providers concentrate more on information concerning the illness rather than to help patients learn to manage their own treatment[628].

- "National survey data do not support the view that use of CAM therapy in the United States primarily reflects dissatisfaction with conventional care. Adults who use both appear to value both and tend to be less concerned about their medical

doctor's disapproval than about their doctor's inability to understand or incorporate CAM therapy use within the context of their medical management."[814]

7.3.1 Diagnosis

Most of the patients that were referred to Alkogen arrived with confirmed diagnoses made by medical practitioners, including medical specialists. These diagnoses excluded any laboratory tests regarding energy metabolic deficiencies and this were requested from the major laboratories in South Africa.

The differential diagnosis of chronic fatigue (as an example of NED) is extensive and includes medical disorders, altered physiological states (e.g., pregnancy, exertion), psychiatric disorders, lifestyle derangements, drugs, and controversial entities (e.g., chronic candidiasis, food allergies, environmental illness, and chronic fatigue syndrome). The most common diagnoses are psychiatric disorders, including mood, anxiety, and somatoform disorders. A comprehensive approach to diagnosis and management is necessary, including structured psychiatric interviewing, functional assessment, and elicitation of the patient's diagnostic beliefs. Patients often believe they are suffering from an organic medical disorder (e.g., viral or immunological) and resist psychiatric labelling of their symptoms and referral to mental health practitioners[602, 603, 605]. Patients with fatigue reported more medically unexplained physical symptoms, greater perceived stress, more pathological symptom attributions, and greater worries about having emotional problems than did other patients[606].

7.3.2 Non-compliance

Non-compliance is higher in chronic conditions, in activities requiring change in life-style, and in clinician-initiated visits. Non-comprehension of instructions is held to be the most frequent cause of non-compliance. Non-compliance is a threat to the course of treatment, increases unnecessary diagnostic procedures, and complicates evaluation of effectiveness[576]. Evidence from compliance research shows that digressions from the prescribed treatment is the rule rather than the exception[578]. Clinical features such as positive symptoms are associated with non-compliance but the strongest clinical relationship is with a "dual diagnosis", usually with an associated alcohol abuse. Patients' and relatives' beliefs about the disorder and about medication are of considerable importance in determining compliance, and can be understood in terms of the treatment paradigm. The costs of poor compliance to sufferers and to society alike are considerable, and effective ways of improving it are a crucial part of good management[579].

7.3.3 Involvement of Family Members

After having lived for many years with someone who suffers from NED, companions and others who are involved adapt to the person's condition, often referred to as co-dependency. As soon as the recovery has started, they must adapt again and often find this difficult to accomplish. Treatment is furthermore hindered, because those who are involved often suffer from similar conditions, which in turn require treatment. Clinical data at Alkogen Treatment Network shows that NED runs in families and that most family members are also suffering from NED, most oftenly as co-dependency. It means that the treatment professional cannot really rely on the loved ones of the identified patients to

cooperate fully, without addressing the loved ones' NED. Research indicates that people choose companions who are similar to themselves. This is referred to as assortative mating. Assortative mating can be defined as the process of choosing a mate on the basis of characteristics that are shared by both partners[14, 148, 147, 75, 78, 85, 109, 201].

7.4 MEDICAL MANAGEMENT

A base-line assessment was established during the first interview. Relevant special examinations were arranged if deemed necessary. If no contra-indications were found, the physician issued a prescription for NAD Therapy and the supporting medication, as was determined clinically and based on the calculated energy levels per the blood tests. Supporting medication was initially only prescribed for the first week and renewed at the follow-up visits. The frequency of follow-up visits, in the case of acute patients was also determined by the physician. If there were medical reasons for hospitalisation or other interventions, the physician arranged it in consultation with the rest of the practitioners. Medication, which was being abused at the time, were phased out in time and this was explained to the patient. The consulting physician monitored and adjusted conventional medication prescribed for the specific disorder in accordance with the improvement on the initiated NAD Therapy.

- "The public's increasing use of complementary and alternative medicine (CAM) poses unique challenges for primary care physicians in knowledge and patient communication. The objective of our study was to assess Alberta family physicians' interest in CAM information and the type of information sources they currently use. Response rate was 34% (n = 346). Physicians indicated having limited knowledge of CAM, but were interested in evidence-based CAM information such as randomized controlled trials and systematic reviews on acupuncture, herbal medicine, massage, chiropractic treatment and meditation. Most respondents did not make use of reliable information sources that are available on the Internet."[809]
- "Responses were obtained from 149 GPs (40% response rate after one reminder) and 24 nurses and 32 other primary care team members. One hundred and seventy-one (83%) respondents had previously referred (or influenced referral) for CAM treatments, the main reasons cited were: patients request (68%), conventional treatments failed (58%) and evidence (36%) (more than one reason could be given). Only 12 respondents (6%) were against any integration of CAM in mainstream primary care. Most respondents felt that CAM therapies should be provided by doctors (66%) or other health professionals trained in CAM (82%). Twenty-six percent of respondents agreed with provision of CAM by non-state-registered practitioners. It was felt that the integration of CAM could lead to cost savings (70%), particularly in conditions involving pain, but also cost increases (55%) particularly in 'poorly defined conditions'."[815]
- "The results of major surveys show that there is an increase in the use of complementary and alternative medicine (CAM) in the United States. The best predictor of CAM use is higher level of education. Currently, more than 70 medical schools offer some type of training in alternative medicine. As patients have greater access to information, their needs and values change. They become more involved in their overall health care and are taking a more natural and holistic approach to achieving well-being. Physicians need to be familiar with proven CAM therapies in order to advise patients about these modalities and

the potential benefits and limitations. CAM practitioners should be licensed and regulated in scope of practice to provide a high standard of care, and be sufficiently educated in conventional medical science(s) in order to recognize how, where, and why their respective complementary practice is most effective for integration."[816]

- "Female physicians, particularly those who were especially health conscious or at higher risk of heart disease or osteoporosis, used supplements at rates at least equal to those of women in the general population. Half of the physicians took a multivitamin-mineral supplement; 35.5% of these did so regularly. However, </=33% took any supplement other than calcium and <20% did so regularly. Regular vitamin-mineral supplement use increased with age, and antioxidant intake was higher in those at high risk of heart disease. Those with a history of osteoporosis were nearly 3 times as likely as those with no history to take supplemental calcium regularly. Those who took any supplement regularly also consumed more fruit and vegetables daily than did occasional users or nonusers."[818]

7.4.1 Supporting Medication

Additional prescription medicine is normally in the form of thioridazine (10 mg) and clonidine (0.025 mg), which the patient keeps at hand with his nutriceutical supplements and which can be used regularly during the day. Clinical practitioners found, that clonidine can be prescribed for use as often as six times or more per day, to deal with withdrawal from substances or other addictions. Research indicates, that thioridazine helps to recycle the NAD in the body. A dopamine blocker, like flupenthixol (0.025 mg) can be added for persons, who suffer from serious anxiety. Chlordiazepoxide (5 mg) can be used for a short period. Zopiclone (for dealing with sleeping problems) can also be used for short periods. In the case of drug abuse and abuse of prescribed agents, it is recommended that bromocriptine must be used in the morning and afternoon. In instances of serious aggression, 50mg carbamazepine must be started immediately.

Supporting medication normally consists of clonidine (0,025 mg), which the patient carries on his person and uses during the course of the day. Clonidine can be prescribed up to and as often as six times or more per day for dealing with withdrawal from a substance[340]. Clonidine is recommended for treating other forms of dependency. Clonidine blocked lactate-induced panic in four of ten subjects, a significant effect[412]. Clonidine has been found useful in the treatment of obsessive-compulsive behaviour, anxiety, panic attacks, phobias, mania, memory defects, schizophrenia and narcolepsy... The major side effect of clonidine is tiredness or a feeling of being sedated. Fortunately, this is often short-lived and usually disappears by the end of the first week or two"[58].Clonidine produced significantly greater decrements in anxiety within one hour in the patients with panic disorder than in the controls[413].

A dopamine blocker, like thioridazine (10 mg) or flupentixol (0,25 mg), can be added. "The effect of the phenothiazines, thioridazine and chlorpromazine, on the increased hepatic NAD level of rats fed clofibrate, a hypolipidaemic drug, has been investigated. Short-term (6 days) addition of phenothiazines to the diet negatively affected diet intake and body-weight gain, but increased liver weight and hepatic NAD levels... In the hepatocytes, NAD was maintained at the high level until the phenothiazine concentration was increased to 0.2 Mm".[656] "Phenothiazine therapy brings about cognitive restoration -

with a decrease in psychotic thinking, projection, suspiciousness, perplexity, and ideas of reference - and a normalization of psychomotor behaviour in both retarded and hyperactive patients"[657]. "Mellaril or other major tranquillizers with minimal side effects can be used to relieve neurotic anxiety or psychotic symptoms. Drug abusers tend to have a very low tolerance for the side effects of phenothiazines. They also dislike the noneuphoric effects of these drugs. When patients can be persuaded to take them regularly, they can be very helpful"[115].

7.5 NURSING MANAGEMENT

The nursing sister forms the pivotal core of the solution to the almost insurmountable problems our society faces in caring for the chronically ill of all ages. Alkogen Treatment Network Nurses-led Centres provide excellent care and guidance of NED and NAD Therapy to young mothers and their small children, families, adults and the elderly who suffers to get along as best they can with the strengths they have. The nursing sister is the essential consultant in NAD Therapy and the integrated model of energy metabolic management of the patient's programme, patient's family, community, and employers. The principal concerns of the nursing consultation are patient advocacy and delivery of safe, optimal nutriceutical nursing care. The nursing programme starts with the collection of blood samples for despatching to the pathologists for analysis and determination of the metabolic NED indicators.

Prior to administration of the nutriceutical supplements, nursing sisters must be knowledgeable of indications, actions, use, side-effects, and adverse reactions associated with the supplements. The nursing sister must be competent in nursing interventions and their implementation. The nursing sister is accountable for achieving effective implementation of the NAD Therapy, and for evaluating and documenting deviations from an expected outcome, including the implementation of corrective action. Patient support requires that the nursing sister act in the best interest of the patient. Professional autonomy requires that the nursing sister practise within the defined scope of nursing practice.

The nursing sister provides monitoring, supervision, routine quality control, and expertise regarding nutriceutical supplements and procedures. Assessment is based on knowledge, experience, and observation. Observations include patient status and review and interpretation of data. Assessment should be documented and communicated to other members of the healthcare team. Monitoring optimizes the benefits related to NAD Therapy. Monitoring of the patient include clinical data, patient response and compliance to the NAD Therapy.

Comprehensive patient education is the key factor in the delivery of NAD Therapy in the outpatient setting. The nursing sister should build a comprehensive education program for the NED patient population based on the patient's and/or caregiver's physical and mental capabilities; ability, desire, and demonstrated participation in care; education and support of family and significant others; introductions and descriptions of roles and responsibilities of other treatment professionals involved in the patient's care; record keeping required of the patient and significant others; and proper use, care, storage, and disposal of all products and equipment used in the patient's treatment.

"She must furthermore also determine from the patient, whether he is indeed using the medication. Some of them feel that they do not really have to drink it, like the doctor prescribed. The nursing sister must provide some information on the treatment, arrange appointments and so forth. I think, that the nursing sister is responsible for the patient, during almost 99% of the time, during which the patient is with us. Then, if all goes well, she ensures that he will see the clinical psychologist, behavioural geneticist and dietician. She will put the patient at ease, by letting him feel that he is being cared for"[34].

The patient is also informed about, and encouraged to use, prescribed medication. In the case of re-entering NAD Therapy after relapses a history of medications used must first be obtained, in order to determine whether the patient indeed used the medication, followed the dosage and maintained the usage intervals[340].

- "With an ever-increasing number of consumers reportedly using non-conventional methods of disease management, nurses have now been recognized as key providers in education on complimentary and alternative medicine (CAM). The risk of herb-drug interactions secondary to consumer use of alternative medicines further increases the need for nurses to assume the role of patient educators in the area of CAM. Many nurses, however, feel rather ill-prepared to properly care for patients using CAM due to inadequate instruction on the subject matter during their training. A survey questioning CAM education was administered to 148 nursing schools and collected over a 3-month period. The results indicate that nearly half of the responding schools offered some form of education on CAM in their curriculum with electives being the primary form of instruction."[811]

7.6 DIETARY MANAGEMENT

"Diet-therapy represents an elective approach to the treatment of several inborn errors of metabolism. According to the type of disease, dietary intervention can be addressed to three different goals: a) dietary restriction (global or partial) of one or more nutritional components that become "toxic" because of the occurring enzymatic defect; b) supplementation with a given defective nutritional component; c) elimination through the use of diet and drugs of the accumulated "toxic" compounds. These interventions are aimed at bypassing the metabolic block and to avoid the accumulation of intermediate "toxic" substrates"[596].

"Diet therapies promoted for the relief of CFS symptoms by the authors of five CSF self-help books were evaluated on the basis of nutritional adequacy and scientific rationale. Unproven diet therapies for patients with CFS include megavitamin/mineral supplements; royal jelly and other dietary supplements; and elimination, avoidance, and rotation diets. Claims that these therapies relieve CFS symptoms and promote recovery are anecdotal and have not been substantiated by clinical research. The yeast-avoidance and sugar-free diets, both promoted to combat Candida Albicans overgrowth, are of questionable value in treating patients with CFS. The rotation diet is not balanced and does not meet the current recommended dietary intake levels. Diet strategies that call for the avoidance of food additives, preservatives, sweeteners, and other ingredients are not supported by available evidence and are not practical for patients with CFS. A diet plan for patients with CFS should be based on sound nutritional principles and common sense"[519].

- "More than 900 dietitians in the state of Washington were surveyed to determine their personal patterns of dietary supplementation. Seventy-five percent of the population responded; of the respondents, nearly 60% reported the use of some nutritional supplement. The most commonly used supplements were multivitamins plus minerals and vitamin C only, with 21% and 19% of the population choosing these supplementation patterns, respectively. Among subgroups of the population, supplement use was most common among pregnant and lactating women and underweight individuals. It is clear that many dietitians have chosen to utilize some nutritional supplement for personal health."[820]

7.7 PSYCHOLOGICAL MANAGEMENT

The role of the psychologist could be compared to that of a conductor of a large orchestra. In other words, it is all about rendering important psychotherapeutic input, but also harmonising, synchronising and making NAD Therapy part of the daily lives of the patient and his loved ones. The persons must be enabled to continue with their lives with dignity and independence.

The primary purpose of psychological treatment in NAD Therapy is to therapeutically guide the sufferer of NED, so that he grows into a mature and independent person. The characteristics of a psychologically healthy person, amongst other things, includes the person's utilisation of energy. Healthy adaptation is the effective utilisation of energy without wasting any. The psychologically healthy person has a low level of fear, not many worries and few emotional conflicts that require energy. The available energy can therefore be utilised to achieve the set objectives. Furthermore, the person depends little on ego defence-mechanisms and thus does not use energy in order to maintain it and therefore available energy can be channelled into appropriate behaviour[233].

- "Respondents to a mail survey of a random sample (N = 424) of Clinical Members of the American Association for Marriage and Family Therapy provided information about their contexts of practice, use of complementary and alternative medicine (CAM), and relationships with CAM providers. Consistent with both national trends and the experience of psychologists as reported in a similar survey, the results of this survey suggest that marriage and family therapists have been affected significantly by and have a growing awareness of CAM practices."[817]

7.8 PASTORAL MANAGEMENT

The practice of pastoral counsellors is not well understood by most health professionals, although evidence suggests that advantages can be gained by increasing the interaction between the two groups[508]. Spirituality is an important aspect of health care that is not often addressed in primary medical practice. Controversy surrounds the role of spiritual issues in medical practice. Some of this originates from confusing spirituality with religion[511]. Spiritual healing is accepted by only 5% of the surveyed general practitioners

in Australia[507]. Clinical intervention that would increase a patient's level of spiritual awareness and his or her level of comfort associated with a personal perspective on disease could help decrease the patient's level of psychosocial distress. Despite the medical establishment's bias to the contrary, religion and spirituality are positively associated with both physical and mental health[461].

- "While the growth in usage and practice of varying forms of complementary and alternative medicine (CAM) continues apace, social science has increasingly turned to CAM's often individualistic approach to health and illness. CAM has been perceived as both partly a cause of and a response to the well-documented ideology in modern healthcare of 'individual responsibility for health'. This occasionally manifests in a 'victim-blaming' ideology amongst both orthodox and CAM practitioners alike. These issues emerged as key themes in an ethnographic study of a Centre for spiritual healing in the North of England."[821]

7.9 PHARMACEUTICAL MANAGEMENT

Psychopharmacological developments ensure that a constant stream of new medication is introduced, which could be to the benefit of those who suffer from NED. Although a variety of pharmacological agents has been used to treat patients with chronic fatigue syndrome none has been shown to effect a complete resolution of symptoms. Data obtained from studies suggest that the underlying pathophysiological abnormality is a disorder of sleep regulation. This results not only in profound fatigue and lethargy but also reduced sensory threshold for pain, disordered temperature regulation, cardiovascular abnormalities, disturbed higher cerebral function and mental depression[526].

- "Four hundred eighty-four responses were received, with 77% of respondents indicating that they had personally used CAM and 60% correctly identifying that CAM was comprised of more than just botanicals and nutritional agents. The most commonly used CAMs were herbal and vitamin supplements (74%), which was significantly above use of the next most frequent CAM, massage therapy (6%). Most pharmacists (71%) reported offering CAM products for sale; however, 27% of these practices did not have access to CAM information for pharmacy staff or patients. Pharmacists generally viewed CAM positively and believed that they enhanced the customers' image of pharmacy (57%), increased customer numbers (87%), and could increase annual sales (72%). Ninety-one percent of respondents believed that it is necessary for pharmacists to have knowledge of both CAM and conventional medicine to be able to inform patients about their treatment options."[810]

7.10 MANAGEMENT OF CHILDREN'S PROGRAMME

"Children are our future, they are our best hope, their suffering our worst fear. Our actions can help or hinder their development. With the resources that the world has at hand, it is possible to break the cycles of poverty and disease." (Nelson Mandela). Many children under the age of 12 years depend on multiple sources of care, and they rely on school personnel as important sources of health information. Many parents do not know where they could go for confidential services or for other services their children may need[553]. Society is failing to meet the developmental needs of its young children. Social

and cultural changes have created an urgent need for interventions that promote healthy development in young children struggling with role ambiguity, the breakdown of family and social support networks, and a future that seems vague or even absent[556].

NED is a major causative factor in the presenting disorders for which children need help. Some of the presenting disorders include academic stress (concentration problems, reading problems), autism, eating disorders, bed wetting, sexual problems, dyslexia, asthma, attention-deficit-hyperactivity disorder, Tourette syndrome, violence addiction, chronic fatigue syndrome and various others. One South African study found a niacin deficiency (a major precursor of NAD) of 4% amongst white, 12% amongst Indian and 28% amongst black pupils[213]. In general, health care programmes do not achieve the goal of collaborative, coordinated, and integrative services to young children with chronic or disabling conditions[552]

- "The use of vitamin and mineral supplements by children and teenagers in NHANES II was examined for relationships with demographic variables, dietary intakes from food, and biochemical measures of nutritional status and was compared with use reported in other nutrition studies. The number of regular supplement users decreased with age until about age 13, when the percentage of boys using supplements plateaued at about 10% but the percentage of use among girls increased. In general, children were more likely to receive supplements if they came from families with a household head who was white and better educated."[813]
- "More than half of all US 3-year-olds (54.4%) were given some vitamin and mineral supplement. The most common supplements consumed were multivitamin-mineral with iron (59% of supplement users) and multivitamin-mineral without iron (26.4%). Children who received any supplements tended to have mothers who are non-Hispanic White, older, more educated, married, insured, receiving care from a private health care provider, have greater household income, and took supplements during pregnancy. Child health characteristics associated with supplement use included first birth order and having eating problems or poor appetites."[819]

7.11 SELFHELP APPROACH

Regarding the selfhelp approach to NAD Therapy Alkogen Treatment Network wholeheartedly subscribes to the following statement by Dr Abram Hoffer (on his official website): "No one should take any supplements until they have become familiar with their properties and how to use them. It is advisable always to work with a knowledgeable physician. But if they can not find any physician or orthomolecular nutritionist they should go ahead on their own using the information now readily available on nutrition and vitamin supplements. They should advise their doctors what they are doing and which supplements they are using. By listing the vitamins and dose ranges I am not suggesting that every person need to take them all. This is an individual matter based on discussions with their doctor. The vitamin and mineral supplements are compatible with medication and with the diet". (Dr Abram Hoffer)

- "Over half of U.S. adults use vitamin or mineral supplements, and some are likely using supplements to treat chronic diseases or risk factors for disease. Information on the relationship between supplement use and medical conditions

is useful to health professionals to understand the self-medication behaviour of their patients, and important for researchers because medical conditions may be potential confounding factors in observational studies of supplement use and disease risk. Supplement use (mean number used at least once a week) was higher among respondents who were older, female, highly educated, Caucasian, and of normal body mass index. For several conditions, the relative odds of using specific supplements were consistently higher for men than for women. Supplement use was associated with many medical conditions in this cohort."[812]

NAD Therapy Outcome: Renewed Life?

"For many years, Dr. Maltz had a flourishing practice as a reconstructive and cosmetic facial surgeon. He was inspired to move from treating "outer scars" to "inner scars" after observing that so many patients' unhappiness and insecurities were not cured, as they and he had believed would occur when he gave them the perfect new faces they desired. Dr. Maltz first wrote of this discovery in his book "New Faces, New Futures." In this groundbreaking book, Dr. Maltz suggested that many people "see themselves" inaccurately, their perceptions distorted by unchallenged and often erroneous beliefs imbedded in the subconscious mind."[768] In line with this phenomenal work we can view the success of NAD Therapy in a similar light, the psychological consequences of NED lasts longer and outshine for some time the beneficial effects of a renewed and energized body by NAD Therapy. "No man having drunk old wine immediately desires new, for he says, 'The old is better." (Luke 5:39).

"I also want to tell you about the child, both children. The mother has two children, a son and a daughter. A neurologist diagnosed the little girl as suffering from Tourette's syndrome, for a long time. She does not suffer from the full extent of the syndrome. The little girl was held back for a year at school, because she did not perform well. She did not perform well, in spite of the fact that she had been a dedicated pupil, since she is hyperactive. In any event, the other day we gave her the capsules with magnesium. After her mother had arrived at home (her daughter was going to write a history paper the following day), she asked her to come over, so that she could test her. She was amazed. She could not believe that her child had overcome the problem - her daughter knew her history! She had been using the capsules for approximately a week. At this stage, she has not yet noticed such a marked difference in the little boy. Perhaps one has to add other medication. The little boy is however calmer. He immediately stopped twitching his eye. His face was always contorted and it was very distracting when he pulled his little face in this way. The only thing that he is still doing, is to clear his throat"[162].

The success of any treatment is determined by various factors, like the nature, etiology, extend and type of disorder that has to be dealt with. Previous treatment efforts also affects the success of the current treatment. The cost of the treatment is another important factor, as is the patient's ability to pay for the service. The patient's perception of his disorder and frame of reference also determine the treatment's success. The same applies to the theoretical approach and frame of reference of the persons, who provide support and health professionals. Some of these factors will be discussed in greater detail.

Current treatments for NED are symptom-based, with psychological, pharmacological and rehabilitation treatments providing some relief but no cure[524]. Most chronic illnesses start at a cellular level. Though biological causes differ, the symptoms they cause are similar. Fatigue, pain, loss of energy and sleep problems are not uncommon. These symptoms often interfere with everyday life and may require a change in the patient's social activities. Other common problems with chronic illnesses are depression, fear and concern for the future. It is important to learn that because similarities exist among chronic illnesses, the central management tasks and skills one must learn to live with different chronic illnesses are also similar.

You must learn problem-solving skills, how to respond to trends in your disease, as well as overcoming physical and emotional problems. Other skills include developing and maintaining exercise and nutrition programs, learning relaxation techniques to deal effectively with stress, making decisions about when to seek medical help, working effectively with your health care provider, appropriate use of medications, finding and using community resources, talking about your illness with family and friends, and if necessary, changing social activities. Take control of the illness rather than let the illness take control of you. In order to do this, it is essential to understand the characteristics of your chronic illness and the role of NED. The patient's experience and understanding are often the best indicators of the path's course. Self-management is most effective when the clinician encourages and facilitates learning by the patient and the patient responds by participating in decisions.

8.1 RENEWED HOMEOSTASIS

For our bodies to maintain homeostasis (a good state of health) it needs NAD energy from cellular to systems level to function together in harmony. Homeostasis reflects the ability of the body to maintain relative stability and to function normally despite constant changes on any level of being. Changes may be external or internal, spiritual, psychological or physical and the body must respond appropriately. Our bodies use homeostasis mechanisms to maintain its stable internal environment. Homeostasis mechanisms work much like a thermostat that is sensitive to temperature and maintains a relative constant room temperature whether the room gets to hot or cold. If chronic NED is present it leads the way for infection, genetic vulnerability, the immune system and intricate cell signalling and biochemical pathway alterations to set in and a chronic homoeostasis of chronic illness to develop. In particular, some subtle metabolic changes in cells may be crucial to the striking lack of energy and the marked fatigue that may last for hours or days. Over time we adjust to this state of chronic homoeostasis of chronic illness.[704, 760, 761]

The initiating of NAD Therapy normalizes the NAD energy levels starting from cellular structures to the 11 physical systems and eventually the whole body. This normalising take time and it varies with the bodily structures effected by the NED. Refer to chapter two for the renewal cycles of some of these bodily structures. Some renewal cycles take place on an hourly basis where as others can take years. A given structure makes possible a certain level of useful energy, and adequate energy makes possible the maintenance of the structure, and the advance to a higher and more efficient structural level. The biological idea of stress refers to the difficulty of adapting, and this involves energy, structure, and insight/ orientation. Given enough energy, we adjust our structure to achieve full adaptation, and with insight, we can minimize the amount of energy and structural change needed, for example just by a change of pace or rhythm. Change of structure can involve the growth of new cells, or the enlargement or modification of existing cells, and the shrinking or dissolution (apoptosis) of existing cells, allowing their substance to be used elsewhere. During this normalizing of NAD energy and the renewal of bodily structures the NED sufferer has to adopt to the development of a more healthy homeostasis. This is often experienced as unsettling and needs time to adjust to.[704, 760, 761]

"Body composition studies conducted during correction of protein energy malnutrition (PEM) have demonstrated that a significant portion of weight gain after unintentional

weight loss from catabolic disease represents the addition of body fat and extracellular fluid, not added protein mass. Correcting PEM is multifactorial and requires a greater length of time to reverse than to develop".[763] Muscle dysfunction is linked to inadequate intake of energy and protein, providing evidence for defects in morphology, physiology, and function. Important during any recovery phase from chronic NED is the diet and proper nutrition. The relationships between energy and protein intakes on protein metabolism depend on the nutritional and clinical state of the patient. The efficiency with which protein retention occurs is greater in depleted or starved patients than in patients suffering from accidental trauma, acute infection or burns. The latter patients are often hyper metabolic with a decrease in lean tissues and a net loss of proteins from the body. NED-sufferers experience a similar loss of lean body mass and the replacement with fat tissue. It is therefore important to identify the nutritional and clinical conditions of the patients when one deals with the complex problem of energy-protein relationships.[763]

Even if it does not feel like it all the time, the patient can be assured that the NAD Therapy performs its function fully on the biochemical level. Dr Petrus Retief (consulting medical doctor at Alkogen Treatment Network) summarizes it as follows: "The chemical imbalance develops as a result of an NAD deficiency and immediately after you have administered the NAD you will have restored the chemical imbalance. They immediately experience an improvement in emotion, they sleep better, are more positive and their regular processes of thought can occur much easier and better." The capsules contain natural nutrients that are part of our biochemistry since the day of creation. In other words it is not just natural ingredients like herbs or cannabis, but are essential metabolic coenzymes and cofactors that form an integral part of our biochemistry. Some people experience an initial discomfort when their biochemistry normalizes due to the NAD-Therapy. A similar discomfort is experienced initially when one get a new pair of spectacles that are 100% correct according to the result of your eye test.

"The sudden restoration of nutrient intake, especially carbohydrates, in severe malnutrition will suddenly reactivate a number of dormant metabolic pathways. Lack of key micronutrients, especially thiamine and other B complexes, will allow glucose to go through oxidative phosphorylation resulting in lactate (lactic acid). The sudden availability of carbohydrates will exceed down regulated cell demands, necessitating energy for fat production and leading to a further energy deficit. In addition, there will be a shift of the previously depleted electrolytes, potassium, phosphorous, and magnesium, back into cells, resulting in potentially severe hypokalemia, hypomagnesemia, and hypophosphatemia. These compounds must be returned into the intracellular compartment".[763]

8.2 OBJECTIVE MEASUREMENT OF TREATMENT OUTCOME

In chapter 9 various studies were quoted some of which included double-blind studies regarding the treatment outcome of NEDRS with NAD, derivates or precursors of it. At Alkogen Treatment Network it was not deemed necessary, since it was easy to follow the objective parameter of the energy values based on the pre-treatment blood test results done by independent pathologists. Both normative and ipsative measurements are possible because of the available energy values. An ipsative assessment measures the patient's improvement against his or her own previous energy value. A normative assessment measures the patient's energy value against the known normal energy values that are available. In NAD Therapy, a patient's improvement is compared with his

own earlier energy value, with a view to determining whether any improvement has been made. In all cases, however, the benchmark energy value against which any improvement is measured is the person's own improvement - not the improvement of groups or subgroup of patients as a percentage success figure. On average the average energy block of patients on NAD Therapy shows an improvement from a pre-treatment level of 52 to a follow-up treatment level of 81 after 6 weeks on NAD Therapy. This biochemical improvement is also experienced on physical, emotional and spiritual level.

8.3 SICK ROLE AND BENEFITS

In practice treatment professionals should proceed in a manner that communicates concern, supports functionality, and avoids dysfunctional illness behaviour and accidental validation and reinforcement of disability[525]. Chronic conditions such as NED could lead to acceptance of the sick role by the person, which, to a large extent, takes away his own sense of responsibility and leads him to surrender to a state of dependence. This poses an obstacle in the process of recovery and return to the community. Benefits usually go hand in hand with the acceptance of the sick role and impedes the success of the treatment[178, 233]. It sometimes appears as if the patient is afraid to accept his recovery and to take up his responsibilities.

8.4 FUNDING

"The National Chronic Care Consortium advocates for a next-stage reform strategy that is rooted in principles of care critical to serving people who have chronic diseases and disabilities. People with chronic diseases and disabilities are the fastest-growing, highest-cost, most complex user segment in healthcare. Almost 100 million Americans have one or more chronic conditions. Chronic conditions account for about 80% of all deaths and 90% of all morbidity. Seventy percent of all medical costs relate to people with chronic conditions. One half trillion dollars a year is spent on problems of chronic illness. If we are going to adequately address the cost containment problems of the future, if we are going to maintain quality care over the long term, it is absolutely vital that we give more attention to the problems of chronic disease and disability"[582].

8.5 RESPONSIBILITY

Self-care is an important element in the successful management of a long-term illness. However, people with chronic illnesses are often reluctant to adopt self-care behaviors[353]. "Long-term care, public health, home care, and alternative therapies are likely to become more mainstream. The foundation of care is likely to move from hospitals and nursing homes to the home and to community care centres which empower people to define and manage their own care through the use of new self-care technologies, reinforced by institutions that blend the expertise of public health, primary, acute, and long-term care"[582].

8.6 THE "HONEYMOON PHASE"

Although all NED sufferers' bodies beg them for NAD Therapy, some first need convincing by their blood before they will do it. A very few dislike life so much or are in such a state of despair that they do not want to do it at all. It is very simple to do, but 90% of those who eventually do it will stop or interrupt it while in their honeymoon phase.

A privileged 60% will quickly resume doing it again out of free will. The rest, if still fortunate enough to be able to remember it, will eventually be forced by their chronic suffering to do it again. Even though the necessity for it is clearly indicated by the NED sufferers' blood tests results and the daily suffering from their chronic illness, most will reject NAD Therapy after a few weeks in a false belief that their bodies can now make it on their own. When one enters the honeymoon phase of NAD Therapy it is important to remember that one's feelings and outlook will change as NAD Therapy goes on. After the first few weeks of slight discomfort on NAD Therapy, which first clean the blood and cells of many toxins, one feels much more oneself, more alert and less fatigued. This is called the "honeymoon phase".

The honeymoon phase, can be very seductive where people retain their improvement with little or no NAD Therapy for the first few months or so following the treatment. As time goes on, however, the full impact of the regained energy required to maintain the quality of life and to manage this chronic NED one is suffering from, will hit home. One will not necessarily feel progressively better, one's spirits may drop, and discouragement and disillusionment may set in as one's body has adopted to the increased energy levels gained from NAD Therapy. This is quite normal and the staff and existing patients will be of help if one let them know how one feels. Keep in mind that others have been down this road before. It is difficult to rely on family and friends to assist during this phase because most often they also suffer from NED, mainly as co-dependency or religious addiction.

8.7 GOOD NUTRITION

"Fad diets that restrict the types of food we eat may actually jeopardize our overall health. Such weight loss schemes are based on the erroneous notion that eating only a few specific foods can lead to better health. On the contrary, says University of Arkansas anthropologist Peter Ungar - humans evolved to consume the widest possible range of foods, and limiting that variety can lead to serious health risks. Rather than whittling your diet down to a select group of foods, a healthier approach to nutrition is to expand the variety of foods you eat. After all, says Ungar, that's what four million years of evolution has designed the human body to do".[794]

The following abstract regarding athletes' nutritional needs can be seen as a perfect way of dealing with the nutritional needs of the NED sufferer. "Athlete" is replaced with "patient" for explanatory purposes. "Good nutrition is one of the elements necessary for optimal performance. The patient should consume a diet composed of a wide variety of foods to help ensure that nutrient needs are met, whereas maintenance of ideal weight is the indicator of adequate calorie intake. The best diet is one that considers physiological, sociological, and psychological factors, i.e. an individualized diet. The meal should consist of foods the patient likes, tolerates well, and usually eats. The main nutrition consideration during the all-day meet is fluid replacement, and patients should be encouraged to drink ample water, especially when in a hot environment. Foods and beverages the patient likes, taken in small amounts throughout the day, can ward off hunger, provide needed calories, help maintain blood glucose levels, and meet fluid needs. Although vitamins and minerals taken at levels in excess of the RDA have been shown not to benefit performance, use of high levels of supplements is not uncommon among patient. Patients are often unaware that some nutrients can be toxic when taken in excess"[345].

8.8 DELAYED RECOVERY REACTION

"To be honest however, I had serious doubts about it (NAD Therapy) during the initial phases, and I rejected the treatment. But, with hindsight I realise that the NAD supplements worked miracles for me, without any real effort on my part. While the number of treatments had been accumulating gradually, I regained my mind and ability to think rationally. The most dramatic aspect of my treatment is that it didn't require any great effort on my part. All that was required, was merely patience, compliance and tolerance"[47].

Just as it takes some time for some of the negative effects of NED to crystallised into symptoms, it can take just as long before the full effect of NAD Therapy becomes visible. "Delayed recovery-reaction" is a state which develops when improvement occurs after a long period of treatment and after the initial treatment had been ceased. The individual, in this instance, finds it difficult to associate the improvement with the therapeutic interventions which induced it. The opposite is also true. The side-effects of certain medications can become visible only after a long period and are then attributed erroneously to more recent events[244].

8.9 THERAPEUTIC ATMOSPHERE

"We think about individuals and families in terms of patients who are recipients of our care, rather than as active participants, if not primary managers, in the ongoing care process. When we think about self-help strategies, we think about individuals doing for themselves what healthcare professionals might normally do rather than empowering individuals to maintain an ongoing, quality, healthy lifestyle, regardless of their stage of disability. We need to integrate care with the values, norms, and conditions of those we serve, as well as their family and community of residence."[582]. NAD Therapy advocates patients' involvement and co-responsibility from day one of contact. Patients are empowered and motivated to take effective control of their abilities to manage their lives.

8.1 SETBACKS AND RELAPSES

"Then I went to Alkogen Treatment Network. They really helped me a lot and meant a lot to me. Then I also regained control. I became used to it. I felt, that I could wait for longer periods, before getting my NAD supplements. Instead of, for example, every month, like I had used to have it, I stretched it to two or three months. I also abandoned the little green and blue pills. I stopped using them completely. I stopped everything. I then had an irresistible craving for a drink. I was salivating, that is how much I craved a drink! Instead of driving to Alkogen Treatment Network, I gave in to temptation. The craving for a drink was stronger than the desire to go to Alkogen Treatment Network. I had a drink and this has happened a few times, since I have been using Alkogen Treatment Network"[217].

"Then my brother-in-law had arranged my admittance and there the clinical psychologist and I started with this treatment and the assortment of NAD supplementation and medication, which he arranged to be administered to me. Suddenly I had felt well and I could take on the world. I think it was a little arrogant, I had a little too much self-confidence. I was there for about two weeks. I left. My wife and I then went on holiday and didn't experience any problems. I returned to my practice. Initially, I had continued

with the medication and everything remained under control. I didn't have any problems. After a while I thought 'No, I no longer need this'. After a little while I merely started using pethidine again. More and more, at an increasing rate"[32].

The main reason for setbacks and relapses is contained in the above-mentioned extract. It is difficult for persons, who suffer from NED, to accept that it is chronic in nature and requires continuous treatment on all levels. The medications and other treatments have a slow effect and after their use has been ceased, it also takes a long time, before the therapeutical effect disappears completely. Patients find it difficult to link the effect of NAD Therapy with the consequences, after its use has been ceased. This is similar to the situation that prevailed initially, during which the initial effect of undesirable behaviour or substances could also not be linked to the subsequent consequences.

8.11 CYCLICAL AND SEASONAL EFFECT

"Yes, terribly, especially at this time of the year. My doctor calls it "seasonal depression". I noticed that I had felt exactly the same last year and when I had again felt the same this year, I went to receive NAD. I notice it, because I had not received it last week and felt extremely tired and listless last Friday. I then went to the doctor, this time just for NAD. He had a nice chat with me. He told me, that I would also have to use medication with it and also receive NAD. After a few months we shall take another look, after I shall have used NAD with vitamins, to see what it does to my system. I however feel much better. Then I indeed felt much, much better. One becomes completely relaxed"[342].

With NAD Therapy there are periods of improvement and lapses according to the person's available energy level and energy expenditure. The literature refers to this, amongst many other things, as binges, relapses, setbacks, dipsomania, post-acute withdrawal and craving. This could also be related to what literature describes as cyclical or seasonal effects. The NAD Therapy must be adapted accordingly during these periods. Patients use the medications in the same way, as they would previously, for example, have used the prohibited or undesirable substances. In other words, more NAD infusions or capsules are taken prior or during these relapses.

During winter an increased loss of heat occurs amongst persons with seasonally affective disorder (SAD)[6]. There is an atypical increase in appetite for carbohydrates, increase in mass and drowsiness during winter amongst their group of SAD sufferers[128]. There is a decline in tryptophan, which is an important precursor of NAD, that is followed after the summer by depression in the winter, when they suffer from SAD163. Biological factors, which contribute to SAD, run in families[135]. Studies confirm the role of genetical factors and the role of serotonin in SAD[206].

8.12 IGNORANCE

"I think that this is precisely, what my problem was. I would, in my opinion, never have solved it, because what is offered as therapy now, is in fact in a way the exact opposite of what any doctor would have recommended, namely 'You must take in energy with food, so that your body can burn it, because you don't have the levels of energy, which you ought to have'. If you receive any other treatment, they would not have addressed this and you would, in my opinion, have been at the mercy of a route, that would have led you to nowhere. This treatment uses the natural vitamins and minerals, which your

body needs. The other side of the coin is that your overall pattern of thought becomes positive and you say to yourself 'I am not so bad'. I didn't lose my self-image completely during the process"[181].

Ignorance, even on professional level, contributes significantly to unsuccessful treatment. NAD Therapy is based on recognised evaluations, objective and independent blood tests' results and proven findings from research. It is also well-documented in "Dreams for Fragile People"[222]. This book is based on more than 600 scientific articles, which are readily accessible to those who are interested. Knowledge is within the reach of everyone, who truly desires it. Knowledge promotes insight and understanding, which have therapeutical value on their own. Knowledge is also the cornerstone of all treatment.

8.13 SUPPORT GROUPS

Support groups are in particularly popular amongst persons, who suffer from chronic conditions like NED. Although it fits into the treatment of NED, it is often wrongly considered to be effective treatment on its own and soon turns into addiction to support groups. Support groups are very popular amongst the relatives of persons, who suffer from NED, and become the focus of treatment, instead of a source of assistance. No support group or any other therapeutic intervention can restore or stabilise the NAD Energy Deficiency of any NED sufferer. Only the correctly formulated NAD supplements at the correct dosage and with regular use can, at best, lead to stabilising it. Another danger, which is inherent in support groups, is that they normally operate without ongoing professional guidance and then they can easily be taken over by a member, for other purposes than the reason for which the group was intended.

8.14 USERS' EXPERIENCE OF NAD

Most of the below-mentioned abstracts are from personal interviews, that had been conducted with individuals, for inclusion in the book "Dreams for Fragile People"[222]. It is recommended, that readers study the complete interviews for more details to get the full picture.

- "In December he was still lying in the fetal position. He did not know, what was happening around him. He seemed to be completely senile. We kept on administering the NAD supplement, while my husband was not here. Suddenly I realised, that he started asking questions; he wanted to know more. He was aware that we were doing something to him, but did not know what it was. In spite of his state of confusion, he said that this stuff was working. What is quite remarkable, and I do not know whether it was a coincidence but I had noticed it, was that whenever we administered the NAD supplement, he sat still, in spite of his confusion and disorientation. He did not move his hand or arm while the NAD supplement was entering. He just stared at me with his beautiful eyes and said softly that it was working. The next thing we knew, was that he was walking around"[162].
- "I last received the NAD supplementation two or three months ago and feel now, that I am starting to tire. It therefore definitely makes a big difference. One can definitely feel when one uses the NAD. You feel much, much better during the next few days. I feel much healthier. It is like the clinical psychologist explained,

that when you are in a state of depression everyone tells you to do something else, or to tackle a new project, or that you must occupy your mind with something else, but you lack the energy. Now I have the energy to do it. I started last week to lecture temporarily at a college. This is something, which I previously would never have considered. This is something new that I tried, which I would never have accomplished previously, because I had not had the energy to do it"[247].

- "I no longer use the NAD supplements intravenously, but rather in capsules, that is the vitamin capsules that contain NAD, and I am very certain that it is the reason why I am still moving around. It enables me, to get up and make my bed on my own"[127].
- "I also battled with sexual needs. Since I had started using NAD supplements, I also have more control over sexual impulses. I think that I have more energy to manage sexual issues. I went to the so-called escort agencies on several occasions to deal with sexual urges. It bothered me a lot, because I am a believer. This lead to a lot of guilt. I did not know what I should do and then thought about contacting Alkogen Treatment Network. I also completed a psychometric test. It indicated, that when I am under pressure, I am readily inclined to do wrong things, like these sexual matters. I am not dependent on alcohol or such things, but sex was my weakness. It appeared from the tests, that I suffer from low levels of energy and cannot overcome my problems. Then I received NAD supplements"[246].
- "I wanted to stop smoking. My father suffered a heart attack. My little daughter said to me: 'Daddy, you will die if you don't stop smoking'. This and the NAD supplements suppressed 'you feel like smoking, you feel like smoking, you feel like smoking'. It was a psychological matter for me, together with the NAD supplements. The NAD supplements helped me and relieved the withdrawal symptoms greatly. This was my experience. It felt to me, as if I slept better. Previously, I slept very badly and restlessly, and it feels now as if I am more peaceful, more relaxed"[165].
- "I received a NAD supplement for the first time a few months ago. During the entire year I had literally spent every waking hour praying, but started to think that prayer on its own would not help. This sounds awful, because I believe that God can accomplish anything. I truly believe this, but he did not do anything for me until I had made this incredible effort. Admittedly, I drink the little pills now and receive the NAD supplements. I assume that it probably calmed me down. Indeed, I only felt like doing things, after I had started to feel better. Then I completed the course in gardening"[341].
- "I realised, that if I don't set aside time and get the NAD supplements and the support from the medicine, I shall lose everything that is dear to me in life. This includes my work and the desire to work amongst the congregation. It was therefore a radical decision in favour of important and urgent issues, which enabled me to say 'Today I shall go to Pretoria"[35].
- "Well, this was after I had no longer been using sleeping pills. My daughter told me about Alkogen Treatment Network and that I must speak to the clinical psychologist. It certainly helps. It has been helping me for months. When I say that it helped, I mean that I didn't have the urge to do anything. Well, how can I describe it? It provides me with energy, a lot of energy. I am not tired, like I used to be. I always used to be very tired. The business that I owned produced a lot of stress and the sleeping pills helped to alleviate the fatigue. After today's NAD supplementation I shall sleep wonderfully for a few days. I use my cholesterol

tablets and pills for diabetes together with the NAD supplementation. I use magnesium and carnitine every day"[215].

- "I had been using cannabis for approximately three months, before I was caught. You don't notice it while you are smoking the cannabis, but nothing bothers you. You go through life with your eyes closed, if you know what I mean. You don't care about anything and if anything bad happens to you, you just accept it. You feel, that it doesn't matter. Your attitude is 'Let's roll another zol'. It numbs your brain, if you ask me. What bothered me the most, was that my brain was so clear, approximately two weeks after I had started with the NAD. I could concentrate at school. It felt, I don't know, as if I was somehow happier. I also use other pills. I find that the NAD gives me a lot of energy during the day. I don't get as tired, as I used to. Last year and this year it helped me to concentrate. The little blue pill definitely helps me a lot. If I get anxious, I immediately take one of them"[184].
- "But I come for my NAD supplementation. Twice per week during the first three weeks. But what happened then is that I had thought that it is this miraculous substance, which they were giving me, the NAD supplement. I woke up the next morning. I could still see the walls and I could not yet fly. What was going on? But after the fourth or fifth, I had noticed that something was happening. I am clearer. I can think better on my feet. I am still as active, but I am much calmer. I can still hit the ceiling, but I can be controlled. Getting angry... because I have a terrible temper ... but I can control myself now"[113].
- "My daughter, Anneretha, 'collapsed' in August 1997, as a result of fibromyalgia (burnout). She was in grade 11 at that stage and didn't go to school during the last two quarters of last year, but rested at home. She received very good medical, psychological and pastoral support. Her recovery was however very slow. In February 1998 a friend, who was working part-time as a nurse at Alkogen Treatment Network, encouraged us to visit the psychologist at Alkogen Treatment Network. From conversations with him, we became aware, as a family, of the complexity and sensitivity of one's body. Since then, Anneretha has been participating in the support programme and her progress accelerated. This year she could attend approximately half of her classes and passed her examination in June. We are confident, that she will be able to complete her grade-12 year this year"[608].
- "Since I have stopped drinking and have been using the NAD supplements, I can think more clearly. I am not limited to making impulsive decisions and stick with my choices. I think more about them and about the advantages and disadvantages, before I take the plunge. Previously I had simply decided that I liked it, did it and that was it. And that possibly meant trouble"[255].
- "I don't feel anything, but I can feel the effect afterwards. I already feel it the following day. It has already happened, that I think about alcohol. I would, for example, sit and work in my workshop. Then I cannot concentrate on the ring or bangle, which I am making. I start to think about alcohol. Then I think 'I must go and get the NAD supplement'. The next day, I go. The day after the supplementation, I had noticed that I was no longer thinking about alcohol. Then I concentrate on my work"[217].
- "The NAD also changed my personality very, very significantly. Previously I could spend days on my own, without speaking to anyone and being as happy as a lark. Now I like to be amongst people all of the time and to go out and so on. Quite amazing. Very different"[60].

- "In a demanding and busy job, NAD had restored my flagging energy and brought back a healthy balance to life, since I had received energy to always remain positive and could make (considered) decisions much more easily. My energy recovered to such an extent, that I want to and can take on new and additional tasks and tackle them. The recovery of the levels of NAD in my body provided physical and emotional energy, so that I can now effortlessly visit more members of the congregation and provide pastoral support. My appetite improved markedly and I am therefore physically also more healthy. Paying attention to my family in a meaningful way became a joy, rather than a duty. NAD isn't just another miraculous cure on the market, it's simply a physiological necessity for the demanding time, in which we are living. In short, NAD helped to put back the swing in my step, the smile on my face and the song in my heart!"[609].
- "I had already felt that I had more energy after the first NAD supplementation. I immediately started to drink fewer dieting pills and completely ceased using them within 2 weeks. I had more power to fight against the binges. It was as if I could think better and more realistically about everything. I had the strength to fight against my problem. My head felt open and my thoughts were clearer. As time went by, it became easier to manage my problem. I didn't suffer any side effects from the treatment. The capsules helped me between the supplementation. Whenever I had felt that I could no longer carry on, I used additional capsules. They provided me with the energy, that was required to carry on"[610].

Applications for NAD Therapy: NAD Energy Deficiency Related Syndromes (NEDRS)

1. Energy by Confirmed Diagnosis

Fatigue (being without physical energy, strength, power) is one of the most general and least understood symptoms of many chronic and disabling conditions. Clinically, the spectrum of syndromes associated with primary disorders of energy metabolism is widespread[320]. This review must be seen as only explorative in nature and not as the setting of rigid rules or the making of any diagnostic, etiology or treatment claims regarding the disorders reviewed as possible NEDRS. Furthermore the main aim is to stimulate further research and also to highlight the possible role of an underlying NED in the disorders discussed. We will only record the metabolic indicators of NED for each disorder included. This review is not supposed to be an exhaustive list of all possible articles related to each disorder.

9.1 CRITERIA FOR INCLUSION

The metabolic indicators of NED (refer to as Energy Values I, II, III and the Energy Block) as well as treatment with NAD Therapy will apply as basis for inclusion of the listed disorders. Since 1989 we have treated various disorders associated with NED with NAD Therapy at Alkogen Treatment Network. The application of NAD Therapy have to be investigated further, especially on an empirical level. Most patients receiving NAD Therapy showed good clinical improvement substantiated by the post test improvement in their energy blocks as per follow-up blood tests. The time span of improvement varies per disorder treated. The rationale for the improvement is possibly one or more of the biochemical functions of NAD and/or the other cofactors of the energy metabolic cycle.

9.2 PRO VISOR ON NAD THERAPY AND NEDRS

No claims what so ever are made in this chapter for the cure of incurable diseases by the application of NAD Therapy. The results speak for themselves. The discussion has been kept on a factual basis. At the same time it must be remembered that many patients come for NAD Therapy after they have tried everything else and they are in a state of despair. We are only endeavouring to show that NAD Therapy has definitive and science based therapeutic value. Of this there can be no doubt when all the facts are carefully considered, the opponents of NAD Therapy notwithstanding. The reader should acknowledge the fact that NAD Therapy has advanced beyond the experimental stage. Sixty years have passed since NAD Therapy made its original appearance as a treatment modality for alcoholism and the broad principles from which it emerged is now better understood from the latest biochemical studies on coenzyme NAD.

9.3 APPLICATION OF NAD THERAPY

The blood tests results done by independent pathologists were obtained from the clinical records at Alkogen Treatment Network or participating practitioners. The diagnoses were made by the treatment professionals of the patients that they consulted prior to joining the Alkogen Treatment Network treatment program. They include medical specialists like psychiatrists and neurologists. In all cases the NAD Therapy was only initiated after the patients were examined by a medical doctor and a recommendation to this effect. In all

cases NAD Therapy was requested by the patients. Since 1989 various medical doctors formed part of the multiple professional treatment team of Alkogen Treatment Network. Some notes refer to the clinical use of NADH, one of the derivates of the NAD coenzyme others are NADP and NADPH[366].

9.3.1 STEPS IN NAD THERAPY

"I went there and met the clinical psychologist. He chatted a little with me and explained some stuff for me. He didn't make any sense to me. Let me be honest. Nothing makes sense to anyone, when they go to Alkogen Treatment Network for the first time. They tell you about your deficient NAD level and so on, and these things don't make sense to you, because you aren't a medical expert. The language and so on, which he uses, makes no sense at all to me, but I was willing to give it a try. I took my first NAD supplement. The blood tests were done. They then didn't say anything after that and I didn't understand what was going on. I however went there for my NAD supplements. Twice per week during the first three weeks. During the fourth or fifth week I however noticed, that something was happening. I feel clearer. I reason more logical. I am as active as before, but much calmer. I can still blow my top, but are in control".[113]

It is always good to be fully informed about all the particular details before one commences with any new thing, especially therapy. Keep in mind that memory impairment dominates the cognitive complaints of patients with chronic fatigue syndrome[527]. The same finding is also found at Alkogen Treatment Network which shows that prospective patients are easily flooded with all the new concepts and detail of NAD Therapy, because of their average energy block of 70 instead of 100 plus. The rapid physical changes which take place in the NED sufferer during the first few weeks on NAD Therapy, impede the process to meaningfully assimilate new information. So based on this observation it is recommended to first follow these 8 steps set out in this synopsis. The detailed rationale and treatment application of NAD Therapy can then be studied as and when the physical energy level improves due to the effect of NAD Therapy.

No one's life is perfect. We all have dreams, tough circumstances, problems and losses to deal with. But some people's lives appear to be more enjoyable than others. Have you ever questioned why? A vital difference is most often the amount of physical energy they have available to deal with what happens to them or to let things happen in their lives. Although we always have a choice, 10% of persons are born with NED, that if untreated, stops them from realizing their choices. During the journey of life, the energenetic participant's dreams come true, while the passive spectator's dreams often turn into the worst nightmares.

So do not reframe the Dreams of NED Sufferers, rather help them change their Physical energy Levels and then let them reach for their Dreams.

If you think that you or someone special to you has a problem with a chronic disorder, you will particularly benefit by studying this chapter to see if the condition is associated with NED. Even the fact that you are reading this synopsis is an exceptional victory. It means you are considering an energenetic life for yourself or someone precious to you. The following 8 steps provide a synopsis of NAD Therapy for persons who might be suffering from NED.

- **Step 1:** Please read these steps carefully, arrange a consultation with your health professional and discuss this information before making a final decision. This synopsis is based on more than 600 relevant scientific sources and clinical experience with more than 6 000 patients on NAD Therapy prescribed by 140+ private practitioners. These are discussed in the rest of this e-book. This e-book is made available free of charge to all truly concerned individuals. It is therefore strongly recommended to give a copy (printed or electronic) to your health professional. On their journey to an energenetic life, most persons will not overcome the following stumbling block: "The distance is nothing; it's only the first step that is difficult" (Marquise du Deffan).
- **Step 2:** Arrange for the lactate and pyruvate blood tests to be done. No prior fasting is required. These tests are internationally in use and are reliable indicators of your biochemical energy level. The blood tests' normal values ensure that 95% fall within the normal range and only 5% of testees will present with NED. The tests are generally done by most pathologists. Prior arrangement must however be made, to ensure that the required test tubes are available. For full details on blood tests see chapter 6. If it is impossible to do the two blood tests look up your disorder or a disorder of similar severity and use the Average Energy Block as basis for your NAD Therapy.
- **Step 3:** Use the results of the blood tests and calculate the energy levels and determine the energy block. The formulae are outlined in Chapter 6. The online calculators to calculate the energy values and recommended NAD Therapy Programme are available at http://www.energyequalsempowerment.com
- **Step 4:** Use the calculated or identified Energy Block and determine the recommended NAD Therapy Programme
- **Step 5:** Consult your family doctor concerning the use of the supplements and if need be a prescription for the NAD IV-therapy and/or any supporting prescription medication. You or your family doctor can consult with our resident pharmacist to clear any possible uncertainties.
- **Step 6:** Follow the recommended NAD supplementation program or prescription of family doctor for 12 weeks and then arrange for follow-up blood tests to be done in week 12. Guard against the "honeymoon phase" and use the new gained physical energy in a responsible manner. For instance during weeks 6 to 12 work attentively through the NAD e-book to update you on the treatment rationale.
- **Step 7:** Use the results of the follow-up blood tests to determine the maintenance number of capsules to be used. Keep in mind that this is the minimum required and can be increased during periods of excessive physical energy expenditure on both positive or negative stressors.
- **Step 8:** Gradually start to take care of any psychological and/or spiritual energy blockages that have developed over your years of living with NED. Consult with councillors who are knowledgeable in your appropriate problem domain and the NAD Therapy approach. Regularly work through the NAD e-book and similar literature to familiarize yourself with the new insights that accompany your gradual improvement over time.

List of NED Related Syndromes (NEDRS)

NED Related Syndromes - A	Average NAD Energy Value (normal 100+)
Academic Stress	74
Acute Renal Failure	50
ADHD (Attention-deficit-hyperactivity-disorder)	75
Ageing and Longevity	81
Alcoholism	66
Alcoholism in Remission	81
Allergy and Food Intolerance	66
Alopecia	62
Alzheimer's Dementia	71
Arthritis	77
Asthma	47
Autism	70
NED Related Syndromes - B	**Average NAD Energy Value (normal 100+)**
Bipolar Disorder	92
Breast Cancer	56
Brucellosis	77
Bulimia Nervosa	78
NED Related Syndromes - C	**Average NAD Energy Value (normal 100+)**
Cancer	55
Cannabis Dependency	72
Cardiac Disorders	78
Chronic Fatigue Syndrome (CFS)	74
Chronic Sinusitis	66
Cocaine Dependency	72
Co-dependant Child	78
Co-dependant Husband	71
Co-dependant Mother	70
Co-dependant Wife	78

Concentration Problems	72
NED Related Syndromes - D	**Average NAD Energy Value (normal 100+)**
Depression	70
Diabetes	64
Down's Syndrome	59
Dyslexia	53
Dystonia	56
NED Related Syndromes - E	**Average NAD Energy Value (normal 100+)**
Enuresis (bed wetting)	88
Epilepsy	64
NED Related Syndromes - F	**Average NAD Energy Value (normal 100+)**
Fanconi Syndrome	80
Female Incontinence	78
Fibromyalgia	62
NED Related Syndromes - H	**Average NAD Energy Value (normal 100+)**
Hallucinogen Dependency	77
HIV / AIDS	54
Hypercholesterolemia	63
Hypertension	77
Hypoglocemia	71
NED Related Syndromes - I	**Average NAD Energy Value (normal 100+)**
Impotence	48
Infertility	62
Insomnia	83
Irritable Bowel Syndrome	80
NED Related Syndromes - L	**Average NAD Energy Value (normal 100+)**
Lupus Erythematosis	98
NED Related Syndromes - M	**Average NAD Energy Value (normal 100+)**
Marfan's Syndrome	34

Migraine and Headaches	78
Multiple Chemical Sensitivity Syndrome	77
Muscular Dystrophy	63
Myalgic Encephalomyelitis	80
NED Related Syndromes - N	**Average NAD Energy Value (normal 100+)**
Nicotine Dependency	67
NED Related Syndromes - O	**Average NAD Energy Value (normal 100+)**
Obesity	63
Opioid Dependency	73
Over-training	77
NED Related Syndromes - P	**Average NAD Energy Value (normal 100+)**
Parasuicide	59
Parkinson's Disease	60
Pathological Gambling	79
Peripheral Arterial Occlusive Disease	73
Porphyria	69
Prescription Medication Abuse	73
Psoriasis	89
Pulmonary Emphysema	74
NED Related Syndromes - R	**Average NAD Energy Value (normal 100+)**
Religious Dependency	62
NED Related Syndromes - S	**Average NAD Energy Value (normal 100+)**
Seasonal Affective Disorder	53
Sedative Dependency	69
Self-mutilation	53
Sex Dependency	60
Stress and Burnout	74
Stroke	88
Stuttering	88
Suicide	56

NED Related Syndromes - T	Average NAD Energy Value (normal 100+)
Thyroid Disorders	66
Tourette's syndrome	75
Trichotillomania	41
Turner's Syndrome	48
NED Related Syndromes - V	**Average NAD Energy Value (normal 100+)**
Violence Dependency	69

Applied NAD Therapy: Diabetes as Case Study

In chapter 9 a comprehensive list of chronic disorders associated with NED was given. On most of these disorders hundreds of articles and books are published and new research findings are reported virtually on a weekly basis. Health professionals rightfully ask questions on the relevancy of NAD Therapy for each of the NEDRS listed. In this chapter a brief outline is provided using the knowledge gained in the previous chapters to illustrate the relevancy of NAD Therapy to diabetes as an example. By referring to the literature references provided for each NEDRS a similar outline can be developed for each NEDRS.

10.1 THE PATIENT AND HER HUSBAND'S COMMENTS ON NAD THERAPY

"I've been a Diabetic for 21 years, underactive thyroid, high cholesterol, high blood pressure and kidney damage. After the birth of my child, I started experiencing very low energy levels. My husband was lucky if I pitched up at work to do the banking, before 2pm the afternoon. Even when I had a quiet weekend and lots of sleep and rest, I still didn't have enough energy the Monday to start the week. My immune system was non-existent. I had colds the whole winter through; if somebody with a cold gets close to me I would get it".

"When we looked at alternative treatments for my child, we heard about NAD. We had our blood tested and started the treatment immediately. I have experienced a drastic change within two weeks. I could get to work at 9:00 a.m., helped in the shop, do my child's therapy and some house work. Another wonderful thing is that you do not experience dips like when you take a tonic, your energy levels are constant. If it was not for NAD, I think even my wonderful husband's patience would have run out."

My husband's Comments: "The NAD Therapy has given me back my wife. We can now have an active family and social life. Praise God for those that helped and guided us with the NAD Therapy. For our lives have turned for the better, a lot better."

10.2 HER NAD THERAPY PROGRAM

Based on the results of her blood tests the following NAD Therapy program was developed for her. Her husband also received NAD Therapy because of his low energy values.

10.3 BIOCHEMICAL MARKERS OF NED IN DIABETES

The patient had an NAD Energy Block of 67 which is a bit higher than the average NAAD Energy Block of 64 measured by patients with diabetes.

10.4 ABSTRACTS FROM INTERNATIONALLY PUBLISHED ARTICLES ON NED AND DIABETES

"In diabetes, glucose metabolism via the Krebs cycle is impaired, and this leads to reduced cellular energy and elevated blood sugar levels. When a cell is damaged by oxidation injury, cytosol NAD levels fall and ATP levels decrease, If the DNA strand breaks can be repaired, and the cell regains lost NAD, the energy system can function

again, but frequently cell death ensues. Thus organ failure is the result of energy failure on a cellular level, because of oxidation damage of the mitochondrial membranes and/or low NAD. In the case of the beta cell in the pancreas this means that proinsulin production ceases until NAD levels in the cytosol are restored[639].

"Thus, in diabetes, aerobic glycolysis gradually shifts to anaerobic glycolysis under ischaemia, with accumulation of lactate and acid metabolites that in turn induce myocardial deterioration.[644]"

"Nicotinamide adenine dinucleotide (NAD) and its derivatives NADH, NADP and NADPH have regulatory functions in the generation of triose phosphates and pyruvate from glucose. In many studies of the influence of the diabetic state on relationships between pyridine nucleotide and glucose metabolism, the focus has been on the sorbitol pathway. Less attention has been paid to other aspects of the role of pyridine nucleotides in pyruvate formation from glucose, in particular the effects of the NAD precursors nicotinamide and nicotinic acid on glucose metabolism... Reference is also made to the following three current hypotheses for mechanisms underlying diabetic microangiopathy:

1. Chronic glucose overutilization, caused by hyperglycemia, in tissues which lack insulin receptors and therefore are freely permeable to glucose. 2. Enhancement of sorbitol pathway activity with an ensuing decrease in the ratio of NAD/NADH. 3. Enhanced utilization of both glucose and pyridine nucleotides in formation of triose phosphates and pyruvate. Therapy with NAD precursors like nicotinamide might have corrective effects on these proposed biochemical aberrations, thereby retarding progression of microangiopathy".[607]

"Taken together, it is proposed that high doses of nicotinamide primarily affect ADP-ribosylation reactions in beta-cells as well as in immune cells and the endothelium. As a consequence, cell death pathways and gene expression patterns are modified, leading to improved beta-cell survival and an altered immunoregulatory balance[645]".

"Autoimmune processes are involved in pancreatic beta-cell destruction in type 1 diabetes... Generation of free radicals, DNA strand breaks, activation of the enzyme poly (ADP-ribose) polymerase (PARP), and depletion of intracellular nicotinamide adenine dinucleotide (NAD) appear to be common factors in beta-cell death, whether mediated by oxygen radicals, nitric oxide, or streptozotocin. Nicotinamide, a soluble B group vitamin which offers protection against these toxic stimuli, is at high doses a free radical scavenger, a potent inhibitor of PARP, and protects against depletion of intracellular NAD. A sound scientific rationale therefore exists for its use in human prediabetes, and promising pilot studies have been performed in ICA-positive first-degree relatives and school children. No serious side effects have been reported from its use at the doses proposed in man or other species[646]".

"The causes of cytokine-induced beta cell death are less well defined, but important factors may be nitric oxide-mediated DNA damage, depletion of NAD levels and toxic effects of oxygen free radicals and eicosanoids generated in addition to nitric oxide[647]".

"As a result of beta cell destruction, islet cell antibodies (ICA) can be demonstrated in the circulation. These antibodies can be detected up to eight years prior to overt IDDM. Nicotinamide, a vitamin B3 derivative, interferes with the immune mediated beta-cell

destruction by reducing the content of FR and NO and thereby reducing their deleterious effects. At the same time, nicotinamide increases the intracellular NAD pool, thus increasing the energy supply of the cell. Nicotinamide protects against chemically induced as well as spontaneous diabetes in animal models of the disease. Recently, open clinical studies have suggested that nicotinamide when administered to humans can prevent or delay clinical onset of IDDM[648]".

"In hypoxic tissues these vascular changes are linked to metabolic imbalances associated with impaired oxidation of NADH to NAD and the resulting increased ratio of NADH/NAD. In hyperglycemic tissues these vascular changes also are linked to an increased ratio of NADH/NAD, in this case because of an increased rate of reduction of NAD to NADH. Several lines of evidence support the likelihood that the increased cytosolic ratio of free NADH/NAD caused by hyperglycemia, referred to as pseudohypoxia because tissue partial pressure oxygen is normal, is a characteristic feature of poorly controlled diabetes that mimics the effects of true hypoxia on vascular and neural function and plays an important role in the pathogenesis of diabetic complications"[649].

NAD Therapy: The Nutriceutical Supplements

"The potential of NAD and niacin therapy to treat diseases is now going forward in South Africa. Theo Verwey and his group of clinicians are now the future of this movement to reform medical therapeutics. It is the concept of NAD as a medicine, which must not be ignored: the needed research must be allowed, encouraged, the results evaluated, acknowledge and passed on to the young physicians of today". [697]

"Some supplements and food products promise to cure everything and improve your health - sounds too good to be true? The answer is probably yes. Dietary supplements have few regulations about what claims they can make."[652] This warning on the American Dietetic Association's website is echoed by many other health professionals. Oftenly this "too good to be true" stigmatization of a genuinely good supplement are based on ignorance due to the following phenomenon: "Although researching a product is always a good idea, Evers says most consumers don't want to spend the time it takes to check out a product thoroughly."[653]

To assists the reader in critically evaluating the information recorded in this e-book a few questions are referred to. What questions should be asked before a nutritional supplement is recommended by a health professional or used by a consumer? Evers[653] suggests asking the following:

- "**Have you heard of the company?** If a product is truly beneficial, then there will probably be a well-known company associated with it". According to Evers if the company selling the product is one you have never heard of before, ask yourself the next two questions.
- "**Have you heard about the supplement in the news media?** Breakthroughs in science make good news. Before a new "cure" or other product becomes available to the public, it will be reported by the news media".[653]
- "**Where is the science?** Has the product been thoroughly researched at a university? Keep in mind that testimonials are not research. Look to see if the product's claims can be tested for validity".[653] In considering this question keep the following in mind: "Nutraceutical manufacturers are not required to do controlled clinical trials-scientific studies in which the effectiveness and safety of a product is measured against a dummy pill (placebo) or a proven competitive product. Because most nutraceuticals are natural substances that cannot be patented, there is little incentive for manufacturers to spend many millions of dollars on clinical studies.[654]

11.1 IMPORTANCE OF NUTRICEUTICAL SUPPLEMENTS

Vitamin and mineral therapy are accepted by only 23% of the surveyed general practitioners in Australia[507]. Statistics for South African practitioners is not available. However, several doctors, including specialists such as gynaecologists and specialist physicians, are already prescribing and dispensing the nutriceutical supplements of Alkogen Products to their patients. The supplements are also dispensed to their patients by some dietitians, homeopaths, pharmacists and nursing sisters. It is also recommended by pastoral counsellors and psychologists to their patients.

Many inborn errors have now been described that can be treated by alterations in the diet. Such treatment requires an understanding of both the biochemistry of the defect and of normal nutritional requirements. The principal strategies are cofactor therapy, steps to prevent accumulation of toxic metabolites and the replacement of essential nutrients that are deficient as a result of the metabolic block[595].

It is important to note the latest research findings regarding niacin and nicotinamide. It appears that most of the therapeutical benefits ascribe to these compounds are actually possible by means of its conversion to NAD in the cells. For example: "The beneficial effects of nicotinamide for the treatment of HIV infection appear to be linked to cellular utilization of NAD. Nicotinamide appears to be void of any cell-free reverse-transcriptase inhibition or virucidal activities. However, several cell-associated observations link HIV, nicotinamide, and NAD. HIV-infected cells demonstrate an increase in the ADP ribosylation of proteins, a phenomenon in which NAD is used as the ADP-ribose donator to covalently modify proteins. As a general feature, nicotinamide inhibits ADP ribosylation reactions. Protein ADP ribosylation can occur in the nucleus, in the cytoplasm, and on the cell surface of lymphocytes. PARP is a nuclear enzyme that catalyzes the formation of ADP-ribosepolymers that attach to multiple different proteins. The activity of PARP is critical to the integration of foreign DNA, including proviral DNA; inhibition or absence of this enzyme interrupts the HIV life cycle. Along with poly-ADP ribosylation, monoribosylation steps also involve proteins in cells, including the ADP ribosylation of both HIV Tat protein and cellular defence. The antimicrobial action of nicotinamide might also work through the modulation of certain histone deactylase reactions (i.e.,Sir2 proteins) that use NAD in the silencing of chromosomal DNA".[767]

11.2 NECESSITY FOR NUTRICEUTICAL SUPPLEMENTS

No medication exists that can replace or imitate the required nutrients or energy metabolic cofactors and coenzymes which a patient is deficient in or dependant on. It can only be supplied as a nutriceutical supplement with the identified nutrients as ingredients. With medical treatments, approximately 25% of fibromyalgia patients improve, but the beneficial effects of medical treatment rarely persist more than a few months. All subjects in one study had received some form of medical treatment prior to taking the nutritional supplements, but none with enduring success. Nutritional supplements resulted in a significant reduction in presenting symptom severity, with continued improvement in the period between initial assessment and the follow-up[591].

"A detailed review of the literature suggests a number of marginal nutritional deficiencies may have etiologic relevance. These include deficiencies in various B vitamins, vitamin C, magnesium, sodium, zinc, L-tryptophan, L-carnitine, coenzyme Q10, and essential fatty acids. Any of these nutrients could be marginally deficient in CFS patients, a finding that appears to be primarily due to the illness process rather than to inadequate diets. It is likely that marginal deficiencies not only contribute to the clinical manifestations of the syndrome, but also are detrimental to the healing processes"[523].

The 84 studies reviewed in patients (n= 2570) with predominantly chronic conditions living in the community suggested that: oral nutritional supplements produce demonstrable clinical (including functional) benefits, but the nature and extent of these benefits vary with the underlying chronic condition; oral nutritional supplements increase total energy intake with more than 50% of the energy additional to that from habitual

food intake; improvements in body weight, enhanced total energy intake and body function following oral nutritional supplements appear to occur more frequently in individuals with a BMI < 20 kg/m>2 than in those with a BMI 20 kg/m^2.[592]

Nutritional approaches are available for the management of several different classes of inborn metabolism errors[593, 595]. The inherited defects lead either to alterations of the apoenzymes or to deficiencies of enzymes involved in the processing or reutilization of the vitamins. The application of pharmacological doses of vitamins can be useful in these disorders in order to overcome diminished apoenzyme binding, to saturate residual activities of defective processing enzymes, to compensate for pathological losses, or for acting as electron carriers[594].

11.3 BRAIN FUNCTIONING AND NUTRACEUTICAL SUPPLEMENTS

Patients with chronic fatigue syndrome without psychiatric comorbidity were impaired relative to controls and patients with chronic fatigue syndrome with concurrent psychiatric disease on tests of memory, attention, and information processing[604]. Each brain cell is a functional unit and messages are transmitted between the brain cells, by means of neurotransmitters crossing the synapses. Brain cells can create several synaptic links to other brain cells[183, 264].

The three nutrients, tryptophan, tyrosine and choline, when administered in the natural form or simply ingested in food, act like "drugs", resulting in important changes in the chemical functioning of the brain. This illustrates a novel aspect of nutrition's effects on the brain and provides the basis for new modes of therapy for patients with metabolic, neurological or psychiatric brain diseases[517]. The levels and possible function of several neurotransmitters can be influenced by the supply of their dietary precursors. The neurotransmitters include serotonin, dopamine, noradrenaline, histamine, acetylcholine and glycine, which are formed from tryptophan, tyrosine, histidine, choline and threonine[514].

In particular precursor availability to the brain influences the rates of synthesis of serotonin, the catecholamines, and acetylcholine by brain neurons. The diet readily influences brain neurotransmitter formation via this mechanism[515]. Dietary amino acids have also been found to alter pain tolerance thresholds[518]. Research evidence suggests that neurotransmitter precursors can be helpful in patients with mild or moderate depression[516].

11.4 THE BRAIN AND CHEMICAL SUBSTANCES

Chemical substances, in the form of allergens, drugs, toxic materials, medication or even food, can change the synaptic functioning dramatically if they are ingested. Chemical substances can be taken deliberately, unwittingly with food, or can be produced by activities that take place in the body. Exercise, as an example, places stress on the body and the body responds by secreting hormones and endorphins, to counter or stop this unnecessary exertion. This leads to a temporary feeling of happiness and satisfaction[76, 257, 263].

Natural substances that are ingested can also act as chemical substances in some persons' bodies, for example in allergies to food. Chemical substances also have a

neurotoxic, genotoxic or carcinogenic effect on the user. Some of these chemical substances are also absorbed in the brain[132]. There are several ways in which chemical substances can alter the natural functioning of neuronal transmission. The following eight mechanisms, with which chemical substances modify the activity of neuronal transmission are briefly described:

- chemical substances can increase or decrease the production of neurotransmitters;
- certain chemical substances impede the movement of neurotransmitters to the axons' ends;
- storage of neurotransmitters in the vesicles, that are found in the axons' ends, is often also affected in various ways by chemical substances;
- chemical substances can also affect the release of neurotransmitters by, for example, releasing them prematurely;
- chemical substances can affect the enzyme that is responsible for the metabolism of the neurotransmitters;
- chemical substances can inhibit the re-absorption of neurotransmitters in the axons' ends, by blocking the gaps in the ends;
- chemical substances can activate the receptor in the post-synaptic brain cell, by imitating the activity of a neurotransmitter, and
- chemical substances can also block the receptor, in which case the appropriate neurotransmitter cannot activate the receptor for the purpose of carrying the electrochemical message any further[139].

11.5 SUPPORTING ENERGY METABOLIC COFACTORS

In addition to NAD various other important cofactors exist both in the NAD energy system and in the general biochemistry of the human body. The cofactors identified as important from the independently done blood tests for Alkogen Products and which are included in the various nutriceutical supplements are related here for informational purposes only. Hundred's of research articles clearly illustrate that a number of nutritional deficiencies may have etiologic relevance in NED. These include deficiencies of various B vitamins, magnesium, zinc, L-tryptophan, L-carnitine, coenzyme Q10, and essential fatty acids. Any of these nutrients could be deficient in NED patients, and it appears to be largely due to the illness process rather than to deficient diets. It is likely that nutritional deficiencies not only contribute to the clinical manifestations of the syndrome, but also are detrimental to the healing processes. Because of the rarity of serious adverse reactions, the trouble in ruling out marginal deficiencies, and because some of the therapeutic benefits of nutritional supplements appear to be due to pharmacological effects, it seems logical to supplement NED patients with nutrients[523].

Alkogen Products is constantly in a process of refining the physical measurement techniques with a view to eventually determine a cost-effective method to differentiate treatment more accurately per patient. The more accurate one measures, the more one learns. Unfortunately this also increases the cost of measuring. This process is constantly updated to enable one to give a specific treatment to a specific patient. However, most physical deviations in NED require the same underlying nutriceutical treatment, such as carnitine, magnesium, NAD and other vitamins.

A Bird's Eye View of NAD Therapy

Some people are completely unconcerned about their age. They will also readily say, that they do not know how old they are. They have a youthful attitude towards life and also possess the obvious lust for life, which much younger people have. I think that it is safe to say, that all of them simply continue to grow. They are set in the conviction, that they are as old as they feel.

All of us know such people and one sometimes wonders, why there are so many days of depression and fatigue, which destroy your dreams of feeling youthful. Your dreams changed into deceit. Depression then is mercifully a suitable diagnosis. A little pill will hopefully help.

Thoughts have a very great effect on your health. On the other hand, it is also true that there must be stability in your body, at the cellular and biochemical level, in order to be able to be of healthy mind. As long as there are no stable bodily processes, dreams will always be deceitful. There can be no predictability or confidence, without stable bodily processes. People, who lack this stability, are often trapped in an addiction to a chemical substance, money, relationships and/or food. If the body is not stable, it is very difficult to live with yourself.

There is a particular area of instability in the biochemistry of our bodies, which contributes to problems with memory, irritability, problems with concentration, depression, a decrease in mental energy, anxiety, chronic fatigue and a craving for alcohol, nicotine and sugar. This condition is a deficiency in nicotineamide-adenine-dinucletide (NAD). We refer in this instance to a metabolic energy deficiency!

You read correctly: We are dealing here with a measurable energy deficiency. Most of the symptoms, which are referred to in the above-mentioned, are merely masks which hide the actual problem. Behind these masks there is most probably a genetic defect - and you can definitely do something about it.

All human activities require energy. Each cell in your body has a particular function and requires energy, to be able to do its job. This energy is produced by various chemical processes in the cells, in little "power plants", which exist as small parts in the cell. We refer to such a power plant as the mitochondrium.

Food, which we consume, is converted into glucose by means of digestion. The glucose is the fuel in the power generators. Most processes in a power plant, which releases energy, however require a particular assistant. We call such an assistant a co-enzyme. Without the co-enzyme, the power plant will simply not function.

NAD is a co-enzyme, which maintains the processes in all power plants. It is therefore clear, that if there is a deficiency in NAD or if there are too few power plants in the cells, that there is an energy deficiency. NAD is also produced by the body on its own, from food.

A metabolic energy deficiency refers to a deficiency in chemical energy, with which 10% of all people are burdened. As a result of a genetic deficiency in mitochondria (power plants), this energy deficiency will clearly be observed in families, where various masks

hide the deficiency. Grandmother might therefore suffer from obesity, her son from workaholism, her daughter from depression and her granddaughter might be a drug addict.

The egg cell of the woman starts with a shortage of power plants. The children inherit no power plants from their father, because all of his "power generators" are located in the tail of the sperm cell and the tail is discarded during conception. The daughter and son will therefore inherit an energy deficiency, but the son can marry a woman, who has enough power plants. The problem therefore ends at that stage. The daughter however spreads the problem.

There are standard laboratory tests, which indicate a metabolic energy deficiency. A blood sample is taken and lactate and pyruvate blood tests are used, which are good indicators of the biochemical energy level. Three NAD Energy Levels and the NAD Energy Block are then calculated. The NAD Energy Block is then used as basis to recommend a NAD Nutrition Protocol.

International Application of NAD Therapy

The lactate and pyruvate blood tests used to determine the NAD Energy block values are internationally in use and the relative affordability of these tests make them available to most people.
The NAD Energy Block value can be calculated with the accurate and easy to use NAD Energy Level calculator at http://www.energyequalsempowerment.com
The NAD Energy supplements are internationally available through an E –post service and can be ordered online at http://www.nadenergy.net

A Letter from the Father of NAD Deficiency Diseases

Dear Theo

I would like very much to contribute to your e-book and perhaps explain how my interest began and the experiences that changed my life when the truth about NAD therapy was revealed to me in 1980. I feel very much an obligation to help humanity with my discovery. The future of the world is truly in our hands. We must face powerful interests that want to suppress our discovery i.e.. the medical establishment and the pharmaceutical companies, perhaps even some of our governments. My own government who I served as a medical officer during the Vietnam War prosecuted and imprisoned me for 3 years after I tried to help some drug addicts with the niacin therapy I had developed for use on alcoholics.

That is why I could not treat any more people; my license was revoked by a federal judge. I turned to the library and the laboratory to continue my work on the discovery. In prison I met the most afflicted members of our society; the real predators that suffered so much from addictions, so my 3 years were not wasted. We had vitamins in prison and I found a case of acute pancreatitis that was in severe pain. I gave him 250 mg capsule of time-release nicotinic acid (commonly called niacin) and the pain was gone in about an hour. I had hoped to try this on other pancreatitis suffers but never had the chance; it was my most dramatic response to niacin. A Mafia man from Chicago had asked me to see the black man who suffered from the pancreatitis and was most impressed with the outcome. After that many others began taking niacin and benefited from the effects. The other diseases in the prison population included early diabetes and in several cases they reverted to normal with niacin 500 mg daily and exercise. Hypertension was another that reverted to normal on the same niacin therapy. It was the results of my prison "doctoring" that developed my thinking about NAD Deficiency Diseases.

John Patrick Cleary, M.D. was born in Kenosha, Wisconsin on October 16, 1933. He graduated from Washington Park High School as valedictorian in a class of 351 on June 6, 1952. He corresponded with Albert Schweitzer about working in Africa at his Hospital, but was advised to go to medical school first. Medical training was begun at UW-Madison in 1952 in the premed program and resulted in the degrees of Batchelor of Arts with a minor in German Language in 1956 and Medical Doctor in 1959. Internship was served at Santa Barbara Cottage Hospital and Santa Barbara County Hospital in 1960 in Santa Barbara, California. A Residency in Psychiatry at University of Colorado Medical Center was served for the only first year in 1961 Interest in Psychiatry began during his undergraduate training when he studied Anthropology, Psychology and Primatology. Reading Sigmund Freud was a helpful start to develop his later theories on the Predator Response Mechanism since Freud had no good explanation for the psychopathology of sociopathy or criminal behaviour. Dr. John MacDonald was his advisor at the U.of C. Medical Center and criminal behaviour was his special interest. John left after only completing the first year of the three year program because of family needs His wife and 3 children were not doing well with the low income and lack of time with him. He quit and went to work at Camarillo State Hospital in California where he was placed in charge of a research ward that was treating schizophrenia in a randomized study of 5 modalities. After only 14 months he had to leave because of his own mental health. It was just too much for a sensitive person like himself. Looking back you could say that he was being groomed for a real revelation later in life.

His clinical practice began in 1966 when he was drafted into the U.S.Army as a medical officer during the Vietnam War. Prior to this he had been a medical consultant to the State of Wisconsin Disability Determination Unit. It was a desk job dealing with claims for disability filed with Social Security in his State. Practicing in the Army developed his skills in general medicine that he continued after his 2 years of service were done. Following the Army duty in 1968 he opened his office to practice general medicine. Practice as a rural doctor in the Cross Plains-Middleton area gave him time to think about the drug and alcohol problems that were so evident in the military.

A new way of treating addictions was sorely needed. In 1980 Dr. Cleary was appointed to the temporary position of medical director of Dane County Detox Center for the first 3 months of that year. During this time he saw 20 or 30 patients each day for the full 3 months. The detox program was required to keep patients only 5 days or less and as a result the same hard-core addicts rotated thru the clinic. The County Supervisors asked how he could improve the program if he was given the permanent position of medical director? He replied that the patients needed to stay longer than 5 days if the addiction cycle was to be broken. This was the wrong answer for the Board and the job was given to someone else.

Later in 1980 he was treating a 60 year old man in his private practice for hyperlipidemia with niacin. The patient was placed on niacin 500 mg daily in the form of 250 mg time-release capsules twice daily. He returned after a month and was overjoyed that he had quit drinking 3 or 4 pitchers of beer every night to help him sleep.

The treatment was then tried on 12 more alcohol addicts with the same results in 11 cases. It took 3 or 4 weeks of niacin 500 mg daily to relieve the addiction. The man who failed on the treatment was totally dependent on the social life of his bar and was unable to quit. The best result was seen in a 30 year old man who had worked at a Salvation Army Shelter for Alcoholics. He was cured of his alcohol addiction and went back to college to finish his education. Trials of niacin on drug addicts addicted to cocaine and opiates proved the treatment was fundamental to all substance addictions. Dealing with drug addicts was not a good idea however since it led to conflict the Drug Enforcement Agency. Investigation of addicts was not allowed and the doctor was sent to prison for 3 years in 1984. Prison was a lot like the medieval monastery. One has time to reflect, study and write. His first publications were done from prison.

Living with criminals gave him a chance to study human predators up close. It was soon very clear that addictions to alcohol and drugs of abuse were very prevalent in prisoners confined in medium and minimal security facilities of the federal system. The flow of drugs and alcohol into the prisons was possible because of corrupt guards and high demand from the predatory prisoners. A general theory of addiction was proposed that alcohol addiction had a common pathway in the brain with other drug addictions and that the correct therapy would cure both. The treatment with niacin was proven to work in both alcohol and other drugs of abuse in the small pilot study done in the early 1980's prior to being imprisoned. It was therefore hypothesized that raising brain NAD levels by giving niacin cures both alcohol and drug addictions.

A search of medical literature revealed that Dr. Cleary was not the first to uncover the niacin therapy for addiction. Professor Otenello published in 1946 Minerva Medica his use of niacin and thiamine injections to detox morphine addicts. Hoffer and Osmond

published the results of using niacin and vitamin C in the 1950's to treat schizophrenia and that the alcoholic schizophrenics stopped drinking alcohol with this treatment. Russell Smith published his study of 500 alcoholic priests treated with niacin therapy over a 5 year period with good results in 50 to 60%. Paul O'Holleran reported on his use of NAD by injections to treat over 11, 000 alcoholics and 108 drug addicts. The real question was why has this treatment not become widely used? This question continues to trouble me since I had only wanted to help solve the problem and tell the story of how we can end the war on drugs successfully.

After release from prison I continued my work in the medical library and wrote more articles about niacin therapy. I hypothesized that the secondary diseases of alcohol addicts would respond to niacin therapy since they were also caused by low NAD. In 1987 I started to work in the lab at the University Wisconsin-Madison Medical School and continued until I retired in August 2001. I now live on my farm outside Cross Plains, Wisconsin and try to carry on my quest to make this treatment more available to the suffering public. I feel that Alkogen has done what I hoped we could have done at University Wisconsin-Madison. I congratulate them on carrying out my dream.

God has truly blessed us all.

John Cleary

Closing Notes

In clinical practice, one encounters a group of infants, children, adolescents, adults and aged persons whose depression, alcoholism, chronic fatigue or other chronic conditions fail to respond effectively to treatment, that is currently available. Except for their diagnosed disorders, most of these individuals do experience energy metabolic deficiencies and their conditions are aggravated by the presence of NAD Deficiency. Clinical experience and international research find, that the majority of patients benefit from NAD Therapy. NAD Therapy, in oral supplementation capsules supported by well-founded multiprofessional programmes and internationally used blood tests, form the foundation of Alkogen Treatment Network's treatment approach. Thousands of highly scientific studies have already been conducted in this field, across the world. The findings are however related to studies, which cover a wide field of study, and have so far not yet been integrated meaningfully, in a proper and applicable model of treatment.

NAD is a coenzyme, which is produced or absorbed naturally in the body, from certain nutritional particles. The coenzyme varies continuously between the NAD and NADH compound in the body. NAD has more than 100 functions in the human metabolism. Approximately 10 per cent of humans suffer from a serious and chronic deficiency of NAD. NAD Therapy is in use for the treatment of substance dependency since 1939 and is now only becoming a treatment possibility for the NEDRS listed in this e-book. Although everyone can benefit from NAD Therapy, its use over a long period is essential for approximately 10% of persons, in order to ensure that they can maintain their quality of life. NAD Therapy is more effective if supported by individualised, multiprofessional treatment, which includes a personal diet, prescription medication, pastoral counselling and individual psychotherapy.

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I have experienced uneasiness when working in areas where the professional and academic lines were vague. But this too is part of changing reality, especially at the growth point of change, and it is to be expected that the boundaries between academic and professional disciplines will continue to change, with much overlap, and this is to be welcomed. I am grateful for the practical and academic support and help from colleagues in various professions.

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