Negative and Positive Side Effects of Vitamin B_3

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Introduction

I think the best way to describe the many properties of vitamin B_3 is to tell the story of my long love affair with this amazing vitamin. It began in 1951, after Dr. Humphry Osmond, Dr. John Smythies and I had developed the adrenochrome hypothesis of schizophrenia.[1] I will not refer to this hypothesis further as it is in relatively good shape and has been adequately reviewed in a series of reports.[2-7] We desperately needed a treatment for schizophrenia. Our hypothesis led to the conclusion that large doses (three grams per day) of vitamin B_3, niacin or niacinamide, might be helpful in reversing the reaction that produced excess adrenochrome. In 1951, I obtained fifty pounds of pure niacin and fifty pounds of pure niacinamide from Merck and Co., and our hospital pharmacist made it up into 500 mg capsules. The largest dosage in commercial tablets was 100 mg but the fillers in these tablets, given 30 daily, would have made our patients sick. A mental hospital in southern California made a halfhearted attempt to try niacin but was not allowed to use anything stronger than 100 mg. Patients became sick on the 30 tablets daily. Before we could start our pilot trials I had to know something about its toxicity. As I suspected, niacin was non-toxic, but did have some undesirable effects and would have to be used knowing these potential side effects; the same of course applies to food and water.

Niacin and niacinamide were available over the counter in very small doses, the usual vitamin doses. It had been given in large doses to some patients with chronic pellagra. Acute pellagra patients responded very quickly to these small vitamin doses but chronic patients often needed up to 600 mg daily. Over sixty years ago, during the height of the great depression, this dose of pure niacin was very high and was not encouraged. The literature did not contain very much material about toxicity, chiefly because it was considered safe by all the established medical associations who commented on it. Merck prepared comprehensive bulletins outlining its properties. When we started in 1951, only one physician had given the doses we were going to use, (three grams per day). Dr. William Kaufman began to use niacinamide in 1945 for treating diseases of aging including the arthritides. He gave 500 mg four times daily but I did not know this until 1957. We were the second group to go above 600 mg daily. We did that because it had been used in much smaller doses for treating patients with depression. A small proportion responded but most did not. We assumed that had it been therapeutic in lower doses for schizophrenia this would have been reported, and our hypothesis called for enough niacin to absorb methyl groups and thus to decrease the formation of adrenalin and therefore of adrenochrome.

Our first pilot studies were successful. The first three patients I treated at the General Hospital in Regina and the first eight patients Dr. Osmond treated at the Saskatchewan Hospital in Weyburn all responded. This was exciting but we did not consider it proof, and therefore we started the first of six prospective, randomized, double-blind controlled, therapeutic trials. These became the basis for orthomolecular psychiatry. Since then over 50 reports which followed our original protocols have corroborated our findings. A few reports did not corroborate, but neither did they treat the same kind of patients. We used patients early in their diagnoses.

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Very chronic patients did not respond. Later we discovered that chronic patients will respond, but it will take much more time and much more patience. Most of these corroborative papers were published in this journal beginning about 30 years ago.

Factors that Determine Toxicity and Side Effects

The dose is a main factor in determining side effects and toxicity. With all substances, toxicity and side effects increase as the dose increases. The difference between the toxic dose, as defined by animal studies, and the optimum therapeutic dose is called the therapeutic range. With vitamins the therapeutic range is very high as the toxic dose is so large. With drugs the therapeutic dose range is much narrower. This is why one should always use the lowest possible effective dose. Any factor that allows one to decrease the effective dose will decrease the toxicity. An example is the effect of anti-psychotic drugs in inducing tardive dyskinesia. This was common with the early anti-psychotics and still is present, even if to a lesser degree, with modern atypical drugs. When niacin or niacinamide is also used the dose of the drugs can be reduced markedly and this decreases the tendency to develop tardive dyskinesia. Many years ago David Hawkins[8] surveyed a number of orthomolecular psychiatrists who between them had at that time treated about 58,000 patients. There were no cases of tardive dyskinesia among them. If every psychiatrist had used the same approach there would have been no reason to search for the new drugs, except of course that the patents on the older drugs had expired. I have had several patients already displaying tardive dyskinesia at their first visit but have not seen any develop this condition after starting on an orthomolecular program.

Vitamins-as-Prevention Paradigm

The optimum dose range varies from a few mg daily to many grams daily. It ranges from the usual small vitamin doses as defined by the vitamins-as-prevention paradigm to the large or mega-dose level as called for by the vitamin-as-treatment paradigm. The term mega-doses has no scientific meaning and should not be used. The first paradigm is the logical outcome of the search for vitamins which began over 100 years ago with the first one, the anti beri beri vitamin, thiamin. The usual pattern of discovery followed the observation that certain diets made people sick. Japanese sailors given polished rice as their main staple food became sick with beri beri, but on whole grain brown rice this did not happen. This led to the discovery of thiamin. Later the active fraction was isolated and after that the active compounds were synthesized and they became known as vitamins, vital amines, even though later it was found that they are not all amines.

Once the pure vitamins became available large-scale clinical trials were possible, but because these substances were present in such small concentrations, it appeared obvious that they were always required only in small quantities. This became part of the definition of vitamins: that they are chemicals needed in tiny amounts to catalyze reactions in the body and their function was to prevent the deficiency diseases from appearing. Thus, thiamin in food prevents beri beri, vitamin C prevents scurvy, vitamin B_3 prevents pellagra, vitamin D prevents rickets, and so on. Niacin should be classified with the amino acids since it is made in the body from tryptophan and by definition vitamins cannot be made in the body; this was not known for a while and long usage has placed it in the vitamin camp. If it were thought of as an amino acid the large doses so effective in many diseases would be easier to understand. According to the vitamin definition, once the diet contains enough of those substances to prevent the classical deficiency diseases there is no need to give more.

These ideas became the vitamin-as-prevention paradigm, which still holds sway and is defended with relentless vigour. Doctors have lost their licenses to practise because they did not obey these principles. This concept, apparently written in stone, declares that vitamins are needed only in very small doses to prevent deficiency disease. It follows that giving more is useless and even harmful and that giving even small amounts to patients who do not have any deficiency diseases is also not indicated and potentially harmful. The preventive dose ranges in this concept are very narrow even though toxicity does not appear. Doses range from zero, i.e. to depend only on what is present in food, to the recommended daily doses established by government agencies. Those dose ranges only apply to populations of healthy people. They do not include populations under stress, pregnant women, or people who are sick. The recommended doses are not applicable to at least half of any population, yet they are still applied firmly. The recent FSA recommendations (see Editorial p.123) reflect perfectly the vitamin-as-prevention paradigm.

Paradigms, or articles of faith, or systems of thought are not easily dislodged. They are usually changed by evolution or revolution. In medicine it has taken over 40 years before major new ideas were accepted. This applies to concepts which are now part of the modern paradigm such as washing one's hands, using a stethoscope, using electrocardiograms, doing heart catheterizations or using antibiotics. They do change because with continuing investigation the old concepts fail to account for new observations. This is now occurring with the vitamin-as-prevention paradigm. The seeds of doubt were planted by the work of the Shute[9] brothers who reported that large doses of vitamin E were useful in treating heart disease, with the work of Kaufman[19] in treating arthritis with niacinamide, and our work in using niacin and niacinamide in treating schizophrenia.[10] We all broke the cardinal rules because we used very large doses of vitamins to treat conditions that were not considered vitamin deficiency diseases. Shutes' and Kaufman's work had little impact; it was ignored. The first major break in the vitamins-as-prevention armor was our discovery that niacin in large doses lowered cholesterol levels. We used very large, called mega doses, for a condition everyone knew was not a vitamin deficiency disease. This was easy to confirm, but even then it took many favorable confirmatory reports and several decades before niacin became acceptable as the best compound available for lowering cholesterol levels. Our work is considered the first major onslaught against the vitamin-as-prevention paradigm. We need much more.

Vitamins-as-Treatment Paradigm

This modern paradigm was given a tremendous boost by the report by Bruce Ames, Elson-Schwab and Silver.[11] Following Pauling's[12] seminal report, it provides the explanation of why so many patients do need large doses. Vitamins are converted into coenzymes, which combine with enzymes to carry on essential metabolic functions. If the ability of the enzyme to combine with its coenzyme is impaired, increasing the amount of vitamin will increase the amount of coenzyme, thus overcoming the defect and increasing the reaction toward normal. About 50 genetic diseases affecting vitamin metabolism are already known, perhaps 10% of what may eventually be discovered. It is another blow to the original vitamins-as-prevention paradigm and powerful support for the modern paradigm. The basic concepts of the vitamins-as-treatment paradigm are that optimum doses, which may be large or small, may be therapeutic, very helpful, for diseases that are not classical deficiency diseases.

The optimum dose range for the modern paradigm varies with the disease being

treated, but often has to be determined by the response of the individual. Thus, the dose range for lowering cholesterol is 1 to 9 grams daily in three divided doses. The usual dose for treating schizophrenia is about the same, but a few may need much more. The optimum dose can be determined by the dose that causes nausea - the optimum dose is below the nauseant dose. For vitamin C the dose ranges enormously, from a few grams to 100 grams taken orally. For cancer, my patients take between 12 and 40 grams daily. The higher doses are probably best reserved for intravenous administration. The laxative effect level determines the optimum oral doses. If the dose causes loose stools, dosage should be decreased to below that level. We need a therapeutic dose range for every disease. This will be much higher than the usual vitamin dose range. There are no toxic doses since vitamins do not kill, but the higher the dose, the more apt will be the development of side effects.

Vitamin B_3 Dependency and Deficiency

Conditions that require large doses of vitamins are due to genetic errors, due to the disease causing the suffering, or have been created by prolonged severe malnutrition and stress. Niacin was shown to be vitamin B_3 in the mid 1930s. Early pellagrologists were able to study it as soon as they were able to obtain some. They reported that early cases of pellagra improved on the usual tiny vitamin doses, but that if they had been sick for a long time they would not; some needed 600 milligrams daily, an enormous dose at that time. They also found that dogs with black tongue (pellagra), kept on the diet that made them sick, recovered given tiny vitamin doses, but if they were left on the deficient diet too long they would thereafter need very much larger doses. It is clear that prolonged deficiency of vitamin B_3 created a need for a lot more. This is called a vitamin dependency. Whatever happened, those patients could no longer be well with the small vitamin doses. A vitamin deficiency disease is one in which the disease is present because the diet is so poor. On a good diet they would be well. But if they need much more, an amount that no diet can ever provide, they have a dependency.

The response to vitamins depends on the relative condition of the patients. A person with pellagra is severely deficient. They respond to very small amounts rather quickly. I suspect that all patients still in the deficiency area will also respond quickly. However, once they have been moved into the dependency area the response will be slower and less dramatic. People kept in concentration camps in Europe or in the Far East were subjected to absolutely horrible and severe physical, psychological and nutritional stress. I shudder to think about all the populations today who are exposed to prolonged malnutrition, disease and psychological stress. There will be a massive increase in very sick people, who will be vitamin B_3 dependent and will be helped by their physicians or governments if they see that they get enough of this important vitamin, perhaps by enriching their flour and/or rice above the modern standards of enrichment.

In the scientific debate that occurs when one paradigm is in the process of replacing an older one, each side uses the weapons at hand. If one side does not like the concept of using large doses, they may maintain that these doses are harmful, in spite of vast evidence that they are not. If one does not like the concept of using vitamins for conditions that are not deficiency diseases, they will deny that they are effective and/or will declare that even if they may be effective, they are toxic. The modern assault on the new paradigm maintains that they are not effective, not needed in large doses, and that they are dangerous.

Negative Side Effects

The word toxic does not really apply to vitamin B_3 any more than it does when applied to most of the common substances

we use, such as food and water. Nor should the word be used with out specifying what is the toxic dose range. To say that something is toxic is meaningless, since theoretically everything is toxic if the dose is pushed high enough. Therapeutic substances, theoretically should be free of negative side effects at dose levels that are therapeutic. The lethal quality of the compound, i.e. how much will it take to kill the subject, is first determined. The LD 50 is that amount of compound which, over a period of time, will kill half the animals being tested. If this number is high, one can proceed to the next step–to determine whether the substance is therapeutic; if the number is very low, the substance will never become therapeutic. The LD 50 of niacin when tested on dogs was about 5 grams per kilogram body weight. This would be about 350 grams, more than one half a pound, for a 70-kilogram adult. The real LD 50 for people is not known since no one would run the test, and so far no one has died from a high dose of vitamin B_3. One of my patients, a 16-year-old schizophrenic girl, swallowed the whole bottle of niacin pills I had given her, all at once. She took 200 tablets of the 500-milligram size because she was angry with her mother. For the next three days she complained of a stomach ache. Another patient, not mine, increased her dose until she was taking 60 grams daily. At that level her auditory hallucinations (voices) ceased. Eventually she was maintained on 3 grams. No one has ever committed suicide with vitamin B_3.

Another way to determine toxicity is to compare the toxic effect of the substance against the toxic effect of the disease being treated. One of the most toxic drugs is insulin given by injection. A slight overdose can kill by driving the blood sugar down to near zero. Yet it is used safely by millions of patients, and they will continue to use it as the consequences of not taking insulin are so much worse. In the same way all the modern drugs used in treating schizophrenia are very toxic, but the condition being treated is more serious; therefore these drugs are tolerated.

Toxicity or negative side effects can never be considered in the absence of the therapeutic value of the substances. If there is no therapeutic value it will never be used, whether it is toxic or not. If the therapeutic value is great, as for example in the use of insulin for treating diabetes mellitus, even toxic compounds will be used. Doctors are taught how to deal with toxic substances and only they are permitted to prescribe these to their patients. If doctors think a substance has no therapeutic value they will argue that even the remotest degree of toxicity is too much and that substance cannot be used. If they consider that it is valuable, even the greatest degree of toxicity will be tolerated. Thus, the consensus among the psychiatric profession is that vitamins are of no value in the treatment of schizophrenia, therefore they search assiduously for evidence of toxicity and often, when they cannot find any evidence, it is hypothesized or grossly exaggerated. If they consider a drug very valuable, its toxicity is minimized. An example is the drug, Clozapine, which is very dangerous and has caused death, but if used carefully will be tolerated. Another example is Olanzapine, which can cause tremendous weight gain and increases the odds of getting diabetes mellitus but is tolerated. A clinical example is a patient I once saw who was getting on very well with one of the older drugs. Her psychiatrist wanted to experiment with a new one, but on the new one she gained 60 pounds in a few months and this destroyed her life, her self-image. She pleaded with him to change her medication back and he bluntly told her it was better to be fat than schizophrenic. In fact she was still schizophrenic, but he had given her no choice. Niacin does not cause weight gain, but he would not use niacin, perhaps because he considered it too toxic. Thus, in the discussion of toxicity of vitamins some

information must given about their value in treating many conditions.

A good way of comparing toxicity is to count the number of pages in any pharmaceutical compendium for each compound listed. One could count the number of pages listed for therapy and for all the adverse side effects and warnings. Both niacin and Zyprexa are used for treating schizophrenic patients, and niacin and Lipitor are used to bring down blood cholesterol levels. Here is how these three substances compare. (Figure 1, below)

Drugs are described very carefully and the companies that own the patents them vet these descriptions very carefully in order to make sure they are properly described. However, there are no companies that provide the same editorial care for the write-ups of the vitamins, as they are not patented. Over the years I found that these nutrient descriptions tend to be lax and not accurate, usually erring on the side of making them appear more toxic and less useful than is warranted. For many years after niacin was generally recognized as one of the best compounds for lowering cholesterol levels in blood, this was not indicated in the Compendium description.

Each page of the Compendium contains three columns of 80 lines each. The side effects of niacin listed are:
Gastrointestinal: nausea, vomiting, bloating and flatulence;
Blood pressure: hypotension.
Skin: hyperpigmentation, dry, and urticaria.
Blood constituent values: elevated glucose, elevated uric acid.
Liver: elevated liver function test results, pathology.

Merck Manual, 16th Edition 1992, lists the following contraindications for niacin: hepatic dysfunction, active peptic ulcer, diabetes mellitus, severe hypotension, arterial hemorrhage and hyperuricemia. It discusses briefly the toxicity of vitamin D and vitamin K. None of the other vitamins are discussed.

Many patients given a prescription for a drug will read the information on the medication information sheet that is available and will decide not to take the drug. This has not happened with niacin.

The toxic effects of drugs are potentially much more serious than the side effects of vitamins. There have been no deaths from vitamins in 25 years compared to about 110,000 deaths yearly in the United States from the proper use of drugs in hospitals. That is the real comparison of the relative toxic effects of drugs and vitamins.

Finally, one must recognize that very safe compounds may causes idiosyncratic

Figure 1. Comparison of Side Effects of Niacin, Lipitor and Zyprexa.*

	Niacin	Lipitor	Zyprexa
Total pages	<1	2	3
Indications	6 lines	96 lines	6 lines
Contraindications	5 lines	3 lines	2 lines
Precautions & Warnings	12 lines	240 lines	240 lines
Drug interactions	17 lines	–	–
Adverse effects	25 lines	49 lines	240 lines

*taken from the Compendium of Pharmaceuticals and Specialties, Canada 2003

reactions in a very few patients and cause serous side effect. Even the filler in some tablets may cause these reactions. If peanut oil got into a pill taken by a peanut-sensitive patient, it might cause death.

Positive Side Effects

A positive side effect is any reaction that improves the health of any individual when taking a compound for another purpose. Thus, if a patient taking niacin to lower cholesterol levels also finds a decrease in the pain from his arthritis, this is a positive side effect, because the arthritis was not the indication for taking the niacin. I recommended to a colleague that he give niacin to one of his patients because he was concerned about fat deposits (lipomas) in his skin. I suggested that this would remove them, which it did. In addition, this patient had been paranoid and that symptom also vanished; this is a positive side effect. The main action of the niacin flush is to increase blood circulation to the tissues, including the brain. Many of my patients complain of what they call brain fog. I do not know anything more effective in removing this brain fog than niacin. I consider this as evidence for improved circulation of blood to the brain.

Drugs usually are targeted to do one thing, to be used for one indication. Therefore drugs to lower cholesterol levels do that and little more. Vitamins are involved in so many different reactions in the body that they have multiple positive side effects. For most patients they produce a feeling of well being not usually associated with drugs. Vitamins improve energy production and increase the rate of healing. Niacin's vasodilatation properties are very valuable. For many patients the flushing form is much better than the non-flush or slow release preparations. In some patients with diseases such as chronic fatigue syndrome or multiple sclerosis, the red blood cells are too large[13] and have difficulty traversing the capillaries. Increasing the lumen of these vessels permits more blood to flow through the capillaries and thus oxygenates the tissues more efficiently. In addition, it disperses aggregated red blood cells, called sludging, according to Ed Boyle (personal communication). Finally many patients, especially those with arthritis, like the flush and will often take a niacin "holiday" for a few days in order to reactivate the flush.

Here are a few positive side effects: (1) a feeling of well-being and improved energy, do not need as much sleep and rest; (2) longer life;[14] (3) relief from arthritic pain;[15] if the indication is arthritis this will no longer be a side-effect; (4) slows down aging process.[16] McCracken[17] provides a more complete list of positive side effects.

The important therapeutic effect of niacin on blood lipid levels is one of its most important side effects because it was discovered as a result of studying niacin to treat schizophrenic patients. This arose from the collegial relationship I had with Rudl Altschul, Professor of Anatomy, University of Saskatchewan Medical School, in Saskatoon. He had also been my teacher in histology. He was exploring the connection between arteriosclerosis and diet using cooked egg yoke to elevate cholesterol levels in his rabbits and using ultraviolet radiation to decrease it. I had observed that my gums, which had been bleeding for a long time in spite of good dental care, stopped bleeding two weeks after I had started to take niacin. I was taking it because I wanted to experience the flush so I would understand better what patients would experience. I had hypothesized that the niacin had improved the ability of my gums to repair themselves after the trauma of chewing with mal-occluded teeth. Altschul believed that rate of repair of the intima, the inner lining of blood vessels, was a key factor in the pathology of arteriosclerosis. As soon as I heard that I made the association between the rate of repair of my gums and rate of repair of the intima in arteries. I suggested that he try niacin.

Altschul did not know anything about niacin, so I described it and gave him a pound of pure niacin. A few months later he called me. He had given niacin to his rabbits and their cholesterol levels promptly went back to normal. We then collaborated on a human study and found that niacin, even after a few days, was very effective.[18] Since then it has become the gold standard for lowering cholesterol because it does even more. It lowers tryglycerides, elevates HDL and lowers lipoprotein(a). Of course if the indication for niacin use is high blood cholesterol levels, then this beneficial effect is not a side effect, it is the main effect. Niacin was the first vitamin to be released by the FDA to be used in large doses. They would have to consider niacin's effect on schizophrenia, if they ever believe this, is a positive side effect.

The excessive weight gain in schizophrenic patients given Olanzapine is one of the major toxic side effects.[19] This anti psychotic markedly increases serum leptin and triglycerides in schizophrenic patients.[20] Leptin increases appetite, driving these patients to eat too much, especially of the carbohydrates. The elevated triglycerides are very dangerous, increasing the risk of heart disease. Niacin is one of the best compounds for lowering triglycerides levels. This may be considered another positive side effect. Perhaps if Olanzapine is to be saved as a useful anti-psychotic it will have to be combined with niacin. The therapeutic effect on schizophrenic patients will of course be very much better, since niacin is a major anti-psychotic and not as much Olanzapine will be needed.

I will discuss the side-effects in the order in which we had to meet them as our therapeutic trials continued.

Vasodilatation and the Niacin Flush

Niacin is a potent vasodilator, but not a very good one for chronic use since the body adapts to it and the flush eventually ceases or occurs only intermittently. No one should ever take niacin without knowing about this flush because the reaction can be very dramatic and frightening. In Detroit, one of my colleges forgot to warn his patient. This patient took the niacin, flushed, and in fear called the closest poison control center. The person who took the call probably had never heard of it, advised the patient that he had taken a lethal dose and sent the ambulance for him. By the time he arrived at the hospital he was feeling fine. The flush usually starts in the anterior part of the body, in one's forehead, and moves posterially. It first appears as a reddening in the forehead and then slowly or quickly travels down the body, occasionally involving even the toes, but usually only travels as far as the abdomen. The skin is red, itchy, and the patient feels warm but there is no sweating. If the reaction comes on very quickly, the person may feel faint and a few subjects have fainted. One subject who fainted was given the pills by her friend or neighbor and was not told about the flush. The anxiety and fear probably aggravated this reaction. The flush may last up to three hours. The first flush is the most striking and after that with each dose there is less and less, and in most people it is minor or gone in a few weeks. A few never get adjusted to it and of course they will be able to take very small amounts or may have to use the non-flushing forms of niacin.

Factors in the Flush Intensity

1) The amount of niacin taken in one dose. There will be very little flush with 50 mg or less, while most patients will flush with 100 mg or more. The relationship is not linear. There is a threshold effect and the flush does not appear until that threshold is reached. This can be used to introduce niacin gradually. I also use it to decrease the reactivity of patients with severe allergies. I start with 25 mg after each meal, at the same time giving 1 g of vitamin C. As the flush moderates, the dose is very slowly increased by 25 mg per week. The niacin

releases histamine, which is partially responsible for the flush, and the ascorbic acid destroys the histamine dumped into the blood. In this way it is possible to increase the dose to its full therapeutic value.

(2) The amount of food in one's stomach and whether taken with a hot drink or cold drink. The rate of absorption is important and heat accelerates this. Taken right after a meal the flush is minimal; taken on an empty stomach it is maximal. The greatest flush is experienced when it is injected intravenously. I suspect that dissolved in hot tea and swallowed immediately on empty stomach niacin would produce the kind of flush seen after IV administration.

(3) Time elapsed between dosages. Most patients tend to flush more in the morning after their first daily dose because they have gone all night without taking any. This can often be remedied by taking the last dose just before bed.

(4) Aspirin. An aspirin tablet taken once a day, beginning two days before starting on niacin, can minimize the flush. Once the first flush has occurred, aspirin is no longer needed, as niacin itself is the best anti-flush preparation if it is taken regularly. Some anti-histamines can also minimize the flush and the early tranquilizers such as chlorpromazine were very effective in preventing excessive flushing. Schizophrenic patients flush much less than do patients who are not schizophrenic or have other diseases. David Horrobin[21] developed this into a diagnostic test. It is based upon the observations I reported in 1962 that schizophrenic patients are usually less disturbed by the flush. A patch with four pockets each containing different amounts of methyl nicotinate is applied to the forearm, left on for five minutes and then stripped off. In most schizophrenic patients the areas in contact with the nicotinate do not turn red. There is very little overlap.[22] Many schizophrenic patients do not flush after starting to take 3 grams of niacin daily. This inability to flush may well be related to their disease, as an appreciable number of schizophrenic patients begin to flush after several years of medication. This is a good prognostic sign and usually coincides with complete recovery.[23]

(5) Age. Usually patients over age 50 flush less than young people do.

(6) Skin color. Dark skinned people will flush less but the reaction may be just as uncomfortable. Patients who tan very poorly may have more severe reactions.

(7) Patients' need for the vitamin. I have observed that patients who need it the most, such as patients with high blood cholesterol levels, or patients with arthritis or schizophrenia, flush much less than other patients.

(8) Motivation. Patients motivated by the disease that they have and the explanation given to them by their doctors find the flush much more tolerable.

(9) Physicians' comfort with niacin. Parsons[24] in his excellent book makes the point that physicians must know niacin before they work with it. For many patients, the flushing form is much better than the non-flush or slow release preparations, particularly patients with the chronic diseases such as chronic fatigue syndrome and multiple sclerosis, as mentioned earlier, and many patients do like the flush.

Mechanism of the Flush

The niacin flush may be due to the release of histamine and/or interference with prostaglandins. The niacin induced flush is very similar to the flush induced by the injection of histamine, with one major exception: histamine injections will lower blood pressure below normal levels while the niacin flush does not, with few exceptions.

Recently a colleague with high blood pressure discovered that if he took a flushing dose of niacin his blood pressure would fall markedly and then would start to go up again so that in three days it would be high again. Then he would repeat the procedure.

If then he had another flush it would go down again. The amount of decrease is related to the intensity of the flush. He has been doing this for several months. When he took the niacin regularly the blood pressure went back up to its initial high level and remained there.

Dr. Ed Boyle observed many years ago that the vesicles storing histamine in the mast blood cells were emptied after taking niacin. He also found that guinea pigs pretreated with niacin for one week did not die from anaphylactic shock. I have used it for many patients for many years to decrease the response to foods and insect bites in combination with ascorbic acid to destroy the histamine released into the blood stream.

Horrobin postulated that the vasodilation was related to prostaglandin D2. He assumed that this was due to reduced membrane arachidonic acid levels in schizophrenics. Aspirin decreases the intensity of the flush, again pointing to the prostaglandins. I think it is most likely that both histamine and the prostaglandins are involved.

Gastrointestinal Side Effects: Nausea, Vomiting, Pain from Peptic Ulcer

In 1962, I reported that occasionally niacin caused nausea and vomiting. This reaction is dose related. Everyone will react if the dose taken is high enough and this level varies from 3 to up to 30 grams daily. I use this nauseant dose as an indicator of how much is needed. Patients who respond best include schizophrenic patients, patients with elevated cholesterol levels and arthritics. Elderly patients and these patients can usually tolerate much more than younger patients. Niacinamide also has a narrower threshold level than niacin. If the tolerance level is too low, I use a combination of both. If the tolerance level is 1.5 g daily for each, using them both will provide the patient with 3 g without nausea. Nausea must be dealt with immediately as it may lead to vomiting. Most patients will stop taking their medication when they develop nausea but a few are very determined and will not. In one study, reputed to be replicating our treatment, the dose of niacin was set at 8 grams daily. Not only were the wrong patients used, as they were all chronic and the study was to determine the effect on early cases, but the dose was too high. Many of these patients were very nauseated, but the protocol was followed regardless. I cannot imagine patients getting better when they are continually nauseated.

Children may not complain of nausea but will lose their appetite. When that happens, one should suspect that they are nauseated and stop the niacin or decrease the dose. If vomiting is not stopped it will of course lead to dehydration. Niacin increases the secretion of hydrochloric acid, but this is not the explanation since niacinamide also causes nausea when the dose is too high and it has no effect on HCl secretion. It must be due to some central effect. Inositol hexanicotinate does not cause nausea and the slow-release preparations seldom do.

When I first began to use niacin I recommended that it not be given to patients with peptic ulcer. Parsons also avoided giving it to peptic ulcer patients, but as he became more familiar with it realized that it could be given safely to people with ulcers. It must be given after meals, with food in the stomach. The Coronary Drug Project[14] found that 13.9% of the niacin patients complained of stomach pain compared to 7.9% of the placebo group. Nausea was found in 8.5% compared to 6.2% and decreased appetite was 4.1% compared to 1.5% for the placebo group.

Parsons has been using niacin to lower cholesterol levels since 1955. He was the first physician outside of Canada to become interested and has retained his interest. His book is a must-read. His description of niacin and the gastrointestinal system is excellent. After reviewing the few reports about the effect of niacin on peptic ulcers he wrote, “To me the most significant fact

is that my 37 years of further experience (since my 1960 paper) and the Coronary Drug Project experience failed to demonstrate any cases in which the drug activated peptic ulcer. My 1960 report regarding activation of peptic ulcers by niacin was wrong."

Niacinamide can also cause nausea and vomiting and it is apt to be present at lower doses than is the case with niacin.

Effect of Niacin on Liver Function Tests

In 1950, the disease of that year was that produced by methyl deficiency. This caused fatty livers in animals. Niacin and niacinamide combine with methyl groups and are two of the few methyl acceptors. Thus it made sense to think that a large dose of this vitamin would cause a methyl deficiency. Another methyl acceptor is noradrenalin; methylation of noradrenalin produces adrenalin. We hoped to decrease the production of adrenochrome by inhibiting the product of adrenalin from noradrenalin. This was one of many factors that pointed in the direction of this vitamin in the treatment of schizophrenia. But we were concerned about the possible danger of producing fatty livers. In 1942, a study on animals suggested that niacin did injure the liver. Altschul repeated this animal study and, on the contrary, found no evidence of any liver toxicity; their livers were normal when examined histologically and chemically. We tested a small series of patients being treated with niacin and again found no evidence of liver damage. Rarely a patient would develop an obstructive jaundice. I would routinely stop the niacin until the jaundice cleared because of the possibility of a reaction. One of my patients became very psychotic again and I resumed the niacin but his jaundice did not recur. The incidence of jaundice was very rare and I have seen no cases in the past 20 years.

However, when the modern liver function tests came into use some of the patients on niacin and niacinamide showed elevated liver function tests. Most physicians assumed that this indicated underlying liver pathology and warned against the use of niacin. Parsons was also concerned but eventually, with his long and extensive experience with niacin, concluded that elevated liver function tests did not mean that there was underlying liver pathology. He concluded that niacin is not liver toxic. His opinion was reinforced by the results of the Coronary Drug Project conducted between 1966 and 1974. This followed 1,100 men receiving niacin for five to eight years. The lead investigator, Dr. Paul Canner, told Parsons that there were no abnormalities that could be attributed to niacin. Parsons concluded that the elevated tests were not evidence of liver pathology and that they indicated an abnormality only if the liver function tests were elevated two to three times the upper limit: "Minor elevations in enzyme tests reflecting liver function are a normal part of niacin therapy and are not a reason to discontinue treatment." Elevated tests will return to normal in patients while they are still taking niacin, however Parsons pointed out that the slow release preparations were much more apt to increase liver function tests. Nevertheless I do not give this vitamin in large doses to anyone with hepatitis, not because I think it will be harmful but because I know the niacin will be blamed even if it is not responsible if something does happen.

Capuzzi[25] has been studying niacin for several decades. He found that giving patients lecithin, 1.2 grams twice daily, prevents any elevations of liver function tests. McCarty[26] suggested that high demand for methyl groups created by niacin could reduce levels of S-adenosylmethionine, which could lead to an increase in production of homocysteine. This, he suggested, could be avoided by using betaine supplements with the niacin. But lecithin is much cheaper and more readily available. Both lecithin and betaine are methyl donors.

The effect of niacinamide on liver function tests has not been studied.

Effect of Niacin on Carbohydrate Metabolism

Before 1960, I found that in a few patients niacin increased the glucose tolerance. In one-third of the diabetic patients it increased the need for insulin slightly, in one-third there was no change and in the last one-third the need for insulin was decreased. Siblings of diabetics were more apt to show abnormal glucose tolerance tests. Parsons found no difficulty in using niacin in diabetics taking oral hypoglycemics, but recommended against giving it to patients with diabetes type one. I have given it to type one diabetics in order to lower cholesterol levels and to protect them against the sequelae of diabetes and it has been very effective. Elam et al.[29] concluded, "lipid modifying dosages of niacin can be safely used in patients with diabetes and niacin therapy may be considered as an alternative to statin drugs or fibrates for patients with diabetes in whom these agents are not tolerated or fail to sufficiently correct hypertriglyceridemia or low HDL-C levels".

Effect of Niacin on Gout

Parsons found that niacin increased blood uric acid levels slightly but concluded that this should not interfere with niacin therapy. In the Coronary Drug Project the average blood uric acid levels before entering the project was 6.75 and after five years on niacin 6.80. Men on niacin had uric acid levels above 8.0. However, this was insignificant because there was no increase in any of the symptoms of gout including increase in uric acid stones or acute gouty arthritis. This has been my conclusion as well. I do not consider niacin as a risk factor for gout. My father-in-law suffered from both arthritis and gout and they were independent of each other. While taking niacin his arthritis disappeared but he continued to suffer recurrent short episodes of gout in the same pattern as before. Niacin neither increased nor decreased these episodes.

The slight increase in blood uric acid levels may be a positive side effect. According to McCracken, uric acid is a central stimulant and that the increase in uric acid activity, a genetic change about 20 million years ago, was beneficial for this reason. College professors were found to have higher blood uric acid levels than their equivalent non-college controls. Uric acid is also an antioxidant and this is, of course, very helpful. Thus the threat of gout should not deter anyone from using niacin if they need it. If gout does develop it is very readily treated.

Effect of Niacin on Skin

There are three negative side effects in the skin and two positive side effects. The side effects are generalized skin dryness, which Parsons suggests is due to the decreased cholesterol levels, a non-specific rash which is rare, and increased pigmentation. The first side effect is seldom a problem. I think that adding omega three essential fatty acids present in flax seed, in flax seed oil and in fish oils (not the liver oils) will help remove this dryness. The non-specific rash may lead to scratching and if it remains a problem the niacin will have to be stopped.

The third side effect is never a problem except to patients whose doctors are not familiar with it and make them fearful by suggesting that it is dangerous. It consists of an increased brown or dark pigmentation of the skin usually in the flexor surfaces of the body as in the armpits. This is more common in schizophrenic patients but can occur to a slight degree in anyone. It has been erroneously called acanthosis nigricans, which is dangerous, but it is not this condition. Parsons called it a skin change which resembles acanthosis nigricans. It does resemble it but only in color not in pathology. Usually after awhile the dark skin wears away as does an old tan. It can be rubbed off when the skin is wet and leaves healthy skin behind. I think it is due to the accumulation

of melanin pigments, which the body is excreting via the skin. Skin is one of the major excretory organs.

One of my patients turned almost black and it was very embarrassing, but after awhile it disappeared completely. I saw the same pigments in one of my schizophrenic patients. All the nails on her fingers and toes became dirty brown. After being on niacin for many months the pigment deposition ceased and her nails grew out clean. It was the first time I saw the schizophrenic pigment, perhaps from adrenochrome. This female patient had been catatonic and mute, but three months after her nails began to grow clean she began to talk again. This pigmentation can also occur in many patients and normal people on niacin who are not schizophrenic, and it has no diagnostic value. Once it has cleared it never comes back.

Another very positive side effect of niacin is that it clears xanthoma tuberosum. These are due to deposits of cholesterol in patients with high blood cholesterol. They never recur as long as the patients remain on the niacin. Xanthoma tendinosum, cholesterol deposits in the tendons and xanthelasmata, deposits in the eyelids, also clear slowly on niacin therapy.

Niacin has a remarkable effect on the health of the skin. My skin at 85 years of age is normal. A fold of skin when pulled from the back of my hand will return to normal in 3 seconds. Most people over age 60 require much more time before this happens.

Atrial Fibrillation

There was a slight increase in atrial fibrillation reported in the Coronary Drug Project study. It was diagnosed in 4.7% in the niacin group and in 2.9% in the placebo group. Parsons pointed out that since these patients had already had one or more heart attacks before entering the study, the elevated level in the niacin group is not surprising. Again I agree. I have given niacin to several thousand patients since 1955 and I cannot recall anyone that had any atrial fibrillation.

Homocysteine (Hcy)

Elevated homocysteine levels are associated with increased risk of ischemic heart disease (IHD) and stroke.[30] But according to this study these elevated levels are at most a modest independent predictor of IHD and stroke in healthy populations. Garg et al[31] found that niacin increased homocysteine levels about 55% in a series of 52 patients given 3 grams of niacin daily. These two sets of findings have suggested that niacin might also increase this risk. However I cannot take this very seriously since the Coronary Drug Project showed that niacin decreased mortality 11% and increased longevity nearly two years in a large group of men already having suffered one stroke. Even if there is a small risk that niacin will increase the risk for IHD and stroke, how will this ever be established in view of the large scale Coronary Drug Project? Assuming that there is a risk, it is easily removed by having each patient take a B-complex tablet containing pyridoxine, folic acid and vitamin B_{12}. Parsons wrote: "I always advise my patients not to lose any sleep over this. We are a long way from establishing that reducing homocysteine will reduce coronary events or other artery troubles so homocysteine shouldn't yet be considered a correctable risk factor. I would not want something they might read about Hcy to distract anyone from concentrating on controlling the established risk factors: smoking, high blood pressure, abnormal cholesterol profile, diabetes, obesity and lack of exercise." It is interesting that even though niacin elevates homocysteine levels the negative risk effect of elevated homocysteine does not come into play; the effect in lowering cholesterol and in elevating HDL cholesterol compensates for this. Another factor is that niacin modifies abnormal co-

agulation factors that accompany peripheral arterial disease (PAD). Patients with PAD have high rates of cardiovascular pathology and morbidity.[32]

Vitamin B_3 and Cancer

Oncologists are generally opposed to their patients taking vitamins during chemotherapy or radiation. This is based upon conjecture, not upon data. Vitamin B_3 may be very important in preventing radiation and chemotherapy induced cancers, Kirkland and Spronck.[33] Chemotherapy causes DNA damage in bone marrow and it is more severe in niacin-deficient rats. This brings on new treatment related cancers such as leukemia and cancer of the bone marrow. Patients undergoing chemotherapy are 10 to 100 times more likely to develop such cancers, and 3 to 10 times more likely than cancer patients undergoing radiation. Niacin deficiency leads to chromosomal instability. Pellagra is not common anymore in developed nations, but many people still suffer from sub-clinical deficiency, including women and the elderly. About 40% of cancer patients are deficient in niacin. Kirkland and Spronck suggest that these deficiencies increase the risk of developing secondary treatment-related cancers. Skin cancer also may be invoked. In animals, skin cancer is highly influenced by niacin status. Professor James Kirkland, Department of Human Biology and Nutritional Sciences, University of Guelph, Ontario, released a press statement March 25, 2003, with the lead sentence, "Extra niacin could help prevent treatment related cancers, study finds."

Other Negative Side Effects

Other side effects have been reported but they are so rare it is impossible to draw any conclusions. As with any chemical idiosyncrasies, allergenic reactions to either the active tablet ingredient or to the fillers are possible. The best advice is for patients who start or have been on niacin to tell their doctor as soon as they note any adverse side effect.

Conclusion

Niacin and niacinamide are both important therapeutic compounds with a very wide range of activity including lowering cholesterol, treating arthritis, decreasing the ravages of aging, and treating schizophrenia. They have no toxic effects and must be considered non-toxic; they have very few minor side effects. However, as with any substances, they must be used with care. Parsons makes the point repeatedly that physicians who are familiar with niacin and its properties are very pleased with the results.

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