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Editorial

Ten Questions For Doctors: A UK Cancer Patient's Quest For Ascorbic Acid Therapy

"A new kind of scientific review is needed to evaluate the potential of anti-cancer modalities to work together systematically with geneticists and nutritionists working in tandem."

—Terri Mitchell

New Promise for Cancer Prevention and Treatment, *Life Extension*, Jan. 2004

These questions arise out of my experience of my local UK National Health Service (NHS) refusing to allow moderate-cost intravenous ascorbic acid infusions, which could be carried out in my local surgery, on the grounds that this treatment has not undergone a proper scientific trial. Ascorbic acid, about which some 48,000 medical papers have been written, is one of the most used, most safe and most advocated of substances. I challenge orthodox NHS oncologists to show how the testing of substances by double-blind placebo-controlled trials is almost exclusively the way to medical excellence, and to answer the following questions.

1. Do you believe that there is only one valid medical tradition for health improvement: the one which currently permeates the National Health Service?

2. Was orthodox health care ineffective before double-blind placebo-controlled studies became common? Richard Horton, editor of *The Lancet* (August 2006) made a complementary point, in connection with the treatment of HIV/AIDS: "Why does our definition of science still seem to include only the laboratory experiment and the clinical trial?"

3. With regard to drug safety, how do you account for the tens of thousands, perhaps hundreds of thousands, of iatrogenic deaths and harms that occur in the UK, many of them relating to drugs, while as far as I can establish no one anywhere has ever died from a high oral or intravenous

dose of vitamin C? We all have friends and relations who rely on and are grateful for medicines with high risk factors attached to them. Warfarin is a commonly dispensed orthodox substance that is also used to kill rats and, if it is not carefully monitored, can cause bald patches, purple toes, hepatic dysfunction, nausea, vomiting, hemorrhaging, jaundice and diarrhoea. Oral vitamin C takers risk only diarrhea. Kidney stones, as a much touted side-effect of megadose vitamin C, can be regarded only as a scare story used by people who have not read the literature. Hickey and Roberts (2004) write that the margin of safety for high-dose vitamin C is much greater than for aspirin, antihistamines, antibiotics, all pain medications, muscle relaxants, tranquilizers, sedatives and diuretics.

4. My experience of the insistence by doctors on random control trials (RCTs) suggests that this requirement laid down by the NHS has become routine, almost a dogma, in the NHS. Do you think that this should always come before informed patient choice, especially when cost is not the main factor? Also, is the practice of running RCTs on seriously ill patients ethical?

5. How would you justify the almost total ignoring by orthodoxy of the major successes with ascorbic acid, and the prosecution of good doctors who treat with ascorbic acid? Drs. Klenner, Pauling, Cameron, Stone, Levine, Levy, Cathcart and others must feature importantly and positively in twenty-first century medical practice. Their good science resulted in the saving of life and correction of the lamentable distortion of the early expectations for, and results of, vitamin C. This is the time to press home the reiterated refrain of its advocates, "dosage, dosage, dosage", in order to attain sufficiently high blood plasma levels for it to be effective. Hickey and Roberts (2004) cite the consistently positive clinical results that Dr Robert F. Cathcart III has had over two decades with thousands of patients with "massive" vita-

min C doses, ranging from 15 to over 200 grams up to the bowel tolerance limit and administered in up to 20-25 doses a day.

6. Random control trials frequently do not take into account the interactions of patients' other drugs and substances. Is it not true that when a patient is taking a second drug the trial becomes unscientific? The massive onslaught on the human body of both widely dispersed and localized industrial pollution of water and air, workplace stress, and multiple new sources of radiation? How can medical epidemiology, valuable as it is, deal scientifically with such complexities?

7. If the practice of orthodox western medicine is an unfolding and dynamic one, how does this observation square with the static dogma of random control trials as presently constituted? Hickey and Roberts write, "To object that a study is not double-blind and that treatment should be delayed for several years until such tests had been performed would be ridiculous." When a new treatment has a high safety margin and low cost, it could be made available to patients even before the results of follow-up studies were known, without medical, scientific or ethical objections. The development of penicillin proceeded in just this way.

8. What ethical stand does a doctor take with regard to the "need" for high profit levels in the pharmaceutical industry, and all the injustices that spring from this? One wonders why there is such readiness to accept expensive and frequently ever more unsafe drug treatments. Fortunately I have had orthodox NHS doctors confessing to me that they had no solution to my problem and encouraging me to seek one elsewhere. Indeed, in my own case, an NHS Nurse Practitioner is able to carry out this work only 300 yards from my house, as a cost of only a few hundred pounds depending on the protocol adopted. A typical course of cancer chemotherapy costs between £4,000 and £5,000. There is little or nothing to lose

in allowing a treatment, which is having widespread success, as a second line of defence to orthodox treatment, which is eventually liable, even likely, to fail. It would seem sensible to combine the apparent but limited success of a hormone therapy such as Zoladex (my own present treatment) with intravenous ascorbic acid megadosing. This is what I am seeking for myself.

9. How am I to proceed with my health care when few if any are prepared to read the new and optimistic unorthodox work, and many happy to dismiss and debunk it? I have been receiving high-quality orthodox medical attention from my local general practitioners for many years, as well as from hospital doctors, and I consider myself fortunate in the care that I receive. In my recent serious medical condition, however, I have discovered a resolute inability on the part of doctors who treat me to have a proper awareness of the achievements of other doctors and scientists who work outside the NHS. Perhaps this is due to high work loads or burn-out. I recognize that many doctors, especially in inner urban practices, have an impossibly large health care task. Yet even my hospital has written to say that it cannot find the time to read the clinical documents that I sent through the post. My general practitioner investigates some studies of mutual interest, but there is of course a limit to this. He has written to me that I would be "hard pushed to get any sensible doctor to prescribe" the treatment that I legitimately seek.

10. On what basis do doctors still insist on toxicity testing for vitamin C? Practitioner and researcher Dr Brian A. Richards states: "There is no need for toxicity testing: ascorbate is one of the least toxic substances known. Similarly, double-blind testing (DBT) is not required. We are assessing a gross effect, using large doses. DBT is not required any more than it was, at the time, to test say either anesthesia or surgical asepsis. The dramatic responses require no such subtleties of assessment."

Why We Are Still Waiting?

Figures released from the Department of Health, and a King's Fund report, Future Trends and Challenges for Cancer Services, show that one in three will soon be contracting cancer and one in four dying from it. "Thousands of new treatments are in development but many are high-cost and currently of marginal benefit...We need a public debate with informed media coverage," says the report. There might be a case for making decisions "at a local level, with public involvement in policy-making and developing local criteria for clinical eligibility." Don't we have in the case of ascorbic acid just the kind of treatment, alone or with other substances, and moderate cost at that, which this report might be calling for?

Ascorbic acid is a crucial biological substance in the human body: we all once made it. Almost all other animals make it but a genetic fault somewhere down our ancestry caused us to stop doing so. If a great scientist like Pauling thinks vitamin C is thus the most important substance in the medical world, cannot we "give it a go"?

It is rare to see a local NHS medical centre with a good small library that would encourage self-help and patient co-learning from, for example, the texts mentioned here. My own surgery cannot find space for a small shelf of important self-help medical books, even though there is a table packed with used books on sale for charity. Complementary and NHS practices are described by Dr Rosy Daniel in her excellent and wide-ranging book *The Cancer Directory* (2005). Dr Daniel was an early medical director of the Bristol Cancer Help Centre. My own health centre appears reluctant to make available such an inspiring book.

In referring to the known success of vitamin C with many chronic and currently "incurable" diseases, Hickey and Roberts write: "We still await well-designed experiments to determine the biological proper-

ties of the vitamin. Several researchers have suggested to us that the reasons for this are that the questions are not particularly interesting, or are unlikely to produce positive results. To these, we would point out that it is unscientific to assume the results of experiments before they have been performed. Others suggest that commercial, institutional and financial forces actively prevent such research, at the expense of a sick population. Some critics have gone as far as to describe the actions of these influences as genocide." Strong words, but hardly stronger than the vehemence and ease with which many doctors dismiss the substance under discussion.

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Dedication

To Stanley Switala, PhD, TCM practitioner and osteopath of the Kangda Clinic, Bradford, UK, for his kindness, his generosity of spirit and his wide-ranging medical intelligence.

—Graham Carey

(Edited by Andrew Saul)

The Failure of Medical Science To Prevent and To Adequately Treat HIV/AIDS: An Orthomolecular Opportunity

Harold D. Foster¹

Introduction

The book *What Really Causes AIDS*¹ is dedicated to Foinavon, the horse that won the 1967 Grand National in the slowest time and at the highest odds (444/1) ever recorded. It did so because it was so far behind the field that its jockey could avoid the utter chaos that occurred at what is now called The Foinavon Fence, when twenty or so horses fell or threw their riders.

The chaos surrounding the medical science of HIV/AIDS provides orthomolecular medicine with a similar opportunity to provide society with simple but essential strategies to prevent and treat this deadly disease. In a recent issue of this journal, an orthomolecular model was put forward to explain how HIV-replication caused AIDS by removing the nutrients required to produce glutathione peroxidase.² This publication also proved that the conventional Ho³ model of how this virus causes AIDS is incorrect. Since this is the case, it is hardly surprising that treatment protocols, based on this model, are also faulty.

Treatment

Measuring Disease Progression

Conventional Predictions

In 1996, Mellors and colleagues⁴ published a paper in *Science* claiming that the numbers produced by the viral load test could be used to accurately predict the progression of HIV-positive patients into AIDS. Viral load numbers were soon used by doctors and research scientists as

a method of persuading healthy HIV-positive patients with high numbers to “hit early and hard with the newly approved drugs [highly toxic protease inhibitors], while AIDS doctors throughout the world started using viral load for everything from diagnosing illness to confirming HIV infection.”⁵

The truth is that viral loads are a very poor tool to predict anything. In the *Journal of the American Medical Association (JAMA)*, a national team of orthodox AIDS researchers, led by Rodriguez and Lederman⁶ of Case Western Reserve University in Cleveland, presented the results of studying 2,800 untreated HIV-positive patients. They concluded that viral load measures failed in over 90 percent of cases to either predict or explain immune status. In short, the viral load test is worthless. To cite Rodriguez and colleagues⁶ “HIV RNA level predicts the rate of CD4 cell decline only minimally in untreated persons. Other factors, as yet undefined, are likely to drive CD4 cell losses in HIV infection”.

Orthomolecular Predictions

The orthomolecular model, put forward by Foster,^{1,2} stresses that, as HIV-positive patients progress into AIDS, the virus depletes their bodies of selenium and the amino acids glutamine, cysteine and tryptophan, so causing a decline of serum levels of glutathione peroxidase. If this is the case, then declines in such nutrients would be useful predictors of disease progression. This is indeed the case. Numerous studies have shown selenium deficiency in the plasma of individuals with HIV/AIDS.⁷⁻⁹ The worse the AIDS

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symptoms become, the more depressed the plasma selenium levels. Indeed, Baum and coworkers⁷ have demonstrated that in both HIV-1-serum positive drug-using males and females, depressed selenium plasma levels are far more accurate predictor of mortality than falling CD4 T cell counts. This also was found to be true of HIV-infected children.¹⁰ Baum and coworkers⁷ longitudinal study, for example, collected data on CD4 T lymphocyte count, antiretroviral treatment, and plasma levels of vitamins A, E, B₆ and B₁₂, and selenium and zinc. A total of 21 of the 125 participants, adult drug-users, died of HIV-related causes during this 3.5 year study. Only CD4 T lymphocyte counts over time (RR=0.69, $p<0.04$) and selenium deficiency (RR=10.8, $p<0.002$) were significantly associated with mortality, with a lack of selenium being by far the most superior indicator of who was the most likely to die of AIDS. This was true also of selenium levels in infants.¹⁰

That adults and children who quickly died of AIDS had both depressed CD4 T lymphocyte counts and very depleted plasma selenium stores^{7,10} is no coincidence. Rather, it seems much more likely that this viral decline provides evidence of a positive feedback system in which a fall in selenium causes a reduction of CD4 T cells because this trace element is essential for the production of T lymphocytes¹². Such a drop in the efficiency of the immune system can also be documented by measuring the serum levels of glutathione peroxidase, the selenoenzyme that appears to protect against viral infection and to be a prime target of HIV. These declines in the efficiency of the immune system, caused by selenium inadequacy, then allows infection by other pathogens, resulting in a further decline in selenium. The "selenium-CDT cell tailspin" is beginning its downward spiral.¹¹

It is clear, therefore, that the way to predict the future health of HIV-positive patients is not through measuring viral

loads but by assessing serum levels of selenium and/or glutathione peroxidase. This is exactly what was done in the Mengo Nutritional Trial, recently conducted in Kampala, Uganda and reported on in this journal.¹² This clinical trial found that as glutathione peroxidase levels rose, so too did CD4 cell count, Karnofsky scores (measuring the patients quality of life) and body weights.

In summary, patient serum selenium and glutathione peroxidase levels are far better methods of predicting future health, or lack of it, than are the measurement of viral loads. To illustrate, at the beginning of the Mengo trial, the 160 HIV-positive patients in Group A had a median CD4 cell count of 347 mm³ and median serum glutathione peroxidase levels of 3628 u/L (international Units). One year later, after taking 37 nutrients daily, the median CD4 cell count of this group had risen to 388 cells per mm³ and their median serum glutathione peroxidase levels had more than doubled to 8573 uL ($p=0.0001$). Improvements in weight and Karnofsky scores (showing quality of life) were also highly statistically significant.¹² The serum levels of the selenoenzyme glutathione peroxidase appear to be the optimum indicator of future immune function and survival rates in HIV-positive individuals.

Conventional Side Effects

There is no doubt that antiretroviral drugs, often given as the HAART cocktail, can prolong life in patients who are receiving no other form of treatment. From the time of entering HIV care, the projected life expectancy for a patient is 24.2 years.¹³ The question arises, however, "what is the quality of this life?" To quote from *Science's* News Focus,¹⁴ "Confronting the Limits of Success" six years ago, new cocktails of anti-HIV drugs transformed prospects for infected people in industrialized countries. Now, serious limitations have become apparent. Indeed, two years after the

introduction of HAART, new side effects began to appear in treated patients. These included nausea and anemia, and odd distributions of fat known as lipodystrophy. Other metabolic abnormalities have since developed that lead to diabetes-like problems, heart disease and brittle bones. Research has appeared proving that a common mainstay of HAART, drug AZT (3'-Azido-3'-deoxythymidine), is likely to be carcinogenetic.¹⁵ A European study also has shown that deaths from liver-related disease among HIV-positive patients with similar CD4 cell counts has increased since the introduction of HAART.¹⁶ So too has HIV-associated renal disease.¹⁷ Similarly, the use of combined antiretroviral therapy is a strong independent risk factor for subclinical carotid atherosclerosis in drug-treated HIV patients, clearly showing its cardiovascular toxicity.¹⁸

In addition to the physical decline associated with antiretrovirals, mental disorders also are unusually common among HIV-patients treated with them.¹⁹ One of the reasons for this is that these drugs tend to be large molecules that cannot pass the blood-brain barrier. As a result, the brain acts as a sanctuary for HIV.²⁰ 3-D scans, for example, reveal tissue damage in the brains of many AIDS patients. In colour-coded images, researchers have shown that there may be as high as 15 percent tissue losses in the centres of the brain that regulate movement and co-ordination. Thinning also is seen in the reasoning and language centres.²¹ In addition to these brain scans, the National Institute of Mental Health are funding a long-term brain function study of HIV positive patients that hopes to enroll about 1,600 drug treated individuals. Initial findings already suggest that about 50 percent of such patients have subnormal performance. To quote Clifford²⁰ "They might be slower on computer keyboards, working crossword puzzles or have difficulty keeping track of what's been said

in a conversation. They may even begin to move more slowly".

In summary, antiretrovirals are keeping HIV-infected patients alive longer. However, as a consequence of the properties and side-effects of these drugs, patients are developing lipodystrophy, diabetes, liver and kidney problems, carotid atherosclerosis and brain thinning and associated subnormal performance. It is also likely that they are increasing their risk of subsequently developing cancer.

Orthomolecular Side Effects

The orthomolecular treatment of HIV/AIDS involves diets that are high in specific nutrients that are essential for all human survival. Nutritional intake must specifically provide elevated levels of those nutrients, selenium, cysteine, glutamine and tryptophan, that HIV replications removes from the body.^{1,2,12} There is no evidence that these nutrients, especially if provided in foods such as Brazil nuts, spirulina, desiccated liver or yogurt, cause any adverse side effects. Naturally, they should not be ingested at abnormally high levels.

The author has published several articles, describing open and closed trials, that have established that such nutrients can reverse the downward HIV/AIDS spiral, even when AIDS patients are very close to death.²⁴ Indeed, many of the orthomolecularly treated HIV/AIDS patients claim to be healthier than at any previous time in their lives. Selenium, of course, is known to extend lifespan and reduce the risk of death from cancer²⁵ and cardiovascular disease.²⁶

Costs

Conventional Expenses

According to Schackman and co-workers,²⁷ from the time of entering HIV care, the average patient life expectancy is an additional 24.2 years. Such a patient's medical care lifetime discounted costs,

in the United States, are \$385,200. Undiscounted cost is \$618,900 for adults who begin antiretroviral treatment with CD4 cell counts <350/μL. Seventy-three percent of these predicted costs are to pay for antiretroviral medications, 13 percent for inpatient care, 9 percent outpatient care and 5 percent other HIV-related medications and laboratory costs. If antiretroviral treatment begins in a patient with a CD4 cell count of <200/μL, projected survival time is 22.5 years, with a discounted lifetime cost of \$354,100 and an undiscounted cost of \$567,000.

Orthomolecular Expenses

It is not yet possible to provide similar data for orthomolecular treatment. However, in South Africa, Uganda and Zambia, trials with HIV/AIDS patients have been successfully treated for a year or longer with nutrients costing between \$60 and \$300 annually.^{23,24} These patients have, in many cases, proved so healthy after a few months that it is possible that over a lifetime their treatment cost will be effectively negative. That is, they will require less medical treatment than they would have received had they not been HIV-positive and, therefore, not receiving nutritional supplements. Since they are generally well enough to quickly return to work, the addition of their wages to the economic equation would certainly result in negative costs for the orthomolecular treatment of HIV/AIDS in such Third World patients.

Prevention

Conventional Strategies: Vaccines

In April 1984, the HHS secretary Margaret Heckler held a press conference to announce that Dr. Robert Gallo of NCI had discovered the cause of AIDS, the retrovirus HTLV-III (later called HIV). She expressed hope that a vaccine against this virus would be produced within two years.²⁸

Heckler was no Nostradamus, more than twenty-three years later there is no vaccine for HIV. To quote Horton,²⁹ writing in 2004:

“But contrary to the predictions and promises of most AIDS experts, the signs are that a vaccine to prevent HIV infection will not be found for, at the very least, several decades to come – if at all. Those responsible for carrying on the global fight against AIDS do not accept this grim outlook, at least publicly. Yet it is a conclusion, based on all the evidence gathered so far, which increasingly defies rebuttal. Until the gravity of this scientific failure is openly acknowledged, a serious debate about how to end HIV’s lethal grip on some of the poorest and most vulnerable human populations in the world cannot take place.”

Of course, this criticism by Horton is not new. In 1992, Albert Sabin, developer of the oral polio vaccine claimed: “...the available data provides no basis for testing any experimental vaccine in human beings or for expecting that any HIV vaccine could be effective in human beings.”³⁰

Nevertheless, the search goes on. In 2004, for example, world expenditure on AIDS vaccine research was between \$600 million to \$700 million, \$582 million being provided by the United States.³¹

What has medical science to show for the billions of dollars spent in AIDS vaccine research? Well, in 2007, the cream of the crop vaccine, being tested in the “STEP Study” failed spectacularly. Not only did the vaccine not prevent HIV infection, but those receiving it proved more likely to be infected with the virus than those volunteers receiving the placebo.³² This study included 3,000 males and females, aged 18 to 45 who, because of their lifestyles, were considered at high risk of HIV infection. One hundred of these volunteers were from Seattle, the rest were drawn from 15 other US cities and from Peru, Brazil,

Canada, Australia, Jamaica, Haiti, Puerto Rico and the Dominican Republic.

Orthomolecular Strategies: Soil Remineralization

What are the reasons for the timing of the first AIDS pandemic, and indeed for the increased ability of viruses to cross the species barrier from animals to humans?^{33,34} There seems to be a minimum daily dietary selenium intake above which, as seen in Senegal⁶ and Finland,³⁵ HIV cannot be easily transmitted. This appears to be because the body's antioxidant defense system, especially the selenoenzyme, glutathione peroxidase, acts as an internal defense against viral infection, preceding the formation of antibodies. For this reason, HIV is having its greatest difficulty in infecting those with diets elevated, either naturally or by design, in the trace element selenium and in the amino acids cysteine, glutamine and tryptophan. Together these nutrients stimulate the body's production of glutathione peroxidase.³⁶⁻³⁷

As Foster wrote in the *Well Being Journal*:³⁴ If this is correct, any drop in selenium in the food chain would naturally encourage the diffusion of HIV and indeed many other viruses. In the second half of the twentieth century, coal combustion more than doubled, oil consumption increased by a factor of almost 8 and natural gas was used as a fuel at a rate of roughly 11 times that of 1950. Simultaneously, large parts of the earth were deforested and much of the wood burned. The resulting high levels of sulphur and nitrogen, emitted into the atmosphere, were largely converted into sulfuric and nitric acids, increasing the acidity of associated precipitation. Acid rain altered soil pH and so reduced selenium's bioavailability. Similarly, potassium, nitrogen and phosphorous in commercial fertilizers are further depressing the uptake of selenium in crops. These processes reduce the dietary intake of selenium by humans,

animals and insects, triggering viral mutation and promoting associated pandemics. Naturally, the effects of decreased selenium bioavailability have been most obvious in those unfortunate regions, like sub-Saharan Africa, where levels of this trace element are naturally depressed in the food chain. This is the fundamental reason why sub-Saharan Africa is so badly affected by the HIV/AIDS pandemic.

Field trials in China have shown that the addition of selenium to fertilizers, table salt and/or animal fodder can greatly reduce Keshan disease by slowing the diffusion of coxsackievirus B.³⁸ This is also true of the hepatitis B and C viruses and liver cancer.^{39,40} The addition of selenium to fertilizers in Finland, mandated nationally in 1984, has apparently also significantly reduced the incidence of HIV infection.³⁸

It seems that, for a fraction of the money spent with no return on HIV vaccine research, the AIDS and other viral pandemics could be halted by increasing the global dietary intake of selenium. Such a strategy would be particularly effective if combined with efforts to increase protein consumption worldwide.

Conclusion

As William A. Hasteltine⁴¹ pointed out in a 1992 lecture to the French Academy of Sciences, "The future of AIDS is the future of humanity". Hasteltine, the then chief retrovirologist at Harvard's Dana-Farber Cancer Institute, went on to add that "unless the epidemic of AIDS is controlled, there is no predictable future for our species". Soon afterward he testified to a US Senate hearing,⁴² pointing out that by the year 2000 we might see 50 million people who had been infected by HIV. In his opinion, by 2015 the total number dead or dying from this cause could reach one billion, that is about one sixth of the current global population. Hasteltine may have been a little optimistic: the AIDS

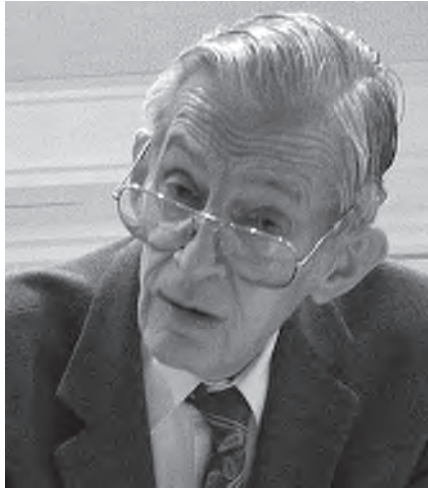
pandemic has not been controlled and by the end of 2000, 57.9 million people had been infected with HIV, 21.8 million of whom were already dead.⁴³ We are at, or near, the tipping point.⁴⁴ If the orthomolecular strategies described in this article are not applied globally, very soon there will be, as Hasteltine suggested, no predictable future for our species.

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In Memoriam:



William Douglas Panton, M.D.

April 24, 1923 – December 20, 2007

Born in 1923, of Irish, Scottish, and British ancestry in the aftermath of World War One, Bill Panton worked his way into the hearts of many of his fellow human beings. His Great-Grandfather John Maclure arrived from England with a contingent of Royal Engineers, or 'Sapper's,' in 1856 to protect British interests during a rush of American gold miners, and to help establish the new colonies. His wife Martha and two children arrived soon after aboard the sailing vessel Thames City. When John's unit disbanded, they together with their children Sara, Susan, Fred, Charles and Sam moved from Sapperton to settle in their homestead at Matsqui Prairie. Aside from entertaining the occasional passing friend such as Sir Matthew Begbie, they operated from their home the Western Union telegraph repeater station, where Sara honed the skills that led her to become, at age 15, the highest paid woman in British Columbia. They established the

brickworks at Clayburn and purchased an area of land they called Abbotsford. Sam went on to a career in architecture. Though he competed and sometimes worked with Francis Rattenbury on commissions such as Government House, Sam's best known building may be Hatley Park, otherwise known as 'The Mansion' in the X-Men movie franchise, and Royal Roads University. Bill's Grandmother, Sara, married John McLagan and together they owned and managed the World newspaper. When John died in 1901 Sara became the first female managing owner of a daily newspaper in Canada. She sold the paper in 1905 to LD Taylor, who later assimilated it into The Vancouver Sun. Sara and John had five children, one of whom was Doris.

William Douglas Panton was born April 24, 1923 to Doris and Dr. Kenneth D. Panton, a WWI Medical Officer, in the family home in downtown Vancouver,

where high-rise apartment buildings now reign supreme. He, his younger brother John and sister Sally were all three educated locally, though as a family they spent many summers at Buccaneer Bay. Under his father's influence, Bill took to medical studies, beginning his studies at UBC but earning his medical degree in 1947 at McGill University in Montreal. Back on the West Coast, Dr. Panton began his medical practice in smaller communities including Hope, Powell River, and Alert Bay, where he met his bride-to-be.

He and Mabel married in St. John's Shaughnesy Anglican Church in 1951. In 1953, he returned permanently to establish a family practice in East Vancouver, including patients of his retiring father. From him he also took over until 1971 duties as an attending physician for the Vancouver Police Department.

As an old-style physician, Dr. Panton was far more interested in his patients and the art of healing than the business of medicine. Long hours, house calls, and middle-of-the night telephone calls were normal. In general he loved his work, but his willingness to use alternative methods when orthodox medicine fell short at times created stressful friction with the College of Physicians and Surgeons. He became very involved with Health Action Network Society (HANS), and in orthomolecular and nutritional medicine, and supported other medical pioneers, some of whom also had grievances with the medical establishment.

Especially important to him in later years was his interest in AIDS research, particularly that of Harold Foster and colleagues at Mengo Hospital. In 1991 the Canadian Schizophrenia Foundation honoured him as the "Orthomolecular Doctor of the Year." Though not much used in his practice, computers became part of his life after his retirement in 1992. Doing his best with the new technology, he spent many hours writing newsletters,

letters to friends, editors and others with a similar flair as that of his news editor grandparents. In spite of increasing physical challenges, he joined with the ministry M2W2, visiting prison inmates in Fraser Valley institutions. As a Rotarian for over 40 years, and two-time Paul Harris Award fellow, he continued attending even if it meant riding his scooter to a 7:30 am breakfast. Bill loved to travel, but his final trip was just as far as Locarno, his favorite beach, and near the once family home.

He died December 20, 2007, at the Royal Columbian Hospital, Sapperton, and was cremated at Forest Lawn Cemetery December 24. Predeceased by his parents Dr. K.D. and Doris Panton, his brother John and sister Sally. Survived by his loving wife of 56 years, Mabel, and his beloved children: Doug (Joanne), Diana, Kathy (Albert), Margaret (Will), Ken, David, and Donald; their families, including many grandchildren and great-grandchildren. He also leaves behind sister-in-law Dorie, several, nieces, nephews, cousins, and countless friends.

- submitted by Mrs. Mabel Panton
and Family

Photo of Bill Panton, listening intently to a colleague at the Nutritional Medicine Today Conference, Vancouver, 2002 by Greg Schilhab

Vitamin K Deficiency Disease

Michael D. Innis, MBBS, DTM&H, FRCPA, FRCPath.¹

Abstract

Vitamin K deficiency bleeding (VKDB) previously known as hemorrhagic disease of the newborn has been classified as Early (0-24hrs), Classic (2-7 days) and Late (1-6 months). Child birth following the maternal ingestion of anti-epileptic drugs such as Phenytoin, is liable to result in early VKDB as well as bone changes in the fetus. Other maternal risk factors for VKDB include medications such as warfarin and antibiotics. Failure to administer vitamin K at birth, prematurity, infective gastro-enteritis, the administration of antibiotics, malabsorption, liver disease, prolonged breast feeding, and malnutrition as shown by hypoalbuminemia have all been associated with VKDB. In view of the pivotal role of vitamin K in hemostasis and osteogenesis it is postulated that the bleeding, bruising and fractures seen in some children thought to be non-accidental injuries such as Shaken Baby or Shaken Impact Syndrome, could be due to a deficiency of vitamin K. To investigate this possibility the reports of three affected children were examined. It was found that the coagulation screen showed an increase in the prothrombin time, a normal partial thromboplastin time, a normal or slightly increased level of platelets and an absence of a family history of bleeding – findings consistent with vitamin K deficiency. It is concluded that the lesions hitherto attributed to non-accidental injury are in some cases due to a deficiency of vitamin K alone, and others occur in combination with vitamin C deficiency which is a well documented cause of "battered baby". Vitamin K deficiency is best detected by the Protein Induced by vitamin K absence/abnormality (PIVKA-II) test rather than the prothrombin time and by the serum under-carboxylated osteocalcin

test which provides the best guide to the state of mineralization of bone and hence the tendency to fracture. A name change to vitamin K deficiency disease would accommodate both the blood and bone lesions found in this condition when vitamin K alone is shown to be the cause.

Key Words

Vitamin K, Fractures, Non-accidental Injury, Shaken Baby Syndrome, Child Abuse, Vitamin K Deficiency Disease

Introduction

Some unexplained fractures in infants, especially if associated with subdural or retinal bleeding or with external bruising, are currently attributed to child abuse by Child Protection Agencies.

Caffey¹ was the first to implicate parental violence in the etiology of infantile subdural hematomas associated with fractures of the skull and long bones. However, Caffey's initial reports were compatible with, and even suggestive of, infantile scurvy or toxic histaminemia.² The first mention of shaking of infants as a cause of subdural hematomas appeared in a paper by Guthkelch³ before Caffey's paper on the Shaken Baby Syndrome⁴ (SBS) was published.

Since then it has become axiomatic in academia that subdural hematomas, associated with retinal hemorrhages, bruising and fractures occurring in infants and young children which cannot be explained by the parents is evidence of non-accidental injury or more specifically the Shaken Baby Syndrome or Shaken/Impact Syndrome.⁵⁻¹⁰ It has been suggested,¹¹ and generally accepted in the English speaking world, that subdural hemorrhages resulting from non-accidental injury can be distinguished from accidental injury by the following:

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1. Age less than 12 weeks
2. Retinal hemorrhages
3. Skeletal fracture
4. Unexplained bruising
5. Inconsistent history

However parents and carers generally vehemently protest their innocence and it is vital, therefore, that the presence or absence of an alternative explanation such as a hemostatic disorder be investigated.¹²

Pregnant women suffering from epilepsy who consume anti-epileptic drugs such as Phenytoin have a significantly greater chance of the child developing vitamin K deficiency bleeding and/or distinctive skeletal abnormalities¹³⁻¹⁷ than those not so treated. Other evidence also indicates that vitamin K is intimately associated with defects in hemostasis¹⁸⁻²⁰ and osteogenesis²¹⁻²³ and for these reasons a vitamin K deficiency was sought as an alternative explanation for the alleged Shaken/Impact Syndrome.

Method

Three children with fractures and bleeding who had evidence of vitamin K deficiency are reported. One of these children has been reported previously but the cause of the fracture was stated to have been "undetermined".²⁴

Case 1

A male infant was born to a 20-year-old mother after a 41-week gestation by normal vaginal delivery. Vitamin K 1 mg (IM) and hepatitis B vaccinations (Hep B) were given. The child was breast fed for two months and then formula fed. The mother smoked during her pregnancy.

At his routine well check at the age of 2 months, his navel had still not healed, and some bright red discharge was noted. Immunizations consisting of diphtheria, tetanus, and acellular pertussis (DTaP), hemophilus influenzae B (Hib), and Hep B vaccines were given. These were repeated 2 months later.

On the night after the second set of vaccinations, the mother said the infant was irritable. The following day the baby's father gave him a bath and laid him on the bed while he attended to some other matter for about two minutes. When he returned, he found that the infant was limp, unresponsive, and not breathing. Shortly thereafter he became blue and was taken to the emergency department of the local hospital where he was resuscitated and his condition stabilized before other investigations were done.

A skeletal survey showed findings consistent with a non-displaced fracture of the distal left tibia. Blood studies showed:

Prothrombin time 17.9 sec
(normal range, 8.2–14.1)
Partial thromboplastin time 35.5 sec
(normal range, 28.0–50.0)
Aspartate aminotransferase 97 U/L
(normal range, 20–60);
Hemoglobin 11.0 g/dL
(normal range, 10–13.5)
Platelets $382 \times 10^9/L$
(normal range, 150– 450)

The recorded diagnoses were non-accidental injury and Shaken Baby Syndrome.

Case 2

During her pregnancy the mother was hospitalized once with signs of a kidney and urinary tract infection and treated with antibiotics. She had difficulty in retaining the prenatal vitamins she was prescribed because of morning sickness which lasted the entire nine months of her pregnancy. The child was given an injection of vitamin K at birth and was breast fed.

At the age of 10 weeks blood was noted in his diaper and in his urine.

Urine examination confirmed the presence of blood. No coagulation studies were done at this stage.

Hematology Report

1. Hemoglobin 11.8g/dL
(normal range, 11.5–16.5)
2. Platelets $506 \times 10^9/L$
(normal range, 150–500)

Four days later when the father picked up the infant from his crib, he stiffened as though having a seizure and turned red in the face. His lips were purple and he suddenly went limp. The baby stopped breathing and was admitted to hospital.

A skeletal X-Ray showed healing posterior rib fractures of the right 10th and 11th ribs and recent fractures of the anterior aspects of the right 6th and 7th ribs. Extensive subdural blood of mixed density was seen overlying the right greater than left cerebral hemispheres.

Laboratory Investigations.

1. Liver Function Tests

Aspartate aminotransferase 399 U/L
(normal range, 20–60)
Alanine aminotransferase 138 U/L
(normal range, 6–50)
γ-Glutamyl transpeptidase 92 U/L
(normal range, 11–82)
Alkaline phosphatase 202 U/L
(normal range, 110–320)

2. Hemorrhagic Screen

Prothrombin time 18.3 secs
(normal range, 11.5–14.5)
International normalized ratio 1.6
(normal range, 0.9–1.2)
Partial thromboplastin time 33.7 secs
(normal range, 24.0–35.0)

A diagnosis of non-accidental injury was made.

Case 3

Shortly before the birth of her child the mother had high fever with vomiting and watery bowel motions. The child was born by vaginal delivery and a large bruise was apparent on the right side of the face

involving the eye. The hospital record does not mention the use of forceps. Vitamin K 1 mg was given IM. The infant was formula fed and the mother noticed that the right eye remained closed when the infant was feeding.

Immunizations were carried out at 2 weeks. Following this the mother complained the baby cried literally 20 hours a day and was not feeding properly and had frequent bouts of diarrhea. When 4 weeks old the urine in her diapers developed a strong smell and her gums were noticed to be bleeding.

At the age of 6 weeks the child again had severe diarrhea and was crying. The father tried to console her but he realized something was seriously wrong when the infant stopped breathing, became limp and unresponsive and later became cyanosed. Pinkish fluid was coming from the nose. An attempt at CPR was unsuccessful and the infant was rushed to hospital where she was intubated but failed to regain consciousness and died shortly thereafter.

Laboratory Investigations

Prothrombin time 15.4 secs
(normal range, 11.5–14.0)
International normalized ratio 1.31
Partial thromboplastin time 26 secs
(normal range, 23–34)
Fibrinogen 148 mg/dL
(normal range, 180–490)
Total protein 3.9 g/L
(normal range, 6.0–8.8)
Albumin 2.5 g/L
(normal range, 3.5–5.0)
Platelets $512 \times 10^9/L$

Urine 4 red cells per high power field.

Radiology

1. CT Scans and X-Rays showed subdural hemorrhage with cerebral edema and healing fractures of the right costovertebral junctions of the 3rd and 4th ribs.

Postmortem Findings

The autopsy findings confirmed what had already been observed clinically and a diagnosis of Shaken Baby Syndrome was made.

Results

Besides a diagnosis of non-accidental injury or Shaken Baby Syndrome the children reported here have in common:

1. Evidence of intra-cranial bleeding
2. Evidence of fractures
3. Prolongation of the prothrombin time
4. Normal partial thromboplastin time
5. Normal or raised platelet counts
6. "Herald" bleeds – navel, urine, bruise
7. No family history of bleeding or congenitality.

In no instance was there evidence of disseminated intravascular coagulation (DIC). Thrombocytopenia, microthrombi in the small blood vessels and thrombi in midsize and large arteries and veins which are markers of DIC were not recorded. Although congenital deficiencies of the coagulation factors are known to occur they are rare and most would be detected by prolongation of the partial thromboplastin time and by the family history. It is clear that the finding of a prolonged prothrombin time is thus most probably due to a deficiency of vitamin K. An associated deficiency of vitamin C cannot be excluded particularly in Case 3 in which there was evidence of malabsorption or malnutrition.

Just 50% of the normal concentration of prothrombin is sufficient to produce a normal PT.²⁵ Prolongation of the PT, even slightly, as in Case 3, is therefore evidence of advanced vitamin K deficiency.

In addition to a prolongation of the prothrombin time Case 2 showed significant abnormalities in the Transaminase levels and is possibly an example of the neonatal hepatitis syndrome in which one expects malabsorption of vitamin K.²⁶

Discussion

The blood coagulation proteins Factors II, VII, IX and X and the bone forming proteins osteocalcin and matrix Gla protein, to be functionally active, must be carboxylated by the vitamin K dependent enzyme γ -glutamyl carboxylase. This action converts the glutamic acid residues of these proteins to γ -carboxyglutamic acid which is a calcium binding amino acid required for the function of vitamin K dependent proteins.²³ In the case of the coagulation proteins this function is the formation of a blood clot and the prevention of bleeding while osteocalcin and matrix Gla protein ensure mineralization and strengthening of bone and the prevention of pathological fractures.

The infant's vitamin K comes partly from the mother via the placenta initially and from the breast milk later. It also comes partly from bacterial fermentation in the gut which in the first few days of life is sterile. If the child develops diarrhea, as did the child in case 3, this source of vitamin K is reduced or lost.

Malabsorption of vitamin K in children may be the result of a variety of causes²⁷ and antibiotic therapy may also lead to vitamin deficiency by destroying the vitamin K forming bacteria in the gut.²⁸ It is these children that are vulnerable to bleeding and pathological fractures and who should be carefully investigated for an alternative explanation of the findings hitherto attributed to non-accidental injury or to the Shaken Baby Syndrome. Both vitamin K and C are intimately connected with the maintenance of the integrity of bone and hemostasis and both are subject to malabsorption.

The children described here were known to have been given vitamin K at birth as recommended but it is obvious from the prolonged prothrombin time that it was not sufficient to sustain normal health and von Kries²⁹ has pointed out that the failure rate is about 0.25 per 100,000.

Osteogenesis is a dynamic process with bone formation and bone resorption occurring simultaneously. Should bone formation be impaired for any reason resorption may predominate with demineralization and fractures the result.

While the role of vitamin K in the prevention of fractures has so far been demonstrated in menopausal women and in subjects with cystic fibrosis in whom there is a malabsorption of fat-soluble vitamin K the evidence of a lack, or abnormality, of vitamin K in the children described here suggests a similar process may be occurring in these children and the fractures are being wrongly attributed to child abuse.

The prothrombin time which is commonly used is not as sensitive as the PIVKA II (Protein Induced by vitamin K Absence/Abnormality) test²⁵ and the serum under-carboxylated osteocalcin test, while well established in the investigation of osteoporosis and fractures in women, has not been applied to the investigation of unexplained fractures in children

These omissions should urgently be addressed by all laboratories dealing with children.

Conclusion

Vitamin K deficiency or abnormality may have a significant bearing on the etiology of the lesions in children hitherto attributed to non-accidental injury, Shaken Baby Syndrome or physical child abuse. The role of vitamin K is not confined to the prevention of hemorrhagic disease of the newborn/(vitamin K deficiency bleeding) but is also essential for the mineralization and strengthening of the infant's bones. Both the hemorrhagic and osseous lesions of alleged child abuse can be accounted for by vitamin K deficiency. However there appears to exist an association between vitamin K deficiency and vitamin C deficiency as both are subject to malabsorption and malnutrition and

it is possible that in some instances of so-called Shaken Baby Syndrome they co-exist.

Proof that there is an association between a prolonged prothrombin time and false accusations of Shaken Baby Syndrome in the cases presented here is provided by the fact that "similar fact evidence is analogous to challenge/de-challenge/re-challenge..." Both are capable of demonstrating causality to the highest standards of proof.³⁰

The investigation should start with a careful and thorough history paying particular attention to any medications such as anticonvulsants, anticoagulants or antibiotics given to the mother during her pregnancy which are likely to reduce the vitamin K reaching the foetus. Smoking may reduce the level of vitamin C in the mother's blood and add to the infant's problems.

Some antibiotics given to a child may destroy the vitamin K forming gut bacteria. Diarrhea, vomiting, loss of appetite should arouse suspicion of the possibility of a vitamin K deficiency and appropriate measures taken.

Although all three children showed a significant elevation of the prothrombin time it is the increase in under-carboxylated osteocalcin and PIVKA-II which best reflect the defects in osteogenesis and hemostasis and the investigation should include these tests which are more informative than the prothrombin time. In addition, the common coagulation and liver function tests should also be performed routinely.

Hypoalbuminaemia is one of the first markers of malnutrition and should always be determined.

Finally vitamin K deficiency disease would seem an appropriate diagnosis for children with subdural hemorrhages, retinal hemorrhages, bruises and fractures which the parents cannot explain and the PIVKA-II test is abnormal.

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Conflict of Interest. I have given evidence for the Defence in Courts in England, United States of America and Australia.

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Orthomolecular Treatment For Schizophrenia: A Review (Part One)

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Introduction

Various segments of the schizophrenic population fall into subgroups of distinct biochemical imbalance. We often see subgroups of essential fatty acid deficiency, inadequate nutriture, dysglycemia, food intolerance, digestive compromise, malabsorption, under-methylation, vitamin B₃ deficiency, vitamin C deficiency, heavy metal toxicity, B₆ deficiency, zinc deficiency, brain hypothyroidism, and hypoadrenia. Complementary and alternative medicine (CAM) have a key role in the treatment of schizophrenia. The goal of optimal complementary treatment is to correct the biochemical imbalance. In schizophrenia, we can assess cases with lab tests and target our treatment accordingly. CAM treatment involves the use of nutritional supplements, nutraceuticals, amino acids, and botanicals. Dietary changes are also implemented in treatment. In Part One of this review we will cover the research on essential fatty acid deficiency, inadequate nutriture, dysglycemia, food intolerance, digestive compromise, malabsorption, under-methylation, vitamin B₃ deficiency, and vitamin C deficiency.

The Essential Fatty Acid (EFA) Deficient Schizophrenic

Chronic schizophrenics have increased phospholipid neuron membrane break down (oxidative stress) which concentrates in the frontal cortex and other brain areas.^{1,2} Pro-inflammatory cytokine involvement in development may set the stage for oxidative stress from early development onward.^{3,4} Omega 3 fats have

a neuroprotective and anti-inflammatory role. Sixty percent of the dry weight of the brain is fat. EFAs, including omega-3 and omega-6, are good fats, not saturated with hydrogen, and, unfortunately, not readily provided in the North American diet. Investigators note an integral need for omega-3 supplementation for schizophrenia, mood, and behavior disorders.^{3,5} EFAs are important components of nerve cell walls and they are involved in neurotransmitter electrical activity and post-receptor phospholipid mediated signal transduction.

Eicosapentaenoic acid (EPA) is an omega-3 fat that is slightly more unsaturated than omega-6 fat. Brain membrane structure is compromised in chronic schizophrenia and EPA has demonstrated some potential in keeping brain neuron degeneration at bay and in reducing psychotic symptoms.⁶⁻¹² Omega-3 EFAs may eventually gain notice as “a safe and efficacious treatment for psychiatric disorders in pregnancy and in breast feeding [moms]”.^{6,13} Fish have high amounts of omega-3s and high EPA supplements are derived from fish. Many EPA fish oil products contain antagonistic fats and the more pure the EPA supplement, the more useful it is for schizophrenics.⁷

A balanced essential fatty acid profile may also be mediated by vitamin B₃ but more research is needed to identify the role of B₃ on the EFA profile of schizophrenics.¹⁴

The Schizophrenic with Inadequate Nutriture

Neurotransmitter production is dependant on amino acid protein building blocks (phenylalanine, tyrosine, tryptophan,

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etc.) supplied from the diet. The catecholamines dopamine, norepinephrine, and epinephrine are derived from phenylalanine and tyrosine. Catecholamines are involved in executive functions and motivation. Serotonin, the 'feel good' neurotransmitter, is derived from the amino acid tryptophan. Protein nutriture is very important for schizophrenia and for general mental well-being. I have seen many schizophrenics respond when they start increasing their protein intake with each meal. A diet that has 40% protein, 40% carbohydrate, and 20% fat is ideal for most schizophrenics.

Many schizophrenics do not eat three meals a day and their diet is invariably carbohydrate dominant. Carbohydrate dominant North American diets release glucose to the bloodstream quickly. Most schizophrenics require a dietary change that incorporates complex carbohydrates. They also do well to avoid high glycemic load foods including junk food, white sugar, white rice, and white bread. If they have a poor appetite, this can lead to inadequate nutriture. Poor appetite may be associated with zinc or iron loss.

Fat nutriture is important in schizophrenia. Cold water fish with teeth have a fat profile suitable for schizophrenics. Salmon, tuna, mackerel, herring, cod, and trout provide the highest omega-3 profile. Other high EFA sources include scallops, shrimp, flaxseeds, walnuts, winter squash, and kidney beans.

Inadequate nutriture can also occur with gastrointestinal compromise, malabsorption, and low thyroid function.

The Dysglycemic Schizophrenic

The brain's demand for glucose is so immense that about 20% of the total blood volume circulates to the brain, an organ that represents only 2% of body weight. The brain demands a substantial amount of glucose to maintain its high metabolic rate. Gluco-sensing neurons regulate glucose availability in the brain as a fail-safe

mechanism to ensure homeostasis of brain glucose levels.¹⁵

In schizophrenia, it seems likely that glucose transporters are compromised with consequent intraneuronal glucose deficits.¹⁵ McDermott and de Silva mention that this hypoglycemic state has the potential to cause "acute symptoms of misperceptions, misinterpretations, anxiety and irritability—the usual features of prodromal and first onset schizophrenia." Epidemiological investigations show us that schizophrenics are at increased risk for dysglycemia.¹⁷ Psychiatric meds also have some potential to induce hyperglycemic or insulin resistant states and this can be addressed, at least in part, with a nutritional adjunct.¹⁸

The hypoglycemic state involves a sharp rise of simple sugars in the blood followed by a sharp decline which robs the neurons of their main energy source; the sharper the decline, the greater the effect on brain cells. Typical hypoglycemic symptoms include irritability, poor memory, late afternoon blues, poor concentration, tiredness, cold hands, muscle cramping, and 'feeling better when arguing'.

Schizophrenics with hyperglycemia, much like diabetics, present with hypoglycemic mental symptoms because the glucose doesn't get into brain neurons. Brain neurons starved for energy behave differently and mental function declines.^{19,20} It is not clear if dysglycemia has a causative role in schizophrenia but it can be deemed an aggravating factor.

It is said that hypoglycemia is 100% treatable in compliant patients. This emphasizes the need to address diet. The dysglycemic schizophrenic requires three solid meals (of 40% protein) a day and sometimes additional protein-containing snacks. Many schizophrenics need to be educated on complex versus fast carbohydrates and the avoidance of junk food and sugar. When schizophrenics increase their protein intake, they release glucose to the

brain at a steady rate and sugar cravings lessen. Chromium and zinc are useful for sugar balance and botanical medicine is useful in advanced hypoglycemia.

The Food Intolerant Schizophrenic

Schizophrenics, just like the general population, have the potential to exhibit mild or severe food intolerance symptoms.²¹⁻²⁵ The digestive tract reacts to food allergens by eliciting an immune response. Undigested food by-products can be toxic (e.g. opioid peptide exorphins), pass through the gut wall, enter the bloodstream, and reach the brain with subsequent brain function compromise.^{23,26-28} I have several clients who have an increased severity and frequency of hallucinations, delusions, depression, anxiety, irritability, and insomnia when they eat an intolerant food. We see schizophrenics that experience a wide range of food related physical symptoms such as headaches, skin eruptions, palpitations, weakness, painful digestion, constipation, diarrhea, and arthralgia. In schizophrenia, gluten, dairy, and eggs are commonly not tolerated.^{22,23,29} Other common food intolerances include tree nuts, citrus, fish, legumes and crustaceans. It is helpful to survey patient responses with a seven-day diet diary. Often schizophrenics are tired, weak, irritated, and moody after eating intolerant foods. Typically they either hate the intolerant food or crave it and this may be due to the toxic effects of opioid exorphin peptides. It is not uncommon to see patients that have fasted in the past and report that they feel better. This is a good indication that they have a food intolerance. An elimination diet followed by provocation is helpful to assess cases clinically. Elaborate lab testing may not need to be implemented but IgG Elisa testing can be quite useful to assess food intolerances that are less obvious.^{21,30} IgG responses are provoked when there is a delayed response. IgG tests report the

severity of the delayed reaction and also provide a rotation diet schedule. Many investigators have noted improvements with dietary restriction of food intolerants. In our clinic, a small but significant portion of schizophrenics experience profound improvements after removing intolerant foods. Some researchers estimate 10% of schizophrenics having severe food intolerances.³¹ More research is needed to understand the pathophysiology, epidemiology, and clinical presentation of the food sensitive subset of schizophrenics.³²

The Schizophrenic with Digestive Compromise and Malabsorption

I constantly see gastrointestinal problems in schizophrenia including constipation, spastic obstipation, bloating, cramping, abdominal discomfort, IBS, and GERD. Compromised gastrointestinal function leads to malabsorption of nutrients. These patients often require higher doses of nutrients and medications. Lack of stomach acid can reduce intrinsic factor and diminish B₁₂ utilization which is essential for methylation and neurotransmitter formation. Poor bowel transit locks in toxins and they build-up, tax the immune system, and reduce the absorptive surface area. Poor bowel transit may be due to lack of peristalsis, low thyroid function, or magnesium deficiency. Adequate water intake is about two liters per day for the average adult. This is essential to keep toxins moving out and bowel contents hydrated. CAM treatment for digestive dysfunction and low thyroid function helps to alleviate digestive symptomology and also reduces the need for high nutrient dosing. Intact gastrointestinal health is a prerequisite for improved outcome in schizophrenia.

The Under-Methylated Schizophrenic

Schizophrenic researchers are well aware that certain brain tracts are overstimulated while others are understimulated (hypofrontality). If we can methyl-

ate efficiently, we have the machinery to form neurotransmitters in areas of the brain that are understimulated and neurotransmitter deficient. In our clinic, we see a good portion of schizophrenics with methylation compromise as indicated by elevated fasting homocysteine levels. Elevated homocysteine levels and methylation compromise are common in schizophrenia.³³⁻⁴¹ Elevated homocysteine levels have also been correlated with an increased severity of extrapyramidal symptoms.⁴²

Nutritional treatment with B₁₂, folic acid, and other methylators can restore methylation status. In schizophrenia, investigators have found methylenetetrahydrofolate reductase (MTHFR) genetic polymorphisms that disrupt folic acid pathways.^{43,44} These schizophrenics have a greater need for folic acid supplementation.⁴² Investigators suspect a causal link between elevated homocysteine and the MTHFR genetic polymorphism.⁴⁵ Many schizophrenics have adequate dietary intake of B₁₂ and folate yet their homocysteine levels are high.⁴⁶ These studies support the hypothesis that schizophrenic pathogenesis may be inherent.

Some evidence suggests that high circulating levels of homocysteine increase the level of homocysteic acid and cysteine sulphinic acid, both of which are NMDA receptor agonists that contribute to neuronal excitotoxicity.⁴⁷ It is not known if neuronal degeneration in chronic schizophrenia is due to elevated homocysteine levels. It is also unclear if NMDA-induced excitotoxicity plays a causative role in schizophrenia. More research on methylation in schizophrenia is required to fully understand the pathophysiological mechanisms.

The Vitamin B₃ and C Deficient Schizophrenic

Schizophrenics are poor at filtering the influx of sensory information and this

causes perceptual dysfunction (hallucinations, illusions). Overstimulated brain pathways have excess neurotransmitter and symptoms are, in part, caused by neurotransmitter overstimulation of the prefrontal cortex. Many neurotransmitter pathways are involved; some overstimulated, others understimulated. In a schizophrenic brain, vitamin B₃ and C (ascorbate) together have the potential to intervene and limit the production and oxidation of excess catecholamines in the brain.

Vitamin B₃ is one of the few methyl acceptors in the body. As a methyl acceptor, B₃ can limit, in a regulated fashion, neurotransmitter production.⁴⁹ When under stress, B₃ can also limit adrenal gland conversion of noradrenaline to adrenaline. Peripherally, this acts as a fail-safe mechanism to prevent excessive adrenaline production and consequent readily autoxidizable catecholamine end-products.⁴⁹

A catecholamine rich cerebral environment is prone to oxidation and oxidized metabolites are neurotoxic and hallucinogenic to humans.⁵⁰⁻⁵³ Oxidized catecholamines and toxic indoles may contribute to synaptic deletion.⁵⁴ In the healthy brain, oxidized catecholamines convert back to a stable form (neuromelanin), a process that has the effect of 'neutralizing' or 'storing' unwanted toxins.^{53,54} Smythies proposes that neuromelanin neutralization is compromised in schizophrenia and it may play a causative role.^{52,53} Both vitamin B₃ and C (ascorbate) have the potential to reduce oxidized catecholamine intermediates.⁵⁵ In the adrenal gland, vitamin C is found in high concentrations to keep oxidation at bay.⁴⁹

As a separate mechanism of action, B₃ and ascorbate are physiologically antagonistic to copper. They can help to limit dopamine overproduction which overstimulates the prefrontal cortex and disturbs executive functions. Excess cop-

per is very common in schizophrenia and copper is a cofactor in dopamine production. When dopamine pathways are overstimulated, serotonin (the opposing 'feel good' master neurotransmitter system) can become downregulated. This may in part account for some of the negative symptoms of schizophrenia.

Vitamin B₃ (NAD) can be found in several supplemental forms; as niacin, niacinamide, inositol hexaniacinate, and NADH. NADH is the reduced form and it is more active than NAD. NADH is dosed in the mg range. The other forms of B₃ can be dosed in the gram range. Niacin and inositol hexaniacinate are dosed safely in the gram range in the treatment of intermittent claudication, hypercholesterolemia, and Raynaud's. Sufficient doses of B₃ for schizophrenia are also in the gram range. Niacinamide and inositol hexaniacinate are flush-free. Pure niacin causes flushing due to the release of peripheral histamine stores. When dosed in the gram range, pure niacin causes a head down flushing response during day 1 and 2 of dosing. This subsides with subsequent gram range dosings. The inositol hexaniacinate form of B₃ is well tolerated and has a great safety profile. Numerous investigators report the use of inositol hexaniacinate in the 4 gram daily range without a single adverse reaction.⁵⁶⁻⁵⁸ Inositol hexaniacinate and pure niacin also promote brain blood flow which can be important in schizophrenic hypofrontality. Vitamin B₃ has an interesting side-effect of longevity. The Mayo Clinic found significant reductions in mortality in subjects with high baseline cholesterol who used niacin alone.^{59,60}

The B₃ deficient state is typified in the disease pellagra, the rarely seen vitamin B₃-dependent disease state. Classic symptoms of pellagra include psychosis, hallucinations, depression, anxiety, confusion, memory loss, anorexia, and fatigue.^{61,62} Pellagrins and schizophrenics

respond well to B₃.

The positive results of B₃ treatment have been noted in six double-blind trials on schizophrenic cohorts and an optimal dosing strategy is indicated.⁶³⁻⁸⁰

Vitamin B₃ and C are anti-stress vitamins. Practitioners who treat schizophrenics with vitamin B₃ and C continue to report positive responses.^{63,81-83}

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Pandeficiency Disease

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Introduction

Diagnosis classifies disease for two main reasons: (1) to improve prognosis and (2) to improve treatment. Prognosis is very important so patients and family can prepare for the future especially if the future is very dim. Estimating when a person will die may be extremely important for all sorts of reasons. Before specific treatment was discovered doctors were judged on their ability to prognose correctly. It would be very bad for the physicians reputation if his prognosis were wrong. Many years ago when I started to practice some of my patients, when giving me their history, would tell me that their doctor had told them they would die but the doctor died before they did. Good doctors were good prognosticators and this depended upon accurate diagnosis.

Diagnosis became even more important when specific treatment was discovered. Diagnosis advised the clinician what treatment to use. It was assumed that patients with the same diagnosis would respond to similar treatment which had already been described by other doctors. I had pneumonia in my early teens. Our friendly family doctor (he was also surgeon, emergency doctor, obstetrician, etc. as he was the only one in the community) told mother I had pneumonia and ordered mustard plasters. It must have been very effective or else my pneumonia was very mild as I was well in a couple of days. That was standard treatment for a disease that killed a large proportion of the victims. This diagnosis was a descriptive diagnosis. By listening to my chest the doctor discovered something wrong and it was most likely pneumonia. No other diagnostic tests were available.

After it was discovered that many

lung lesions were possible it became necessary to distinguish one from another. Was it bacterial and if so which bacteria, staph. or strep.? Was it cancer or silica or tuberculosis? Specific laboratory tests are used. Diagnosis is now etiologic. It is based on the cause of the condition. Until the causal diagnosis is made the treatment can not be very successful. This is the pathway diagnosis has traveled, from description of the site, the organ, and later to the cause when known. If the cause remains unknown the diagnosis remains descriptive. Psychiatric diagnosis is almost entirely descriptive.

Deficiency Disease

Clinical or descriptive diagnosis is not very accurate. It depends too much on the orientation and skill of the clinician and surprises are common. Disease caused by one factor can take a variety of expressions. This means that the descriptive principle of classification can not be used. A perfect example is pellagra. This is a classical deficiency disease caused by a deficiency of vitamin B₃ in food. But the expression is so varied that one can only with difficulty visualize it as one disease. Classical pellagra expressed itself in major skin lesions, in gastrointestinal changes and in mental changes. The pellagrous skin also varies enormously and even today expert dermatologists fail to recognize it. It does not by itself point to the cause. The gastrointestinal symptoms might need the diagnostic skills of a gastroenterologist and the psychiatric manifestations need the skills of the psychiatrist. During the great pellagra pandemic over 100 years ago in the United States, one third of the patients in the south-east mental hospitals in some years were psychotic and could not be distinguished from schizophrenia. When niacin and/or

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niacinamide became available it became simple: If one suspected pellagra (and that was natural in the pandemic areas) one needed only to give them niacin. If they were pellagrin they would recover, sometimes quickly, sometimes it would take much longer. For a physician not familiar with this major disease it would be almost impossible to accept that these conditions could be caused by a lack of only one factor. Doctors specializing in pellagra were known as pellagrologists. We still do not have a laboratory test. Blood assays for this vitamin will not reveal it until they are close to the fourth D of pellagra: death.

Another example is syphilis, a parasitic invasion. Its symptomatology was so variable, so wide spread, that enormous numbers of pages in old medical text books were needed to describe the clinical condition. After the development of the serological test these massive descriptions no longer were needed; one needed only to suspect and then order the test. When the test first came into use it must have been very surprising to the clinician to find so many patients not clinically suffering from this infection who were positive on the test.

The Saccharine Disease

During WWII Surgeon Captain T.L. Cleave was concerned about the physical ill health of many of the sailors. From his studies he concluded that most of them suffered from one disease over all others, he called The Saccharine Disease (1966). I had a copy of his original publication but it was worn out by constant use. This book turned my life around. I became a full time nutritionist. He designated it as the major disease which included diabetes, coronary disease, obesity, malabsorption, peptic ulcer, constipation, hemorrhoids, varicose veins, E. coli infections such as appendicitis, cholecystitis, pyelitis, diverticulitis, renal calculus and many skin

conditions and dental caries. (*Hoffer and Walker, 1978*).

This nutritional disease affected all the organs and systems which were then diagnosed according to the organ or malfunction of that organ. The cause was the diet which was too rich in the sugars and refined carbohydrates and too deficient in food containing its original fiber. It is also deficient in essential fatty acids, vitamins and minerals. The diet was typically refined cereals devoid of their bran and germ such as white bread, polished rice plus a heavy intake of sugar averaging about 125 pound per person each year. Cleave did not consider the role played by the deficiency of essential nutrient factors. He emphasized the excessive intake of sugar and the deficiency of fiber.,

The massive evidence Cleave discussed had little impact except for a sudden interest in bran as if it were a drug especially designed for people with constipation. Cleave did give his sailors bran but he was much more concerned with the white flour they were eating and his message was clear that what was needed was the original whole grain cereals as in whole wheat and rice. Just adding bran provided a partial answer. In 1972 Professor John Yudkin published his book *Sweet and Dangerous*. He presented the evidence that proved sugars were the culprit. His work was ignored.

In 1953 Professor Ancel Keys showed that there was a negative correlation between fat intake and cardiovascular disease. Later it was shown that he had been selective in presenting his data and when all countries where data was available were included, there was no correlation whatever. But he was very persuasive and his hypothesis swept the field. Food fats became the villains and medicine adopted a hypothesis which has been very detrimental; the low fat diet. It was forecast that this diet would eliminate these diseases. It did not but this is old

stuff, why the sudden interest?

Garry Taube in his recent book *Good Calories, Bad Calories* (Knopf, New York) debunks the low fat diet hypothesis. This severe case of mistaken consensus was foisted on us by a process called Cascade. A few highly placed individuals with sufficient self confidence and clout are able to establish ideas which lack sufficient evidence. It was predicted with the utmost confidence that switching away from fats and replacing them with carbohydrates would solve most of our cardiovascular problems such as heart disease, hypercholesterolemia, obesity and more. This view became the ten commandments of modern nutrition and were enshrined in Canada's food rules which emphasized cutting back on meat and fat and increasing carbohydrates. The massive evidence reviewed by Taube shows that none of these goals were realized. Instead we have an even worse pandemic of obesity, cardiovascular disease and a whole host of other condition such as diabetes. Why should this be surprising? If you need 2000 calories a day and if you are going onto a low fat regime you have to make up these calories by eating other food and this usually will be carbohydrates: sugars and products derived from refined flour. The low fat diet favored by all medical institutions in the US and Canada increased the intake of sugar and refined carbohydrates. The new diet and national food rules did not eliminate disease.

The evidence is massive that the major villain was and always will be sugar and refined foods that are converted into sugar too quickly and absorbed too quickly. This is typically the modern high tech diet which is characterized by too much sugar and too little of all the other important nutrients. How could such a massive error be made and imposed on the whole world? This is what makes this book so interesting and valuable for it traces from the beginning the influences which led to

this debacle. There was a relatively small clique of nutritionists who, according to Taube, were not scientists nor clinicians who actually treated patients, who spearheaded the low fat diet movement. It included Professor Fred Stare from Harvard University who once wrote that people would be much healthier if they doubled their average sugar intake from 125 to 250 pounds per person per year. Dr Stare received very large annual grants from various food industries whose products contained huge amounts of sugar. It also included Professor Jean Mayer. Both these professors were violently opposed to orthomolecular concepts. They were as correct in their ideas about orthomolecular as they were about the importance of sugar enriched diets. If we followed the dietary concepts of these two leaders in the field we would all be eating tons of sugar, white flour and white rice, would eat little fat and would never ever take any vitamins or minerals. Our chronically sick population would increase, the current financial sickness crises would get worse and I would be even busier.

Until 1940 clinicians wrote about food and diet and usually advised that one should decrease the amount of sugar and refined carbohydrates such as white flour and polished rice. Dr TC Cleave was emphatic that the modern sugar rich diet was responsible for a large number of diseases he called collectively The Saccharine Disease. One example was what happened to Jews who were expelled from North Africa and fled to Israel. When they arrived they were healthy but probably not very happy. After 20 years on the modern high tech diet they were probably happier but not very healthy. When I was in Israel 20 years ago a public health doctor told me that heart attacks and death, like in North America, were common. Taube provides an excellent review of Cleave's research and adds to it. He adds the metabolic syndrome which is now so common and

has become a major problem in psychiatry with the use of highly toxic antipsychotic drugs such as zyprexa.

The low fat diet originated when Professor Ancel Keys looked up the statistics of over 20 countries that had records of their fat intake and the incidence of heart disease. He selected a third of the countries which fit the correlation he had in mind and showed that the countries with the highest fat intake had the highest incidence of heart disease. Because he was so highly regarded and determined, that became the orthodoxy of nutrition. However when all the countries including the ones he had not used were looked at the correlation disappeared. Almost all the clinical studies show that the problem comes from the sugars and not from the fats. However for many people a low fat diet may have been helpful if it meant they eliminated dairy products (not eggs) from their diet. These people are allergic to dairy containing foods. For many people dairy products are the major source of fat. One should no longer talk about fat but about the foods which contain the fat.

Ever since reading Cleaves book many years ago I have advised my patients to follow a sugar free, refined carbohydrates free diet. I think most of them who followed my advice have been grateful. There is nothing more pleasing than feeling good.

How could this one explanation account for the amazing number of diseases. This is how. Constipation was the main outcome of a diet deficient in fiber rich foods, not in a simple deficiency of fiber. If it were a simple deficiency of fiber one could eat fiber made from wood. This will certainly increase the fiber intake but will do little for one's health. Chronic constipation leads to the other diseases of the intestine. In South Africa it was said you had be English to get appendicitis. The natives who still ate high fiber foods did not. The remaining diseases came from

the high sugar intake. These are diabetes, coronary disease. metabolic disease.

Everyone knows that the major problem with modern food is that they are too rich in fat. But is this really true? When I wrote everyone I was wrong. A few of us did not think so but rather thought that too much sugar, and too little fiber rich foods were much more pathological. But the sugar industry was more adept at deflecting blame from their major source of revenue and the meat and fat industry were too lax in fighting and fell for the same idea. For a complete description of modern foods see Hoffer (1999, 2005).

The Saccharine Disease is also characterized by a deficiency in vitamins and minerals. The foods richest in these nutrients are not consumed. There is really no question about this and it is well recognized by government as well as by the public. If governments concluded that the diets were adequate they would not have mandated the addition of three vitamins and iron to white flour. And I would not have gotten my first job as a control chemist in a flour mill. Vitamin C, thiamin, riboflavin, niacinamide, vitamin D, iodine, calcium are some of the nutrients that enrich our foods. But the most striking was the eradication of pellagra within two years in the United States after it mandated adding niacinamide to white flour in 1942. The Canadian government would not permit this. The American law was adulteration in Canada except that it had to ship the enriched flour overseas to the allied troops and the Canadian Commissioner of Indian Affairs insisted that it also be given to Canadian natives who used it to make bannock.

This is one of the most beneficial public health measures ever, not only in preventing physical disease but in preventing mental disease. Before enriched flour became available up to one third of admissions to South East mental hospitals in the United States were pellagrins who could

not be differentiated from schizophrenia by clinical examination alone. Pellagra, characterized by the four Ds – dermatitis, diarrhea, dementia and death – was gone. In the whole history of psychiatry there has never been a public health measure as effective. The addition of few pennies of B₃ to flour saved the US billions of dollars of disease generated costs. The addition of folic acid to flour has and will do the same. In our book *Feel Better, Live Longer With Vitamin B3* we summarized the epidemiological literature and reviewed my 55 years of experience in treating these conditions and concluded that about half the population, the sick half, would benefit by taking extra vitamin B₃. About half the population suffers from one or more chronic conditions.

In our book *Orthomolecular Nutrition*, (Hoffer and Walker), we described some of the psychiatric symptoms associated with the Saccharine Disease, with the excess sugar that helps to generate it, including anxiety and depression. The patients were referred to me by their family doctors because of these symptoms. When I first read about the role of hypoglycemia in causing mental disease I was very skeptical but I was also curious. A young female was referred to me for depression. She told me that her main problem was that she was frigid. Psychoanalysis was riding high many years ago and it occurred to me that she would be a perfect candidate for psychoanalysis or deep psychotherapy to explore why she was having this problem. I decided that it was unlikely this was caused by hypoglycemia and she would be ideal to disprove the effect of hypoglycemia. I ordered the five hour glucose tolerance test. The curve was typically hypoglycemic to my surprise. Not expecting it would help I still advised her to avoid all sugar and to increase her intake of protein. To my amazement she was normal in one month. I was now more interested than skeptical. I routinely had

patients with anxiety and depression do the test. Over 75 percent had the typical abnormal glucose tolerance curves. I no longer remained skeptical. Since then I have placed every patient on a sugar free and refined carbohydrate free diet without doing any more tests. The condition was present in every one of 300 alcoholics I treated. I did not realize it then but sugar created disease by playing havoc with the metabolism of sugar, altering it up and down, and because patients were allergic to it. Other the foods like milk, to which patients are allergic, will also give the typical glucose tolerance curves. Over the years I concluded that if every doctor who referred their patients to me were to first test them and treat them with the special diet I would lose half of my psychiatric practice.

Pandeficiency Disease

Cleave did not consider the fact that the saccharine diet was also deficient in the B vitamins, nor did the host of nutritionists since then, even though massive surveys have shown that it is impossible to obtain enough B vitamins with this diet. Nor did it occur to me until I had had many more years of experience using large doses of the B vitamins. We treated schizophrenic patients with large doses of niacin or niacinamide and ascorbic acid. This was based on our hypothesis that schizophrenia was caused by the excess conversion of adrenalin to adrenochrome, an oxidation product. We used niacin to decrease the formation of adrenalin and ascorbic acid to inhibit its oxidation. Other catecholamines could also be oxidized in the body due to super oxidative stress. Over the following years it became clear that many other diseases also responded to increased doses of some of the vitamins. Eventually my objective in treating patients changed. I no longer aimed at just curing their disease, I was now interested in much more. I planned

to give them a multi-nutrient program which would not only help them get well but which would keep them well as long as they remained on the program and until they died.

Life extension also became an objective as it had already been shown that niacin would decrease death rate and increase longevity. Finally I concluded that I would no longer adhere to the "one disease-one drug" concept that permeates medicine and the drug industry. Instead, I would do what I could using nutrition and relevant nutrients to help patients regain their ability to deal with stress and with disease. People heal themselves if they are given the right tools with which to do so. I have been using this program for many years and have seen a large number of patients recover from different physical and mental disorders using the same therapeutic program. In the same way added sugar and refined carbohydrates will cause the Saccharine Disease, a multiple deficiency of vitamins will cause what I now call the Pandeficiency Disease (name suggested by Frances Fuller). It is a general disorder which may impact on any organ or system or function or combination. About half the population suffers from this chronic pervasive disease caused by the overall deficiencies in modern high tech diets. If the psychiatric professions were to look carefully at the diagnostic system it now uses it could eliminate hundreds of psychiatric disorders and their official numbers. Almost all the ADD diagnosis of children can be eliminated.

The Treatment Program for Pandeficiency Disease

Diet. Sugar free (including fruit juices), no refined grains, no foods one is allergic to.

Vitamin B₃ In decreasing order of preference: niacin, niacinamide and non-flush preparations. Dose varies from 100 mg to several grams after each of three meals.

This vitamin is most relevant. If the dose is too small it will do little. For schizophrenia it is the most important one as this disease is not a multivitamin deficiency disease. It is pellagra. For its many therapeutic properties see Hoffer and Foster. The best and safest non-flush product is niacin itself as the flush gradually goes away with continued use.

Ascorbic acid 500 mg to several grams three times daily after meals. It is a water soluble antioxidant and antistress substance. It is valuable in decreasing the incidence of flu and colds and thus decreases the danger of relapse.

B complex 100s, once daily, any meal. It is likely that if one nutrient is lacking so will many others be. This mixture provides a good mix of all the other B vitamins. It contains 100 mgs of B₆ but sometimes more will be needed up to 500 mg daily.

Vitamin D. I recommend 6000 IU daily in the winter months and 4000 IU in the summer if living in Canada. In the far north I recommend 6000 IU daily all year. Even in California or Florida many do not get enough exposure to sun which they avoid, following advice by dermatologists,

Other Vitamins May be Needed

Thiamine for alcoholics and sequela such as Wernicke Korsakoff and for very heavy consumers of sugars. Dose 100 to 500 mgs three times daily with meals.

Folic acid as an anti depressant, 25 to 50 mg daily (prescription needed) and less to lower elevated homocysteine levels in blood.

Vitamin E 400 to 800 IU daily but up to 4,000 IU for muscle wasting diseases including Huntington's Disease and Amyotrophic Lateral Sclerosis

Essential fatty acids-Fish oil (eg Salmon, non farm) 1 g, three times daily after meals.

Selenium-200 to 600 mcg once daily, any meal. This is especially important

when living in areas deficient in selenium like the west coast of North America. In Victoria, where I live, animals not fed selenium will die of muscle disease. It has major anti-cancer and anti-viral properties.

Zinc citrate-50 mg or zinc sulfate 220 mg once daily, any meal.

Calcium-magnesium-1000 mg Ca with 500 mg Mg daily

The total cost of this program per month should be less than the cost of one pill of any anti depressant or atypical anti psychotic drug. Ideally we need specific laboratory tests that are cheap and will tell us exactly which nutrients are needed. We are not there yet and may never be there. With drugs it is far better to err on the side of too little as they are so toxic but with vitamins it is better to err on the side of a little more as they are so safe, so free of side effects and so cheap. Vitamins will have beneficial side effects. No one dies from vitamins. There are no bodies strewn across the country side as there are with drugs; 135,000 each year in Canada and the United States die in hospital with the recommended doses of drugs. Up to 100,000 deaths from one drug, Vioxx. Merck will pay nearly \$5 billion for the victims of Vioxx in the United States (November, 2007).

Medication

This program is compatible with any medication and has the major advantage that when used in combination the drug dose can be drastically reduced thus decreasing the toxic side effects. During my long career in treating schizophrenic patients with a combination of drugs and orthomolecular treatment, less than a handful of my patients developed tardive dyskinesia. It was never a problem and is easily treated. The basic medical injunction "First Do No Harm" applies to drugs. With vitamins it has much less relevance since they do no harm. Hip-

pocrates probably originated the phrase. One translation reads: "Declare the past, diagnose the present, foretell the future; practice these acts. As to diseases, make a habit of two things — to help, or at least to do no harm."

Some Conditions, Hoffer and Foster (2007)

These conclusions are based upon my personal experience in treating many patients with these conditions. I've described case histories beginning in 1960 in 30 books, in 600 publications in the establishment press and in the alternative press, mostly in the *Journal of Orthomolecular Medicine*. JOM has been blacked out by Med Line, the official censoring organization of the anti-orthomolecular establishment. They probably keep JOM properly hidden in some dark closet and classified as top secret. But their censoring role is coming to an end as JOM is now available at <http://orthomolecular.org/library/jom/index.shtml>

Psychiatric Disorders

Schizophrenia and schizoaffective disorder. The main emphasis should be on vitamin B₃. Hoffer (2007,2007a). Number of patients treated: over 5000.

Huntington's Disease. The main emphasis should be on niacin and vitamin E in high doses. Number treated: 2.

Mood disorders. The main emphasis should be on niacinamide, Prousky (2007). Hoffer and Prousky (2006). Number treated: over 1,000

Alcoholism. Developed in close association with Bill W, the co-founder of Alcoholics Anonymous. Main emphasis is on niacin. Number treated: over 500

Fetal alcohol syndrome. Number treated: 2.

Children with learning and behavioral disorders Hoffer (2005) Number treated: over 2000.

Autism. Pyridoxine very important.

Number treated: over 25.

Physical Disorders

Obesity. Jean Mayer, who was strongly opposed to orthomolecular therapy and practice, promoted the simple view that obesity was due to the very simple rule, too many calories in and too few calories expended out. This has become the standard belief of all anti-obesity programs because it seems to make so much sense. However, according to Taube, his massive examination of the clinical literature provides no support for this idea. There is no relation between the amount of food consumed and the amount of exercise expended and obesity. Many people are not obese no matter how little or how much they eat and too many are too fat no matter how little they eat. The problem is not the total amount of food consumed but the kind of food. According to Cleave, Yudkin, and now Taube and many others, the main factor that creates obesity is the amount of sugar and refined carbohydrates that are eaten. Sugars and foods that rapidly release them into the blood are the villains. It is true that if one eats too many calories there will be a much greater tendency to put weight on but the real question is why do these people eat too much junk food.

I think they do this because they are sick. An example is the intolerable weight gain of patients who are treated with zyprexa, an atypical anti psychotic drug. I have seen young patients gain 60 pounds in six months after being placed on this dangerous psychiatric drug. It increases appetite enormously. But this is relatively rare. A more common reason is the modern high tech diet which is deficient in every nutrient except sugars and refined foods that create this appetite to eat more. I have called this the Wald hypothesis. George Wald got the Nobel prize for his work with vitamin A. He also showed that starving rats ran a lot more but so

did rats on a diet that contained enough calories but did not have any of the B vitamins. This also increased running (Wald and Jackson, 1944). It makes sense that hunger will increase running (activity) in animals since that motivates them to seek food; to hunt. But it is surprising that depriving them of the B vitamins will do the same unless one postulates that the animals sense the B vitamin deficiency as equivalent to hunger and tries to deal with that by increasing activity (Hoffer, 2007). The diet too rich in sugars is also too deficient in B vitamins. Since during evolution animals who did not respond to hunger by searching for food would not be around today, this has become a natural genetic reflex. Thus the modern diet will activate people in the same way.

There are three scenarios. The first will be the modern high tech diet where no one starves, food is plentiful and easily obtained. The hunger for nutrients (food) will lead to too much being eaten and they will get fat. And they will feel better with their obesity because they are getting more of the B vitamins. They remain uncomfortable if forced to remain thin. In the second scenario there is not enough food. In this case populations deficient in B vitamins will not be able to get the vitamins they need by eating more and they will become lean and hyperactive until felled by starvation. In the third scenario in children the drive for the B vitamins will increase activity leading to the hyperactive syndrome and later to obesity. This hypothesis that excess intake of calories from foods deficient in B vitamins increases activity either by eating more and being more active is a good hypothesis and it is easily tested. I have done so to a limited degree. I have tried to help many obese patients with little success using any type of diet. But when I advised them to go back to the stone age diet, to take ample amounts of B vitamins and to eat as little or as much as they wanted they

would lose weight with comfort. These were no longer reducing diets. They were the new healthy life styles.

Arthritis. Main emphasis is on niacinamide and/or niacin. Vitamin B₆ and zinc are also very useful. Number treated: over 50

Cardiovascular. Niacin is most important, followed by ascorbic acid. Niacin lowers total cholesterol, lowers triglycerides, lowers lipo A, elevates HDL and has anti inflammatory properties on blood vessels, while vitamin C strengthens the collagen in the blood vessel walls. Not surprisingly, it decreases mortality and increases lifespan.

Multiple Sclerosis. Most important are thiamin, niacin, vitamin D. Number treated: over 50.

Aging. Most important is niacin. Number treated: over 100

Skin. Most important are niacin and essential fatty acids

Diabetes Mellitus. By controlling levels of the cholesterol fractions, niacin protects against the cardiovascular consequences of diabetes mellitus. Number treated: over 10

Virus infections and HIV/AIDS. see Foster(2002). Most important, selenium, ascorbic acid. According to Foster's views, based on a comprehensive examination of the literature and his own extensive research, life on earth is facing a shortage of selenium due to the use of fossil fuels. This is a main factor in the wide spread of virus such as hepatitis B and C and HIV/AIDS. Foster concluded "In short, these three viruses, that are known to encode for glutathione peroxidase and to diffuse rapidly in populations that eat diets that contain inadequate selenium and amino acids, have infected one third of the planet's population. Clearly, antiretroviral drugs, condom use and demands for chastity, unpolluted water and greater cleanliness will not halt these pandemics. We are still awaiting the often promised,

but never delivered, vaccines against HIV and hepatitis C. The tipping point has long passed. To halt the AIDS and other viral pandemics we need to begin the addition of selenium to most fertilizers and to table salt and the promotion of foods (including green algae) that contain higher levels of amino acids. These strategies will also slow down viral mutation and, therefore, the appearance of new human pathogens".

Bacterial infections. Most important high dose ascorbic acid

Cancer. Most important, high dose ascorbic acid, niacin, selenium and vitamin D. Number treated: over 1500

Patients with these diagnoses will respond to the multi-vitamin, multi-mineral regimen described here. They may not all be needed for a particular disease but as there is no way of determining which ones are most needed for that person and since a deficiency of only one nutrient is very rare it is better to use the whole regimen which is safe and can do no harm. Patient acceptance of this regimen is very high. After the patient has recovered they may find out for themselves which ones are most important by eliminating one at a time to see if it makes any difference. Many patients after they have been well for a long time will gradually modify the program and may go off it entirely. If they relapse, as many do, they will resume the program. The relapse may occur in weeks, months or even after several years.

Following Cleaves' lead in decreasing the number of diagnoses to one he called the Saccharine Disease, I have done the same by calling these diseases the Pandeficiency Disease (Occam's Razor). The Saccharine Disease is caused by too much sugar and refined carbohydrates and too little fiber rich foods. The Pandeficiency Disease is caused by the multiple deficiency of vitamins and minerals. I include the schizophrenias even though they are B₃ dependent i.e pellagra.

Causes

Here is a short list of causes. It will be expanded when research physicians look at this condition more enthusiastically.

Diet. This is the most common reason. During wars, droughts, famine and other catastrophes of mankind the food supply is always jeopardized. This is so well known that in emergencies the first efforts are to provide food and clean water. Africa suffers from these catastrophes in many areas. Their people will surely suffer permanent ill health even after the situation has been corrected. If the starvation and malnutrition is sustained too long and combined with stress they will become vitamin dependent on one or more vitamins. This is what happened to survivors of the far east prison of war camps and of the concentration and death camps in Europe and Asia

Iatrogenic. No attention to the nutritional needs of patients in hospital under very severe stress. Vitamin deficiency occurs in hospitals if patients have to live there too long.

Allergies. I have found a strong association between food allergies and the need for vitamin and mineral supplements. I became aware of this connection when I started fasting my patients to determine what foods they were reacting to. I soon found that some patients who needed 12 grams of niacin in order to control partially their psychotic symptoms could not tolerate nearly that much when these foods were identified and removed. Patients needing this much would do even better on 3 grams. This puzzled me. I think the explanation is relatively simple. Foods to which any person is allergic cause a chronic inflammation of the small intestine which then allows polypeptides that have not been fully

broken down to their basic amino acids to enter the blood (leaky gut) and this also decreases the adsorption of vitamins and minerals. When this continues for a long period of time the mild chronic deficiency caused by the food allergy will become a dependency, especially for niacin and perhaps for other nutrients as well. I have seen many on a milk diet who also showed the Pfeiffer signs of pyridoxine and zinc deficiency. Milk inhibits the absorption of zinc.

Diseases of Gastrointestinal Tract. Any disease of the gastrointestinal system will interfere with absorption of nutrients and if this becomes chronic will convert a deficiency to a dependency condition.

Viral infections. The best example is HIV which produces a selenium deficiency. The symptoms of AIDS are identical with the symptoms of selenium deficiency. (See HD Foster *What Really Causes Aids*)

Deficiency and dependency. A deficiency is present when the amount of any nutrient in the diet is below what the average person needs. Classically it applies to the well known deficiency diseases such as scurvy, beri beri, pellagra, rickets Scurvy is caused by deficiency of ascorbic acid. This deficiency alone has killed millions of people. Pellagra is caused by too little vitamin B₃ in the diet. This was the basis of the old paradigm called vitamins-as-prevention, clearly developed about 100 years ago and reluctantly accepted by the medical profession about 50 years ago but since then it has become so solidly established as if it were writ in stone even though it is totally out of date, wrong and harmful to so many patients. The reason it is inadequate is that it assumes that every one has the same nutritional needs. That is like assuming that every one has the same finger prints. A large

number of our population have needs for vitamins that are much greater than can be obtained from our modern diets and if they depend upon the diet only they will never achieve optimum health. For these people the correct term is dependency.

A deficiency will become a dependency if the deficiency is chronic. The rapidity with which this occurs depends on several factors including severity of the stress, severity of the malnutrition and iatrogenic causes. These are trigger factors. The European concentration camps and the far east prisoner of war camps were ideal for throwing people into the dependency state if they lived long enough. In the Japanese war camps, Canadian soldiers were incarcerated for 44 months. There they suffered severe malnutrition including about 800 calories daily, several deficiency diseases and this was combined with severe physical and psychological stress. One third died in camp. The remaining soldiers remained sick with the exception of few who were given niacin three grams daily.

The risk of becoming dependent varies with malnutrition, its duration and intensity, with the presence of disease such as infection of the gastro intestinal tract, food allergies, and systemic infections, its duration and intensity and with the level and duration of stress. When all three factors are operating at high levels the time needed to become dependent will be shortened. Cleaves found that it took 20 years before the Saccharine disease developed on the high sugar, high refined carbohydrates and low fibre diet, but without abnormal stress. The Canadian soldiers in Hong Kong camps became dependent in four years. But their malnutrition, presence of disease and stress was much more severe.

Prevention and Treatment

Treatment is of course very obvious. The diet must be improved, stress must be alleviated and disease must be treated. In

addition niacin must be given in optimum amounts and other nutrients as well. It is no secret that stress should be relieved and that disease should be treated but the medical profession and the nutritional professions have not yet learned that extra niacin will also be needed. If one expects to endure stress and illness it is wise to start on niacin immediately. Unfortunately the poor will not be able to afford prevention and adequate treatment. Orthomolecular treatment, due to the ignorance of medicine, is available only to people who can afford to seek and find orthomolecular practitioners.

To prevent or treat or both these are the three most important principles (1) Optimize the diet. (2) Remove trigger factors. (3) Use the correct nutrients in optimum doses.

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A Child with Metastatic Sarcoma and A Patient with Cancer of the Head of the Pancreas

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At The Center we see many patients with cancer who have been told to “go home and get your affairs in order, there is nothing more I can do for you,” who respond to the Dr. Riordan intravenous vitamin C (IVC) protocol for cancer.¹ The Center does not advertise itself as a “Cancer Treatment Center,” however, we do treat patients who have cancer when they come to The Center seeking help.

The first patient is a five-year old boy with a sarcoma that had spread to the liver. He was first seen at The Center in March, 2004. He previously had surgery for the cancer and was started on a 12-week course of chemotherapy. This was to be followed by radiation, further surgeries and 42 weeks of chemotherapy. The oncologist did not want the patient to have intravenous vitamin C (ascorbic acid) during any of these treatments. During this three-year period of time, Dr. Kirby, prescribed various nutrients and supplements to help him under these circumstances.

After all the chemotherapy treatments, this thin, bald-headed, anemic young boy started his treatment at The Center. In October, 2006, he was given a 7.5 gram IVC. His post-IVC plasma level was low, 89 mg/dL. The optimal killing dose established by research performed at The Center is between 350 and 400 mg/dL.¹ In November, Dr. Hunninghake increased the IVC dose to 15 grams twice a week. The post IVC plasma level was 148 mg/dL.

The 15 gram infusions were continued until mid-December. The post IVC

level after this series was 153 mg/dL. For the next month the IVC dose was raised to 25 grams twice weekly. In mid January, 2007, the post-IVC was 314 mg/dL. The post-IVC plasma remained stable at high levels. In July, 2007, Dr. Hunninghake noted, “He continues to ‘hold his own’ quite well.”

The patient and his father reported that he is “improving over time.” The father also stated that his son was taking all the oral supplements, including oral vitamin C. He went on to say that “He continues to gain weight and do quite well despite a doctor saying ‘I’m sorry, your son’s chances of a cure are not good!’”

One would argue that it was the surgery, radiation and chemotherapy that accomplished the results seen in this patient. Based on our experience, we know IVC played a big role in this patient’s continued recovery. High dose IVC has been proven to kill cancer cells and it also stimulates the immune system in at least five different ways.² Chemotherapy will severely weaken the immune system.

A diagnosis of cancer of the head of the pancreas is generally followed with a life expectancy of three to six months. We have previously reported on a male patient with this same diagnosis who did very well on high-dose IVC treatment.³ The second patient is a 64-year old woman who came to The Center in early July, 2005, with a prior diagnosis of cancer in the head of the pancreas. The diagnosis was confirmed with various scans and biopsies, and surgery was performed. As a result of the surgery, she became diabetic.

1. The Center for the Improvement of Human Functioning International, Inc., 3100 North Hillside, Wichita, KS 67219

She was started on 15 grams of IVC daily for about 10 days. On July 15 her IVC was increased to 25 grams three times a week. In early September her dose was increased to 37.5 grams daily. In October, 2005, she began chemotherapy. Her oncologist insisted that she stop all IVC and alternative therapy. She stopped the IVC but continued on oral nutrients. During this period her post IVC plasma levels ranged from 112 mg/dL to 226 mg/dL. In May, 2007, she returned to The Center to continue her IVC therapy.

Dr. Kirby started her on 25 grams IVC twice a week and in June the dose was increased to 37.5 grams twice a week. Her last two post-IVC plasma levels were 425 mg/dL and 400 mg/dL, well within the "killing range" for cancer cells. She continues this treatment, along with oral supplements. Since she was now a diabetic and receiving high-dose IVC, she could no longer use her finger stick blood glucose instrument and strips to monitor her blood glucose.

As The Center staff has shown, the blood glucose meter and strips cannot distinguish between the ascorbic acid (vitamin C) molecule and glucose. Immediately after a treatment, and up to six to eight hours after treatment (depending on the dose), a reading of 495 mg/dL, 500 mg/dL or "high" reading plus positive ketones may be obtained on the glucometer. In this patient's case, a serum glucose was performed as the ascorbic acid does not interfere with the hexokinase method.⁴

She has lived two years and six months (and still counting) with a disease noted to kill very quickly. She stated that she is committed to the IVC treatment for quite some time into the future.

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Raising Concerns About Unmetabolized Folic Acid

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Summary

The advent of food fortification with folic acid along with the growing enthusiasm for vitamin supplements have made it quite possible, if not probable, that large populations in several countries are at risk for high intakes of synthetic folic acid. The ramifications of this are unknown, but there is a growing body of evidence which suggests that there may be the risk of serious health problems associated with this practice. Of particular concern are the differences in metabolism between dietary folates and synthetic folic acid and the potential of the latter to yield high levels of unmetabolized folic acid in the circulation. This phenomenon appears to be largely unrecognized, and the potential risks largely ignored. The concerns that have been identified relate mostly to cancer and cognition.

Introduction

Human intake of folate/folic acid is essentially limited to four sources: food, supplements including multivitamins, therapeutic doses taken on the advice of physicians, and fortified foods. It is becoming more apparent that naturally occurring folate in foods must be clearly differentiated from folic acid which is used in supplements and in food fortification, the reason being that they are not in general equivalent. The term folic acid will be used to represent pteroylmonoglutamate (PGA), the synthetic chemical used in fortification, therapy and supplements, and folate to represent natural forms from food sources, both primary as downstream metabolites. While it is true that folic acid (PGA) is converted to

metabolites identical to those obtained from food sources, what is significant is that this process saturates at folic acid intake levels between 200 and 400 $\mu\text{g/day}$ and at intakes above this saturation limit, unmetabolized folic acid (UMFA) appears in the circulation.^{1,2} This does not seem to be common knowledge. Folic acid and dietary folates are frequently viewed as the same substance. It has also only recently been observed that while dietary folate is initially metabolized in the small intestine, the liver is the primary site for the metabolism of folic acid.³ The overall and long-term implications are unknown.

There is a potential problem for the following reasons: (a) no long-term information is available on the safety or possible adverse effects of UMFA or high intakes of folic acid in general; (b) the growing and widespread use of multivitamin supplements as well as B-vitamin supplements increases the likelihood of significant as well as very high levels of UMFA; (c) in countries such as the USA, Canada and a few others, mandatory and voluntary food fortification offers the opportunity for significant intake of folic acid from prepared foods such as bread and ready-to-eat breakfast cereals; (d) there is a growing body of evidence suggesting that high levels of folate/folic acid intake may increase the risk of various disorders including cancer. High intakes of folate/folic acid can only be achieved with multivitamins, separate folic acid supplements, or high consumption of folic acid fortified foods. Thus high folate/folic acid intake may be much more common than generally recognized and will invariably be associated with circulating UMFA. This commentary will address some of these issues.

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The Range of Folate and Folic Acid Intakes

It is well known that for individuals who do not supplement and do not eat fortified foods, dietary intakes of folate are in the 200-400 $\mu\text{g}/\text{d}$ range. Most North American multivitamins contain 400 μg of folic acid per pill, and many individuals take two per day. Some consider the B vitamins so important they take a so-called B-50 supplement which contains 1 mg folic acid per pill. Sometimes this is in addition to a multivitamin. Food fortification was expected to provide 100-200 $\mu\text{g}/\text{d}$ of folic acid, but there is now evidence that the amount may be considerably higher,⁴ and the opportunity exists for rather high intakes by those who fancy large servings of ready-to-eat breakfasts cereals, i.e. intakes of well over 400 μg , the amount per serving, just from this single source. Nutritional drinks and bars can also supply 400 μg per serving. Thus it is possible for intakes from combined sources to reach 1200-1500 $\mu\text{g}/\text{d}$ and in some cases even higher levels can be envisioned, most of which ends up as UMFA. There is little concern, aside from that expressed in a few editorials and perspectives,⁵⁻⁸ about such folic acid intake since the conventional wisdom holds that folic acid is safe; physicians prescribe therapeutic doses of up to 5 mg/d and 1-5 mg/d is common in many intervention studies.

There are a number of incentives that encourage supplementation. Widespread concern among both health care professionals and the general public over the connection between cardiovascular disease risk and homocysteine levels has prompted considerable interest in folic acid supplementation, which will generally produce 20-50% reductions in serum homocysteine, and there have been a number of intervention studies in this context which generally involved doses in excess of 1 mg/d. All women of childbearing age have for some time

been strongly encouraged to take folic acid, typically at a dose level of 400 $\mu\text{g}/\text{d}$, in order to reduce the risk of the folate related neural tube birth defects. This was of course the reason for mandatory food fortification since educational programs designed to motivate women to maintain a satisfactory folate status prior to conception were notoriously ineffective. It is not clear if some women concerned about birth defects in their offspring take a folic acid supplement in addition to a multivitamin, or that much thought is even given to multiple sources of folic acid, either by this group or for that matter by anyone other than a few academics. The USA Institute of Medicine recommendation of an upper tolerable folic acid intake for adults is 1 mg/d from supplements and fortified food and 300-400 $\mu\text{g}/\text{d}$ for children between the ages of 1 and 8. These limits are almost 10 years old and were devised mainly to avoid masking anemia and missing the neuropathy attributed to vitamin B₁₂ deficiency.

Thus it is clear that in some countries there is a strong possibility that high or even very high levels of folic acid intake and circulating UMFA are common. In what follows, evidence will be reviewed relating to why this should be of concern to physicians, those involved in public health, those concerned with both mandatory and voluntary food fortification, and ultimately the general public.

The Cancer Connection

Folate is thought to play a role in cancer prevention. Evidence derived from epidemiologic studies consistently shows positive associations between low levels or intakes of dietary folate and the risk of colon cancer or cancer in other parts of the gastrointestinal tract.⁹ Observational and interventional studies of the relationship between higher intakes of folate/folic acid and the risk of various cancers have produced results which

cover a full spectrum ranging from significant benefits to significant increased risk, but most have produced equivocal or null results. Observational studies must now deal with a range of folate/folic acid intake from dietary sources alone to a mix of dietary folate and folic acid from supplements and fortified foods, with the latter changing over time. The matter is complicated by voluntary fortification of specific foods for market advantage which actually predates mandatory fortification of grains. Intervention studies that included high folic acid intakes have generally employed 1 to 5 mg/d which alone will produce high serum levels of UMFA. The connection between folate/folic acid and cancer is complex as is indicated by the well known effect of folate to promote cell proliferation and in particular the use of anti-folates such as methotrexate as chemotherapeutic agents.

Breast Cancer

Two large meta-analyses have recently been reported, both of which examined studies involving dietary only folate or dietary plus supplemental folate/folic acid.¹⁰⁻¹¹ No association with breast cancer risk was found. However, a recent study from Sweden of women in the Malmö Diet and Cancer Cohort found a protective effect but only when the lowest vs. the highest quintile of intake was compared.¹² In this study only 19% took supplements and the cut-point for the highest quintile was 349 µg/d. One of the first indications that high folate/folic acid might be harmful came from the Prostate, Lung, Colorectal and Ovarian Cancer Screening trial (PLCO). A 20% increase in the risk of developing breast cancer was found for postmenopausal women taking ≥ 400 µg/d of supplemental folic acid compared to those reporting no supplemental intake.¹³ The mean intake from supplements in the top quintile was 738 µg/d and the grand total in this quintile from food (after

fortification) and supplements was over 1200 µg/d. Consistent with all prospective studies,¹⁴ no statistically significant association was found between breast cancer risk and dietary folate intake. The mean intake in the top quintile from food was only 473 µg/d. Ulrich, in an editorial comment on the Malmö study, points out that the Swedish cohort had quite low dietary folate intakes and that it may be that it is in such populations that an inverse association between dietary folate and breast cancer is most likely to be observed. She also points to the evidence from the PLCO trial and suggests that the risk vs. folate/folic acid intake curve may be U-shaped, that women with adequate folate status derive no further benefit from additional intake, and that high folate status attributable to supplement use may increase the risk.⁹

A study from the UK found for women using folic acid supplements before and during pregnancy that 5 mg/d increased all-cause cancer death by 70% when the reference was a placebo or 200 µg/d, but the increase in breast cancer mortality was suggestive but not statistically significant.¹⁵ Also, it is well known that there is an interaction between alcohol and folate and in women with moderate alcohol consumption, taking 400 µg/d of folic acid results in the elimination of most of the alcohol-associated risk of breast cancer—another incentive for supplementation, but probably not common knowledge among the general public.

Colorectal Cancer

The recent report from the Polyp Prevention Study Group by Cole et al¹⁶ presents data indicating that folic acid supplementation might increase the risk of colorectal neoplasms, i.e. aggressive supplementation might enhance the growth of established microscopic lesions. This was a randomized clinical trial where all the participants had a prior his-

tory of excised colorectal adenomas. The endpoint was at least one new adenoma. Data on new neoplasms were collected with two colonoscopies conducted over a period of 6-7 years.

This study employed 1 mg/d of folic acid. Individuals taking multivitamins were not excluded (38% in the placebo group, 34% in the intervention group) and the period of recruitment coincided with the start of mandatory grain fortification in the USA. The percentage taking additional folic acid supplements over and above what was in their multivitamins was about 7% during the first follow-up interval, and increased to 14-18% during the second period. Thus some subjects could have had additional intakes of 400-800 µg/d of folic acid from multivitamins, and an unknown amount from folic acid supplements, and 200-400 µg/d or even more from fortified food. Total intakes of 2 mg/d might have been common, and amounts over 2 mg/d possible. Thus in this intervention study it is highly likely that all the participants had high levels of unmetabolized serum folic acid and some may have had very high levels. The authors admit that they carried out their study in a folate-replete population. It was found that the 1 mg/day dose of folic acid was associated with elevated risk of having 3 or more new adenomas when comparison was with the placebo group. In addition, the folic acid intervention was associated with an unadjusted increase in risk of 67% of developing at least one advanced lesion. Cole et al comment that their results are consistent with a recent observational study¹⁷ that found that adenoma risk is inversely associated with plasma folate levels only among individuals not taking multivitamins. Similar results were found in a study of colorectal cancer risk in women where dietary intakes of folate were significantly inversely associated with risk only among those not taking supplements containing

folic acid.¹⁸ As Kim points out in a recent review, the overall evidence supports an inverse association between folate status and colorectal cancer risk, but that folate appears to possess a dual modulatory effect on colorectal carcinogenesis that depends on the timing and dose of the intervention. For the progression of established neoplasms folate deficiency appears to have an inhibitory effect whereas folic acid supplementation appears to be a promoter.¹⁹ This view was also expressed in an editorial by Ulrich and Potter.²⁰

There is also evidence of added complexity due to gene-nutrient interactions. A recent study by Vogel et al examined the role of folate in sporadic colorectal cancer associated with mutations in the adenomatous polyposis coli (APC) gene. The results suggested that folate enhances colorectal carcinogenesis through a distinct APC mutated pathway.²¹

Finally, it has been pointed out by Mason et al that there is a temporal association between the advent of folic acid fortification and an increase in colorectal cancer rates. They point out that both the USA and Canada have experienced abrupt reversals in the downward trend of colorectal cancer incidence that both countries had enjoyed in the preceding decade and that these changes do not appear to be explained by changes in the rate of endoscopic procedures. The reversal in both countries coincided with the beginning of mandatory grain fortification.²²

In all of these studies the potential role that UMFA might play is ignored even though in some cases the observed adverse effects could be due to this substance rather than elevated levels of folate itself. To give separate consideration to UMFA would obviously complicate most studies, especially given the already very complicated biochemical-genetic system in operation. In fact, it is normal for studies to lump folic acid and folate together in serum assays. This is, however not an

argument for ignoring the potential harm that could arise from high circulating levels of a molecule foreign to human biochemistry.

Prostate Cancer

Studies that examined the connection between prostate cancer and dietary folate/folic acid have been in general inconclusive. However, a study by Lawson et al adds to the concern about high doses of folic acid.²³ This was the NIH-AARP Diet and Health study which involved almost 300,000 men with a follow-up of 6 years. While no association was found between multivitamin use and the risk of localized prostate cancer, an increased risk of advanced and fatal cancers was found among men reporting multivitamin use more than 7 times per week. However, for men who took multivitamins more than 7 times per week and in addition took a folic acid supplement, significant enhanced risk was found for all prostate cancers considered together and for localized cancer.

The Connection between UMFA and Natural Killer Cell Cytotoxicity

Early in 2006 a paper by Troen et al appeared which may well have a very significant impact on the eventual understanding of the possible cancer promoting effect of UMFA.²⁴ In this study it was found that among a group of postmenopausal women, those who consumed a folate-rich diet and in addition used supplements containing > 400 µg/d of folic acid exhibited reduced natural killer (NK) cell cytotoxicity with a dose dependent lower cytotoxicity at higher levels of UMFA. UMFA was present in 78% of the women in the study group. The authors point out that the measured plasma folic acid was lower in this study than in other studies such as that of Kelly et al.¹ Thus even larger suppressions of NK cell cytotoxicity might be present in the

studies discussed above where the intake of folic acid was much higher.

Experimental and clinical evidence supports the role of NK cells in tumour cell destruction and they can be considered the first-line host defence against carcinogenesis.^{25,26} Thus there appears to be justified concern about UMFA. A decrease in NK cell cytotoxicity might contribute to the increased risk of colorectal adenomas observed by Cole et al²⁴ since there is a high probability that most if not all the participants had high levels of UMFA, given that the study dose alone would have been sufficient. The same would apply to the breast cancer study by Stoltzenberg-Solomon et al.²⁷ Troen et al point out that there is no clear mechanistic explanation for their observations and they regard their results as raising concerns about the independent toxicity of high levels of folic acid. It can only be hoped the study of Troen et al stimulates research into the many important questions raised. The suggestion that studies are needed of UMFA in the context of cancer is just now starting to appear in the literature.¹⁹

The Homocysteine Lowering Studies

Once it was generally recognized that elevated blood levels of homocysteine represented a significant risk for cardiovascular disease, there was great interest in attempting to reduce this risk by lowering the levels with supplementation using either folic acid alone or a combination of folic acid and either vitamin B₆ or B₁₂ or both. A number of studies have reported and Bazzano et al have provided a meta-analysis.²⁸ The folic acid doses ranged from 0.5 to 5 mg/d, with most in the range of 2.5 to 5.0 mg/d. The duration of intervention ranged from 6 to 60 months and all involved secondary prevention in patients with CHD, stroke or end-stage renal disease. Percentage reductions of homocysteine levels were

typically between 25 and 50%. The results have been uniformly disappointing with almost all studies yielding only a huge collection of statistically insignificant results for a variety of endpoints such as cardiovascular disease, coronary heart disease, stroke and all-cause mortality.²⁸ While these studies provide no direct evidence of adverse effects associated with high levels of UMFA in the context of the above endpoints, these high levels surely must have existed given the very high doses of folic acid used. It has been argued that the homocysteine lowering might have indeed had a beneficial cardiovascular effect, but that the high folate/folic acid levels had adverse effects which resulted in null results.²⁹ This is highly speculative and there do not appear to be convincing underlying biological mechanisms that might account for the proposed effect. UMFA does not appear to have been considered in this context, just high levels of "folate."

The impact of folic acid supplementation on in-stent restenosis after coronary artery stenting has also been investigated. Daily doses of 1.2 mg of folic acid were used along with vitamin B₆ and B₁₂. In a comparison to the placebo group, those receiving folic acid supplementation had a higher restenosis rate and a higher percentage requiring repeated target-vessel revascularization. After 250 days of treatment, major adverse coronary events were significantly more prevalent in the folic acid compared to the placebo group.³⁰ The mechanism appears unknown.

Cancer was a secondary endpoint in two large studies involving homocysteine lowering, NORVIT³¹ and HOPE 2.³² In the former, a 22% increase in cancer rate was observed for 0.8 mg/day of folic acid and 0.4 mg/d of vitamin B₁₂, but this result was only suggestive since it was not statistically significant. In HOPE 2 a dose of 2.5 mg/d of folic acid was used in combination with B₆ and B₁₂. Increased

risks of colon, lung, breast and prostate cancer were observed, but again, while the increased risks ranged from 11% to 36%, none achieved statistical significance although the 36% increased risk for colon cancer came close. These studies were not powered to produce statistically significant information regarding enhanced cancer risk if it existed and the number of cases was low, but the results are suggestive.

Cognitive Impairment and Folic Acid Fortification

It is well known that vitamin B₁₂ deficiency can produce profound cognitive impairment and that it is an ongoing challenge for clinicians to successfully accomplish differential diagnosis since in many cases this deficiency is easily treated, something that can not be said for other causes of cognitive impairment. Mandatory folic acid fortification has always come under scrutiny because it can mask vitamin B₁₂ deficiency with obvious serious consequences. Thus the study of Morris et al which found that high intake of folate may be associated with cognitive decline and anemia in older persons is of particular interest.³³ This cognitive impairment seen with high serum folate was only observed in individuals with low vitamin B₁₂ status. No information was available regarding the levels of UMFA since it was included in the total folate. Circulating UMFA has been suggested to play a role in either delaying diagnosis of vitamin B₁₂ deficiency by curing anemia, the masking phenomenon, or causing central nervous system problems.^{33,34} However, what is really going on is not well understood but clearly complex. As A. D. Smith points out in an accompanying editorial, there are a number of questions about the interaction of folate/folic acid and B₁₂ that need to be addressed as well as questions regarding food fortification and supplement use in the elderly popula-



tion, questions which include the merits of combining vitamin B₁₂ with folic acid fortification.³⁵

This recent study by Morris et al was consistent with an earlier study based on subjects from the Chicago Health and Aging Project where it was found that higher intakes of folate/folic acid were associated with cognitive decline in older persons.³⁶ In this study, the top quintile of total folate/folic acid intake had a range of 557-1719 µg/d and for those in this quintile, 96.9% used multivitamins.

Conclusions

While it might be argued that therapeutic use of folic acid, including daily doses of 1 mg/d or higher has been common for some time without evidence of adverse effects and therefore must be safe, such applications have not generally been in settings where side effects that develop slowly would be an issue or even noticed. Some patients may have had progressing co-morbidities, and especially in older populations the normal incidence of cancer would be hard to distinguish from an enhanced risk and would in general go unnoticed unless clinicians were especially alerted to the possibility. Most intervention studies using large or very large doses were neither looking for nor powered to detect increases in cancer risk. Those that investigated this question as a secondary endpoint detected enhanced risk. Thus it is not surprising that most of the evidence for risk associated with high dose folic acid has appeared in epidemiologic or intervention studies directed at primary or secondary cancer prevention.

Folic acid is a synthetic molecule which is foreign to human biochemistry. High levels of circulating UMFA are unique in human history. Trace amounts found in nature do not appear to invalidate this view. While it is true that folic acid can be converted into metabolites identical to those derived from dietary folates,

it appears that different pathways are involved and there remains the fact that at high folic acid intakes a metabolic saturation phenomenon exists which results in prolonged exposure to circulating unmetabolized folic acid, the consequences of which have not been investigated and remain largely unknown even though a decade has passed since Kelly et al¹ first raised the issue in a high profile journal. The observation of decreased NK cell cytotoxicity associated with high UMFA levels appears to be most significant since it provides one biological mechanism for adverse effects. But there may be a number of other mechanisms given the complexity of folate metabolism in general and in addition, the complexity of the gene-nutrient interactions associated with folate-mediated one-carbon processes.³⁷

This seems to be an area in urgent need of study, especially since there is growing interest worldwide in folic acid grain fortification and in some countries, ever increasing interest in supplements, and it has become possible to inadvertently consume large amounts of folic acid, especially if fortified ready-to-eat breakfast cereals and nutrition bars are eaten along with what is considered to be a common and safe multivitamin. It is not unreasonable to expect additional voluntary fortification with large amounts of folic acid in a number of prepared foods simply because of the promotional and marketing value associated with this action.

While few would argue with the manifest benefits and success of food fortification in the context of preventing neural tube defects, those benefiting represent a rather small fraction of the total population experiencing enhanced intakes of synthetic folic acid. If a portion of this larger population is indeed put at higher risk for various cancers, mental problems and possibly other as yet to be identified risks associated with high folic acid intake and the consequent high

levels of UMFA, then perhaps the food fortification program as well as voluntary fortification should be re-examined with this in mind. Also, consideration should be perhaps given to lowering the folic acid content of multivitamins if it is indeed true that many are getting 800 µg/d via this route alone. Especially significant in this context is the surprising result that higher levels of folic acid do not reduce the risk of cardiovascular disease even though there is a significant reduction in serum homocysteine. This removes an argument for fortification and for therapeutic doses. Finally, the concerns regarding B₁₂ masking have turned up in a different guise in the observation that high levels of folate/folic acid are associated with cognitive decline in the elderly who have poor B₁₂ status.

Thus significant public health issues appear to arise in the context of high folic acid intake. It would appear that the wrong form of folate is used for supplementation purposes and therapy, but there is at this point no other option. Folic acid was presumably selected because it was cheap to make and had a long shelf-life whereas natural folate was unsatisfactory in this context. This choice was made a number of years ago. About a decade ago questions were raised about adverse effects associated with UMFA but largely ignored and it is unfortunate that UMFA is not even considered in most studies. Nor has it been the central subject of studies such as, for example, its possible role in the early stages of metastasis. Until further research clarifies the question of risks associated with UMFA, it should be recognized that a very small amount of folic acid supplementation, e.g. 200-400 µg/d added to a diet containing modest amounts of unfortified but folate-rich foods will bring individuals up to a folate level which may well be quite satisfactory and certainly at the high end of the folate/folic acid intake observed

for healthy subjects in many older, pre-fortification observational studies, while at the same time virtually eliminating circulating unmetabolized folic acid. A deliberate effort to eat folate-rich foods can also accomplish this same end without supplementation. Fortification was intended to add only about 200 µg/d of folic acid to the diet, an amount estimated to have a significant impact on neural tube defects.

This paper should not be viewed as an attack on supplements but rather a call for considering the chemical form and dose of one very important and popular supplement which is also used for therapeutic purposes.

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Fortieth Anniversary of Orthomolecular

The year 2008 is very significant for the orthomolecular community. Forty years ago two-time Nobel Laureate, Linus Pauling, introduced the term and concept 'orthomolecular' by publishing the paper "Orthomolecular Psychiatry. Varying the Concentrations of Substances Normally Present in the Human Body May Control Mental Disease" (*Science* 1968; 160 (825): 265-71). Since that landmark publication, Pauling's original idea, developed through the pioneering work of Abram Hoffer, has become an international movement in healthcare. Throughout 2008, there will be celebrations of this 40th anniversary and the *Journal of Orthomolecular Medicine* will publish a history of orthomolecular medicine, by Stephen Lawson of the Linus Pauling Institute, in the next issue.

Celebrations in the Netherlands

2008 is also a year for jubilees in the Netherlands. In 1983, 25 years ago, the first edition of *Orthomoleculaire Magazine* (*Ortho*) appeared and in 1988, 20 years ago, the first orthomolecular society of professionals in Europe was founded, the 'Maatschappij ter Bevoordere van de Orthomoleculaire Geneeskunde' (MBOG; Dutch Society for the Advancement of Orthomolecular Medicine).

Orthomoleculaire Magazine (*Ortho*) was the first journal to publish on orthomolecular medicine in a non-English language. Some highlights of the last 25 years follow.

The first article with a lot of clinical impact, about hypoglycemia, appeared in the first year. The concept of a destabilized blood sugar curve, measured with a prolonged glucose tolerance test, was totally new in the Netherlands and appeared to be a valuable tool in the hands



Linus Pauling, 1901-1994, and Abram Hoffer, born 1917, alive and well at age 90.

of naturopaths and biological MDs to help many of their patients. In 1988 the regular column, 'Around the World' was begun, a collaboration with the *Journal of Orthomolecular Medicine* (North America) and the *International Clinical Nutrition Review* (Australia). This collaboration marked the beginning of publishing, in Dutch, the Hoffer-Osmond concept of treating psychiatric illnesses with high doses of niacin and the Carl Pfeiffer concept of histadelia, histapenia, pyroluria and cerebral allergy. Since 2002, the year Bernard Gesch of the University of Oxford published his study with dietary supplements in a British prison among young offenders (*Br J Psychiatry* 2002; 181: 22-8), *Ortho* has been pushing the concept of the influence of nutrition on behaviour. This connection is now acknowledged by the Dutch government. From the beginning in 1983, Gert Schuitemaker is the Editor-in-Chief of the magazine. For more information, please see www.ortho.nl.

Maatschappij ter Bevordering van de Orthomoleculaire Geneeskunde. In 1988 a group of Dutch health professionals who were practising orthomolecular medicine united and founded the MBOG. The purpose was to exchange knowledge and skills, and to disseminate the orthomolecular concept. One of the main activities was the organization of the yearly 'Orthomolecular Information Day'. The first meeting was with Stephen Schoenthaler,

PhD, of California State University, who presented the results of his research on the diet-behaviour connection in young offenders in penitentiaries. This visit

generated a lot of press in the Netherlands and was a good opportunity to expose the orthomolecular concept. In all the years, the top event of the MBOG annual meetings was the one with a direct satellite connection with Linus Pauling. He was invited to come over to Europe, but he rejected this politely by stating that he could not afford to miss three days of research in the Linus Pauling Institute. This direct satellite connection made orthomolecular medicine known to a broader public, since Pauling was

interviewed on the Dutch national television. In 1996 the first 'Orthomolecular Trophée', a beautiful bronze sculpture of Linus Pauling (with beret) was awarded to one of the first nutritional doctors in the Netherlands, Albert Ronhaar. Ronhaar was student of Cornelis Moerman (1893-1988), the pioneer doctor who treated his cancer patients with diet and supplements, and who was inducted into the Orthomolecular Medi-

cine Hall of Fame in 2005. The 20th anniversary of the MBOG will be celebrated in October, 2008, with a special congress and a dinner party in the evening. The meeting, entitled 'Food for Genes', will close with a forum discussion featuring prominent supporters and opponents of orthomolecular medicine. For more information please see www.mbog.nl



- eerste in Nederland -
sinds 1983



Book Reviews

We Don't Die, We Kill Ourselves: Our Foods Are Killing Us!

by Roger L. De Haan

Huntsville, AL: Milestones Pub., 2006
Paperback, 320 pages.

When I was a boy, if you'd asked me what I wanted to be when I grew up, I'd instantly answer, "A veterinarian." After I'd visited and talked with a local vet one Saturday morning, I changed my mind. Drug medicine for animals held no more appeal for me then than it does when used on humans now. And, I believe, it is no more effective.

We Don't Die, We Kill Ourselves is written by an experienced, holistic DVM. But this very readable, non-technical guide to health, is written for people, not pets. This is particularly evident in the book's gentle but strong evangelical character. The author, a former agricultural missionary to South America, sets his thesis out for all to see on the first page of his preface: "Unconditional and unwavering love is the only hope for bringing total health and healing to every level of the spirit, filtering into the soul, and finally transforming the body." Then Dr. De Haan talks about salvaging rice bran, sweet potato vines, and yucca shoots to use as a nutritional supplement for pigs. I like that kind of variety in a book. He also gives good solid advice for people: eat whole foods, and no junk food. He discusses gluten-free eating, avoiding cow's milk, and beating food addiction. Recommended foods are categorized into 16 groups, and the diet emphasizes vegetables, fruits, seeds, legumes, and sprouts. Most grains, fried foods, and desserts are to be avoided. But meals are not overly restrictive: fish, eggs, some cultured dairy products and occasional meats (say, three times a week) are green-lighted. De Haan advocates small family farms and, for the rest of us,

recommends having a vegetable garden outside and growing your own wheatgrass indoors. Overall, it is a very sensible, very nourishing near-vegetarian diet. He also recommends daily nutritional supplementation, saying that supplements save the US 2.6 billion dollars annually, and even more importantly, keep 100,000 people out of the hospital each year.

One of the most interesting parts of the book is about home remedies. De Haan all too briefly discusses several practical uses of homeopathy, Bach flower remedies, aroma therapy, herbs, massage, and meditation. Did you know that overripe bananas are good for stopping diarrhea? This chapter should be greatly expanded, perhaps into another entire book. The book also contains a short suggested reading list and a brief reference section, but no index.

In my opinion, Dr. De Haan had done an admirable job of presenting a fine, faith-based health book. The book may be by a dedicated Christian, but it is written for all. I especially like the way the author's easy, conversational style walks you through your own healthier lifestyle change. Change is never easy, but consider the book's title well. Preferably before your next fast-food meal.

—Review by Andrew W. Saul

The Journal of Orthomolecular Medicine

Since 1970, this quarterly Journal for health professionals has published the best of nutritional research and clinical trials. New articles describing the orthomolecular approach to health management and treatment of disease are accompanied by lively editorials, book reviews, letters and reports. The Journal of Orthomolecular Medicine has led the way for a quarter century in presenting, far in advance of other medical journals, new health concerns and treatments including: Candidiasis; Mercury Amalgam Toxicity; Niacin Therapy for Schizophrenia and Coronary Disease; Chronic Fatigue Syndrome; Vitamin C and Cancer; Allergies and Behavioral Disorders; Drug and Alcohol Abuse; Tissue Mineral Analysis; and Orthomolecular Treatment for AIDS and Cardiovascular Disease.

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Manuscripts. Submit manuscript in duplicate, double-spaced on standard paper. Author's full names, academic or professional affiliations and degrees should be given. A computer disk (Macintosh or IBM format) containing the text of the paper must be included, specifying the file name and program used.

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