INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

NUMBER 297 **MAY 2019** **28th YEAR**

The feature of this issue is a controversial subject, prevention of coronary heart disease. Mainstream medicine has what appears to be a rather ineffective protocol which encourages looking for an alternative which holds more promise and which is more or less evidence based if the absence of randomized controlled studies is acceptable given the problem. In addition, there are in fact some such randomized studies, just not many. There is considerable evidence that multiple actions or interventions are more than simply added benefit. The suggested protocol involves a rather large number of possibilities, but this is consistent with the complexity of the disease. These are just suggestions to consider, not recommendations, and they are justified by reference to the underlying research.

There is also a discussion of the role of the infant and childhood gut on the risk of autism. A recent study offers the first proof of principle of this notion which anecdotal evidence has supported for many years. Dealing with gut problems as well as other suspected causative factors is complex, and two books are cited which are intended to provide guidance from highly qualified experts and should help parents of autistic children. It appears that specialists with experience in multifactorial personalized approaches are rare, but it is clear that this is what is needed because it attempts to target causes rather than use psychological management and training based on symptoms.

Finally, an analysis of a study which made the evening TV news is presented in order to explore its serious limitations. This highlights the problems with nutritional studies which are manifold and cause much consumer confusion, especially when results which have shaped guidelines and become dogma are in fact demonstrated conclusively to be without foundation. Exhibit A is saturated fat as discussed several times in IHN.

Wishing you and your family good health,

William R. Ware, PhD, Editor

A PROTOCOL TO CONSIDER FOR LOWERING RISK OF CORONARY HEART DISEASE

This is probably one of the most complex issues addressed in IHN. To keep it as simple as possible, only actual heart disease is considered. Heart disease can describe many disorders. Here we are concerned with coronary artery disease associated with atherosclerosis in the heart. Plaque rupture from several varieties of plaque can result in sudden blockage, i.e. a heart attack, also called myocardial infarct or MI.

The risk factors that are found in commonly used risk calculators used by physicians when evaluating patients are gender, age, race/ethnicity, diabetes, smoking, family history of heart attack, total and HDL cholesterol, systolic blood pressure and the use of lipid lowering and hypertension medicine. The last two actually increase risk for complicated reasons. At least one calculator includes optional entry of coronary artery calcium score to allow the absence or extent of atherosclerosis to be included. Only smoking, cholesterol and hypertension are considered to be modifiable factors. Patients who smoke will probably receive a lecture. Modification of the other two factors are the basis of huge profits for drug companies, but the absolute benefits of statins are so small (1% to 2% in most cases) that almost all who are treated fail to benefit in terms of prevention of major acute cardiovascular events. This problem is solved by recasting the same clinical results in terms of relative risk reduction which enables patients to be told that they will reduce the risk by 25-40%. Lifestyle risks include unhealthy diet, but there is no real consensus as to what is healthy, inadequate exercise, unhealthy weight, smoking (actually the dominant factor), drinking too much alcohol, micronutrient deficiencies, and psychosocial stress, both domestic, personal and workplace related. Lifestyle risk factors are modifiable, although stress can prove especially challenging.

If the hypothesis that LDL is a critical causative factor for heart disease is indeed false, as has been discussed at length in IHN and in a comprehensive review supporting this contention recently published,[1] then this eliminates lipid lowering as a potential candidate for prevention although the statin drugs may also act as anti-inflammatories and provide a hypothesis for part of their small benefit. However, risks tend to be downplayed. An active area of research is looking for alternative prescription anti-inflammatories. For a good review of the case against the cholesterol hypothesis read Sinatra and Bowden's book[2] which also deals with a wide range of related issues.

The question of prevention is currently strongly influenced by a focus on blood lipids, hypertension, and smoking. The patient's lab results along with other required data are plugged into a calculator, frequently on an iPhone, and the 10-year risk obtained.

Significant overestimation appears to be ignored. This plus a few casual observations and then frequently a prescription is offered for a statin promoted as life-saving, perhaps adjustment of hypertension medication, a few general pieces of advice related to the above lifestyle risk factors, especially regarding weight and smoking, and advice to take a baby aspirin daily (the benefit now disproven), and the patient is out the door.

One observation in connection with the above concerns atherosclerosis. If one does not have plaques in their coronary arteries, then ruptured plaques causing a heart attack (myocardial infarct—MI) are impossible. A non-invasive CT scan has been available for decades and yields a so-called coronary artery calcium score (CACS) which measures almost all the plaque burden since the vast majority of plaque is calcified. If the CACS is zero and this can be as high as 60% in some populations of adults including many elderly, such a result would immediately allow physicians to stratify patients, those who are or are not currently at risk for a heart attack *independent of traditional risk factors*. Frequently, a CACS = 0 also implies low carotid artery plaque. When coronary plaque is present, it generally progresses and this is accompanied by an increasing risk of a heart attack since the plaque burden (calcium score) is a strong predictor of risk. While statins have been found to produce small plaque shrinkage, some consider this and the impact of plaque progression as not clinically significant. This is of course highly controversial.

Related to this issue is the following: Progression of coronary artery calcification is clearly a serious issue. Studies using measured coronary calcium as a surrogate for coronary atherosclerosis burden and progression have investigated the role of conventional risk factors. A 2015 study using MESA data found associations between progression and BMI, family history of cardiovascular disease (CVD), triglycerides, systolic blood pressure, HDL, diabetes, hypertensive medication, statin use, and pack-years of smoking. No association was found with LDL levels or race/ethnicity.[3] The follow-up was 10 years. A study that examined both progression and metabolic syndrome risk factors found BMI and triglycerides qualified, but metabolic syndrome alone was not an independent predictor.[4] A study which examined the issue of prediabetes found that it was not a risk factor for pre-clinical atherosclerosis, but this ignores the common progression of prediabetes to diabetes, which indeed is a risk factor. CACS was the strongest predictor of progression and incident coronary heart disease (CHD). Thus identification of individuals with CACS = 0 has therapeutic and psychological implictions.[5]

A prevention protocol should not only attempt to identify the optimum diet, unfavorable micronutrient deficiencies, and lifestyles that significantly reduce risk but also attempt to influence the incidence and progression of atherosclerosis. The following is presented for consideration by readers but it is not a recommendation. The citations provide the evidence for the inclusion in the list. The following is partly based on the famous INTERHEART study,[6,7] the research concerning coronary plaque of Michael Budoff,[8-11] the research of Michel de Lorgeril including the Lyon Diet Heart Study even though it was a secondary prevention trial[12] and the advice of Dr. Stephen Sinatra and colleagues which is based on years of clinical experience in cardiology, nutrition and anti-aging.[13]

- Consider eating a traditional Mediterranean diet which yields a high Med Diet Score.[14-16] This is the most frequently cited diet for heart health and prevention. Well described on the internet and in a number of books. Note that where this diet is standard, there are cultural aspects of eating and social traditions that may synergistically benefit heart health.
- Note that one of the factors that helps to minimize inflammation, one of the driving forces of atherosclerosis, is keeping the dietary omega-6/omega-3 ratio for polyunsaturated fatty acids in the range of 3:1 or less (see IHN, February 2019)
- Consider avoiding table sugar, high fructose corn syrup and refined carbohydrates (see Chapter 4 of *The Great Cholesterol Myth* by Bowden and Sinatra[2]) Some say sugar is the demon, not fat, in the context of heart disease.
- Exercise daily. This alone significantly increases the overall benefit of the Mediterranean diet.
- Recognize psychosocial stress (domestic, workplace, financial, etc.) as an important and *sometimes* modifiable risk factor for heart disease.[6]
- Do not smoke. One of the strongest risk factors and found in all risk calculators.
- If diabetic or prediabetic, it might be wise to attempt to return to normal glucose metabolism or at least to the threshold of prediabetes as measured by HbA1c and the 2-hour glucose tolerance test by using severe calorie restriction such as the 8-week New Castle Diet repeatedly discussed in IHN.[17] See *The Cholesterol Myth*, Chapter 4 for a discussion concerning elevated blood insulin levels, insulin resistance and heart disease.[2]
- Address an abnormally high waist-hip ratio i.e. the extraordinarily common potbelly by diet.[6]
- Address atherogenic dyslipidemia (lower triglycerides, raise HDL, and lower the apolipoprotein ratio (ApoB/ApoA) with a low refined carbohydrate and low or no sugar diet.[18]
- Take a good multivitamin/mineral to play it safe. Common recommendations suggest it should include at least 800 mg of elemental magnesium[19] and 2000 IU of vitamin D (3 per day)[20] and for men, no iron. Otherwise make up the deficit with additional supplementation.
- Consider supplementing with aged garlic extract in addition to what raw or cooked garlic might be in the diet (250 mg/day). Some consider this the best way to address atherosclerosis. Best-known brand is *Kyolic* which was used in all Budoff's studies.[8-11] Budoff has found that the effect of garlic therapy is enhanced by supplementation with folic acid (300 microg/day) vitamin B12 (100 microg/day), vitamin B6 (12 mg/day,[9]) and the amino acid L-arginine (100 mg/day).[9]
- Consider adding vitamin K2 (MK-7) to the vitamin supplement intake.[21]
- Recognize that the "saturated fat is bad" hypothesis is fast losing credibility and that saturated fat consumption is found to be heart healthy.[2,22]

- The well-known cardiologist Stephen Sinatra and colleagues recommend D-ribose (5-10 g/day, coenzyme Q10 (180-360 mg/day) and L-carnitine (1-2 g/day) to help assure adequate energy production (mitochondrial ATP).[22]
- Consider being sure to have an intake 400-800 mg (elemental) magnesium per day. There is ample evidence that a good magnesium status is one of the most critical aspects of both general and heart health and that many are deficient.[23]
- Consider supplementation with selenium.[24] However, selenium deficiency in the US and Canada is considered rare due to high soil content. However, the soil prevalence is highly variable. The common recommendation is 200 micrograms per day in soil-depleted regions. The official tolerable upper limit is 400 micrograms daily.
- Consider donating blood. For men and postmenopausal women 4 times a year.[25] Iron is highly inflammatory. The object is to keep serum ferritin levels (body iron stores) low[26] and lower blood viscosity.[27] Blood ferritin levels should be measured during an annual physical exam but rarely are, and if high, used to follow progress in lowering them. Blood donation is the only simple way. Regular blood donation has a dramatic effect on the risk of heart attack events.[25] One study found the threshold of elevated heart attack risk is 200 microg/L of serum ferritin,[26] which is way below the maximum in most reference ranges used today.[28]

This protocol is consistent with the 9 modifiable factors involved in the risk of a heart attack found in the famous INTERHEART study[6] which was able to identify risk factors for heart attack which accounted for an average of 90% of the population prevalence in a number of countries. This protocol also minimizes inflammation and oxidative stress and in particular the oxidation of LDL thus limiting the amount of the unhealthy oxidized form.

The evidence prompting the suggestion of aged garlic extract is based mainly on two randomized placebo-controlled trials. One year of treatment with garlic alone or combined with the added supplements, when compared to the placebo group, yielded changes in annual progression of CACS of 11% and 6.8% vs. 22% and 27% respectively. Baseline CAC scores were >70 and >30 in the two groups. The threshold for concern regarding progression commonly cited is 15% per year for significant increased risk of mortality.[9]

Supplementing to combat atherosclerosis provides a good example of another fundamental problem. The initial arterial lesions can appear at any age and will then probably progress in prevalence and size. It may take years to go from a calcium score of 1 to 10 or 100. Reversal from 200 to 100 would be impressive, but one is still not out of the woods and there are no adequate long-term follow-up studies indicating the impact of this change (reversal) on the probability of an acute event. It is simply assumed that it is a reasonable assumption. The disease is silent until, for example, impaired blood flow results in angina. However, the interesting questions are what triggers the initiation and what drives the progression of atherosclerosis and what is

unique about those who never have atherosclerosis, the CACS = 0 group? In a population, this group decreases slowly with age but is still highly significant? What did they do that was different? This has received little attention.

It must be emphasized that an approach such as described has never been tested in a controlled study, and this will probably never happen. It contains elements that are controversial since not tested in large randomized controlled trials. However, given that heart disease is a leading cause of mortality and morbidity, rigorous adherence to the mainstream approach based on the beliefs of mainstream and evidence based medicine may be detrimental to one's coronary health. There may be benefits in trying something different.

AUTISM CRISIS AND THE ROLE OF A DYSFUNCTIONAL GUT

The prevalence of autism is increasing rapidly in many countries. The US Centers for Disease Control and Prevention (CDC) reports that 1 in 59 children at age 8 (1.7%) now have autism spectrum disorder but there are geographical differences. The high is in New Jersey (1/34) and the low in Arkansas (1/77). The dependence on gender is large with boys at 1/37 vs. girls 1/151. Most children are being diagnosed after age 4 although the disorder can be diagnosed as early as age 2. In addition, there is very little difference between the diagnosis rates based the diagnosis manual version 4 and the current version 5, and this covers 24 years by 2018. Nevertheless, there continues to be debate concerning the possibility that this increase has a significant component associated with increased awareness or a changing ethnic mix or some other confounder rather than an epidemic of unknown cause. Others argue that the prevalence is underestimated by the CDC.

Most alarming is the following. If one looks at the CDC data in a graph from 2004 to 2018 it appears exponential. If one takes their numbers and examines the hypothesis that it is exponential by making a log plot, one gets a very good linear correlation. Extrapolation, while of debatable validity, yields for predicted prevalence in 2024 of 1 /33 and 2030 of 1/20. If this is even partly valid, something terrible is going on. One possibility is exposure to toxic chemicals. Since 1990 the agricultural use of glyphosate (*Roundup*) has gone straight up from 7 to 250 million pounds. Cumulative agricultural use since 1974 is about 4 billion pounds.[29] There is no question that some gets into food and that humans carry a body burden of this chemical. However, this is just one of a number of environmental toxins, many of which are being increasingly used not only in agriculture but for many consumer products. However some suspected toxins have decreasing temporal trends. Important exceptions include not only glyphosate but chemicals used as fire retardants, and aluminum as enhancers. Navison has a plot of identical temporal trends of glyphosate application levels on genetically modified corn and soy and California autism prevalence data.[30] The data connecting fire retardants, one of the toxic pollutants with increasing levels, and autism is not clear since the conflicts of interest in the few studies are not clearly stated.

This highlights what is a big problem evolving potentially into a disaster, although some might rightly consider 1/57 already represents an unprecedented crisis. Thus the high priority question—what are the causes? In the Mayo Clinic online discussion of autism, they simply state that there is no single know cause, and given the complexity of the disorder there are probably many. They discuss possibilities including genetics, environmental factors, viral infections, medications, complications during pregnancy and air pollutants. However, toxic exposure in utero and postnatal exposure to toxins involves more than those in the air. In the home, the multitude of pollutants in the building materials, fabrics, carpets, personal care and cleaning products, and electronics is not only in the air but frequently concentrate in the dust which offers great opportunity for exposure, especially since young children frequently play on the floor. Food is contaminated with a variety of toxins, pharmaceuticals such as antibiotics and chemicals that disrupt endocrine functions. Genetic effects are complex since they include epigenetic effects.

The subject of environmental toxins is highly political and subject to heavy influence by Big Agriculture and Big Chemical on government agencies including those granting research money and one cannot avoid the impression of orchestrated risk denial. The Mayo Clinic internet document points out that there is currently no way to prevent autism. This is debatable and ignores the well-established preventive benefit of folic acid before and during the first trimester of pregnancy.[31] This has been recognized and studied extensively over a number of years. In addition, a recent study also implicated supplemental iron as important, both as an addition and alone,[32] and the risk reduction is very large. It would be malpractice and unlikely for a physician not to press the issue of folic acid on first presentation of a patient who is pregnant.

If one looks at various conventional treatment proposals, they involve management of symptoms with the goal of correcting behavioral and learning problems by psychological interventions. One cannot expect treatment focused on causes since they are poorly defined only in the most general terms. It appears that variable success is being achieved, but complete cures resulting from this approach appear rare and hard to distinguish from simply outgrowing a mild disorder.

However, there is one school of thought that maintains there is an alternative to the above views and there are other interventions which in fact work, not always but frequently with spectacular results. This approach involves whole-body strategies which start with the conventional view that the disease is multifactorial but tackles four of the potential culprits, food, toxins, the gut microbiome and stress.[33] In this report we will consider only the gut problem and discuss a recent study which validates the alternative point of view that large benefits can be obtained by treating postulated causes rather than symptoms. The role of the gut in a number of mental problems including autism was already explored in detail in a 2004 book titled *Gut and Psychology Syndrome* by Dr. Natasha Campbell-McBride, MD who also holds post-graduate degrees in neurology and human nutrition. Her book is now available in an expanded and revised edition.[34] A second book titled *The Autism Revolution. Whole-body strategies for making life all it can be,* by Martha Herbert, MD, PhD also deals at length with the role of a dysfunctional

gut in autism.[33] She is a professor of neurology at Harvard Medical School and a pediatric neurologist at Massachusetts General Hospital. Their views are in sharp contrast to mainstream thinking which ignores among other things the very common parental description of a child's autism which includes calling attention to diarrhea and constipation, the former resulting in the need for diapers sometimes long after normal children are toilet trained.

The study of interest here was just published and is a follow-up of an earlier study. The new study was designed to examine long-term results.[35,36] The approach is similar to the relatively new therapy called *fecal transplant* which for example provides a simple cure for treatment- resistant c. difficle infection, a serious and frequently hospital-acquired intestinal problem. For autistic children the goal was as nearly as possible to replace the entire gut biome including both bacteria and viruses with one derived from a group of healthy donors. Distinct from ordinary fecal transplants, the donor microbes were isolated, purified and could be given in doses with a known cell count. Extensive tests were used to assure that no undesirable infectious species were present. The subjects were prepared by destroying the microbiome using various techniques including a 2-week antibiotic treatment and a bowel cleanse. Aside from some subjects who received the initial dose rectally, the new biome was given orally after reducing stomach acid with Prilosec to minimize the acid associated toxicity to bacteria. After the initial inoculation, treatment was continued for 8 weeks with maintenance doses. During treatment, the expected nature of the new biome was observed and it persisted after the end of treatment. There was an 80% percent reduction of gastrointestinal symptoms (diarrhea, indigestion, and abdominal pain) and assessments of behavioral autism symptoms improved significantly and persisted after the end of treatment. Eighteen participants were followed for two years.[35] Changes in the gut microbiota were maintained and autism symptoms were reduced by nearly 50%. At the start of the study 83% of the participants were rated as having severe autism. At two years, only 17% were severe, 39% were mild to moderate and 44% were below the cut-off for diagnosis of mild autism. Parents reported slow but steady improvements in the core symptoms. These results appear sensational.

It is important to recognize that this study targeted only one of the four causes treated by the alternative multifactorial approach.[33] If it had been combined with attention to diet, toxins, and stress, the results might have been even more spectacular. However, these studies provide a firm clinical trial foundation for believing in the major role a dysfunctional gut (dysbiosis) plays in autism.

If the childhood microbiome is that important, one might think that there would be a connection between the incidence of autism and the nature of the birth, i.e. either normal or cesarean. The unborn infant has a more or less sterile gut and inoculation occurs mostly during birth from maternal bacteria in the birth canal. After cesarean birth, the inoculation occurs mostly from the mother's skin and milk, and obviously humans did not evolve to adapt to having birth by surgery. A very large multinational study based on medical records confirmed this suspicion, finding that cesarean section was associated with approximately 26% higher risk of autism, independent of the reason for

the choice (emergency or planned) and the length of the pregnancy. The study had a long enough follow-up to detect autism in most if present.[37] It is quite interesting that almost nothing was said about the large difference the gut microbiome present in these two groups of newborns. In is context, it is also interesting that similar enhanced risk associated with cesarean birth has been seen with asthma, allergies and immune disorders. The obvious solution is so-called vaginal seeding, where there is a bacterial transfer to the newborn using a swab. However, this is opposed ty the American College of Obstetrics and Gynecology, but that is another story. This is important since the percentage of births by cesarean sections is not trivial.

Parents of autistic children are encouraged to read the two cited books. However, it will prove difficult for most to find a physician with experience in the whole-body approach to this disorder. The sad fact is that to even get a microbiota transfer such as used by this group of investigators will probably be impossible for many years, given the current very high barriers presented by the need for regulatory approval and the fact that gut problems are not on the mainstream radar in this context. Dr. Herbert's book should provide guidance to parents as well as physicians. She has a 30-page chapter on the role of the gut which includes a good section on "what you can do." Dr. Campbell-McBride also had a detailed discussion in her book concerning what parents can do. The recent paper discussed is free online as is the earlier study by the same group. Goggle *Dae-Wook Kang Microbiota Transfer.* The research group is mostly based at Arizona State University.

EAT LESS MEAT, LIVE LONGER???

The above headline without the question marks appeared in the New York Times health section, April 11, followed by the statement that men who ate more than a half pound (8 oz) of meat daily were 23% more likely to die (prematurely). The researchers found that a higher ratio of plant to animal protein decreased risk of early dearth. This commentary is based on the paper just published in *The American Journal of Clinical Nutrition.*[38]

The dietary data was collected only at baseline for 2641 Finnish men aged 42-60 years. The mean follow-up was 22 years. Total meat included red and white and offal (e.g. heart, liver and brain). The comparison was between animal and plant-based protein, the former including meat, fish, eggs and dairy. The 23% number which was based on total meat derived protein consumption adjusted for confounding was a **relative risk increase** obtained by comparing lowest and upper quartile over the duration of the trial. The **absolute** mortality rate increase (all cause) associated with total meat can be approximately estimated at 2.6% per year which over a long period is important if correct, i.e. 26% 10-year risk. Note that the cohort mortality over the trial was 46% (23% due to CVD, 13% cancer and 10% other). However, if one looks at the results stratified by type of total plant or animal protein including red meat, processed and unprocessed red meat, fish, eggs, dairy, fermented and unfermented dairy, milk, cheese and finally major plant protein sources (grain, legumes, nuts and seeds), there was not a single

statistically significant result expressed as a confounding adjusted risk ratio, except for plant proteins. Risk ratios were calculated by comparing protein consumption quartile 1 with quartile 4 (Q1 vs Q4). For perspective, Q1 was <55g/d of animal protein, Q4 >74g/d. The sources of animal protein used are listed above. Q4 had a mean of 83 total g/day intake corresponding to 14% of daily energy intake. A medium size sirloin steak has about 74 g of protein. Even keeping to less than the Q4 intake would require significant modification of many diets. Q1 used like a control had a mean animal protein upper limit of 49 g/d or 8.2% of daily intake. Bacon and eggs for breakfast, a tuna salad for lunch, and a small steak dinner would, according to these quartiles, not be a good idea. Breakfast already gets one to 36 g animal protein. Adding a steak for dinner and you are already at the Q4 threshold. Baked salmon for lunch would really put you in the danger zone but could be a typical part of a low-carb diet with protein a significant replacement.

The study had significant limitations. The researchers were unable to take into account changes in diet or confounding factors during the 22-year follow-up. Baseline intake was based on 4-day records kept by participants and then protein intake estimated. Mean protein intake was about 16% of total energy, with 40% from fat and 44% from carbohydrates. Note that the insignificant results included red, processed, and unprocessed meat examined separately. Only the total protein from total meat was statistically significant and the lower 95% confidence limits only exceeded 1.00 by a small amounts (1.00 would mean no statistical significance as would a range in the confidence limit that included 1.00 since 1.00 means the identical result for the events in the quintile in question and Q1, i.e. no increase in benefit or risk. The researchers did not attempt to access diet quality. The cohort included 1094 out of 2641 with histories of type 2 diabetes, CVD or cancer at baseline. However, presence of disease was included in statistical adjustment for confounding. The percentages of disease or family history of disease was high: hypertension, 60%, cardiovascular disease 39%, but cancer was low at about 2% as was diabetes. However, the risk of these diseases goes up with age as the study progresses. Thus the study was really based on a cohort that contained a very significant number of unhealthy individuals, a cofounding factor which implies multiple additional confounding factors which would be difficult to account for.

Plant based protein came through with flying colors. However, one cannot look just at the protein. The plant-based diet contains a lot of nature’s pharmacy and of course has merits. However, the diet also has dangers that may need to be addressed with supplements. Totally plant based diets vs. a diversified diet such as the Mediterranean diet is controversial.

In conclusion, after noting that it applies only to males, it appears advisable not to accept this study at face value because its individual assessment was only at baseline, an important issue due to the long follow-up, and many of the subjects were not healthy (disease free). Stratification except for plant protein never produced a single statistically significant result and there is a huge range in possible age at the study end (64-80). This provided for many of the cohort ample time to develop chronic and potentially fatal diseases, acquire new confounding factors, and suffer from polypharmacy, all of which

could not be taken into account. Finally, the results apply only to those living in Finland. These problems are common in nutritional studies and may have a large impact on the most difficult variety, nutritional cohort studies.

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Editor: William R. Ware, PhD

INTERNATIONAL HEALTH NEWS is published 10 times a year by
Hans R. Larsen MSc ChE, 1320 Point Street, Victoria, BC, Canada, V8S 1A5
E-mail: editor@yourhealthbase.com World Wide Web: http://www.yourhealthbase.com

ISSN 1203-1933