

INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

NUMBER 190

SEPTEMBER 2008

17th YEAR



Welcome to the 190th issue of the first health newsletter on the Web!! This issue is being published early since Hans Larsen (the publisher) will be away on vacation at the time this month's issue is usually published.

This issue features an update of the use of so-called calcium scans to determine the risk of cardiovascular disease by directly measuring the presence and extent of calcified coronary artery plaques. This CT scan was popularized by the book "Track Your Plaque" by the cardiologist William R. Davis, M.D. (iUniverse Inc, 2004). Over the past decade calcium scans have become quite popular and as well, there has been an explosion in research concerning their prognostic and diagnostic value. In addition, measuring coronary calcium has become a popular tool in studies of the factors associated with the incidence and progression of atherosclerosis and has the advantage over carotid artery ultrasound of examining a more relevant vascular territory while still being non-invasive.

New vitamin D research is also featured in this issue. Included is a discussion of an email exchange between the mother of an autistic boy and Dr. J. J. Cannell, whose paper on the connection between vitamin D and autism in "Medical Hypotheses" was reviewed in a previous issue. The editor is indebted to a reader for bringing this information to his attention. Readers with an autistic child should find this exchange very interesting, as should any friend in the same situation. While Dr. Cannell is presenting anecdotal results, the vitamin D doses are well within the range currently being recommended by experts and his comments on the adverse interaction of vitamin D and vitamin A, especially preformed retinols, is of general and considerable interest. This will be discussed in a future issue. Recent results related to cardiovascular health and vitamin D, diet and garlic supplementation are also presented.

"The Prostate Monitor" will resume next month and will be included in IHN every other month.

Please bear in mind that the cost of publishing this newsletter is solely defrayed by income made from the on-line vitamin store. Without this, there would be no IHN. So, if you need to restock your supplements, please remember that by ordering through the on-line vitamin store you will be helping to maintain the web site and database, and the publication of IHN. You can find the store at <http://www.yourhealthbase.com/vitamins.htm>.

Hope you are enjoying a great summer,

William R. Ware, PhD, Editor

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CORONARY CALCIUM UPDATE

In 2001, Scott Grundy suggested that coronary plaque might be used as a replacement for age as a risk factor for CHD. Part of the incentive was the profound effect that age has on the 10-year risk of adverse CHD events calculated with the so-called Framingham Risk Score. Age in fact becomes the dominant risk factor after age 50 and it was suggested that the connection is the presence and

progression of atherosclerosis, but the huge variation in the extent of atherosclerosis at any age made age as a risk factor a significant weakness of the assessment. Grundy presented a table where points assigned to age were replaced by points determined by the coronary calcium score.

The advent of electron beam tomography for the detection of coronary calcium deposits and the development of a quantitative score by Agatston led to an explosion in research in this area with dozens of studies correlating the coronary calcium artery score (CACs) with risk factors and event rates. For example, a study of over 10,000 asymptomatic individuals revealed increased risks of CV events with increasing CAC scores and in another study of the same size, CAC scores predicted all-cause mortality. It is currently suggested that individuals with intermediate risk according to Framingham (10-19% 10-year risk of a fatal or non-fatal heart attack) should be screened for coronary calcium. Not everyone agrees.

Coronary calcium is detected by cardiac computed tomography techniques without the use of contrast media. Electron beam tomography is a commonly used technique, but contrary to the name, it is an x-ray scanning technique where the x-ray beam is moved by moving the point of impact of the generating electron beam on the tungsten anode of the x-ray tube. Calcium scores are also generated by other forms of x-ray coronary computed tomography and in addition this technology is also used to accomplish coronary CT angiography which provides information regarding blockage but, in contrast to cardiac catheterization, is non-invasive. These CT techniques are evolving rapidly and may well become the standard approach to triage in the emergency room setting, partially replacing cardiac catheterization. Several commentators have described the use of non-invasive CT angiography where patients presenting with non-exertional chest pain and found to have completely normal arteries were sent home 2 hours after arriving at the ER. The following is a brief review of very recent studies.

CAC Scores and Coronary Blockage.¹ A recent study has found a strong correlation between the extent of coronary blockage and the CACS. Obstructive stenosis, as it is called, was measured by CT angiography using Multi Detector Tomography (MDCT). The study group of over 650 individuals was drawn from individuals who were referred for MDCT because of CACS \geq 400 or for those $<$ 400, CT when symptomatic or multiple

significant risk factors were present. For individuals with a CACS of zero, no obstructive stenoses were found. This reinforces the view that a zero CACS can be regarded as an indication of insignificant risk. For individuals with CACS in the range of 401 to 1000, the odds of having $>$ 60% stenosis was 3.1 whereas for a CACS score of $>$ 1000, the odds climbed to almost a factor of 7. The reference (odds = 1) was a CACS $<$ 400 and these odds were corrected for traditional risk factors. In connection with the relation between CACS and high cholesterol ($>$ 200 mg/dL total cholesterol), there was no significant trend over the CACS range of 101 to $>$ 1000 and 63% with a CACS of zero had hyperlipidemia. Since zero CACS is now almost universally regarded as indicating negligible CHD risk, this is an interesting result. There was a very strong trend however with hypertension as a function of CACS.

CAC Scores and All-Cause Mortality in the Elderly. Most studies concerning the merits of CAC screening have not included the elderly. Nevertheless, CAC screening appears to allow an evaluation of the importance of risk factors in this age group. A study just reported examined the association between CAC, risk factors and age in over 35,000 individuals covering an age range from youth to the elderly with an even distribution between genders.² Follow-up averaged about 6 years. In the age group $>$ 60 years, as might be expected, the percentage with low calcium scores ($<$ 100) decreased whereas those with higher scores increased. Mortality, which of course increased with age, was strongly correlated with the CACS. In the entire cohort, 58% had zero CAC and their annual mortality rate which was low ranged from 0.3% to 2.2% for patients aged 40-49 and \geq 70, respectively. The question of reclassification according to the Framingham categories of low, intermediate and high was examined. The use of the CACS allowed reclassification of more than 40% of the patients \geq 70 years old, more often by reducing risk in those with $>$ 3 risk factors. Unfortunately, no attempt was made to account for comorbidity, but diabetes and family history of CHD were included. The authors comment that these results are consistent with a study of 1800 asymptomatic individuals of mean age 71, where it was found that the risk of cardiovascular events was very low in patients with CACS of zero to 100 and increased 8.2 fold if the CACS was $>$ 1000.³ These results support the suggestion of Grundy mentioned above that there is merit in replacing age with the CACS. While he was specifically concerned with

CHD, this notion also appears to apply to overall mortality.

CAC vs. Exercise Testing. One of the common tests for the presence of significant atherosclerosis is the exercise test where exercise induces an abnormality in the concurrent electrocardiogram (ECG) or blood pressure, or causes arrhythmia or complaints of chest pain. A recent study compared the exercise test with the measurement of CAC.⁴ The results of the exercise test were divided into positive, non-diagnostic and negative. The subjects were patients with chest pains or other symptoms suggestive of CAD who had normal resting ECG and no elevated cardiac serum markers. It was found that the coronary calcium score (CACS) was significantly superior to exercise testing as a triage tool and a cut-off of CACS < 10, when used as a criterion for taking no action proved to be highly effective over 4-12 months follow-up when the endpoint was a coronary event or a finding of coronary obstruction. At the opposite extreme, CACS ≥ 400 was highly predictive of the presence of obstructive CAD or a coronary event, and again significantly superior to exercise testing as a predictive tool for the endpoints of the study. The authors conclude that this study provides justification for using the CACS as the “gatekeeper” for additional invasive and non-invasive testing.

CACS vs. Carotid Intima-Media Thickness. At issue here is the comparison between a non-invasive ultrasonic measurement of atherosclerosis in the carotid arteries (that run along the neck to the brain) and the plaque level in the coronary arteries as measured, again non-invasively, by CAC. This is not a simple matter since there is the question of how one compares these two distinctly different quantitative measures, one a score for calcified plaque load in the coronary arteries and the other a measure of thickening of the carotid arteries. It was concluded that for the asymptomatic 45-84 year year-old US adult, the CAC appeared to be a better choice over carotid ultrasound for predicting CHD events, but ultrasound was “modestly better” in its ability to predict stroke, a result that probably reflects the different vascular territories examined by the two scanning techniques.⁵

CAC and Type 2 Diabetes. It is well known that diabetes vastly increases the risk of cardiovascular disease and peripheral artery disease. A recent study examined the relationship between CAC and cardiovascular events in type 2 diabetics. A 4-year follow-up found for a CACS of 11-100, an enhanced risk of about 5 fold, whereas it was 10 fold for

scores between 101 and 400 and 12 fold for 401-1000. Aside from insulin resistance, no other conventional or novel risk factor (CRP, homocysteine, HbA1c—a long term indicator of average glucose, lipids, or lipoproteins) independently predicted cardiovascular events. The relationship between LDL cholesterol and the CACS in this cohort was flat from a score of zero to 10,000, i.e. no association what so ever.⁶

How Low-Risk is a CACS of Zero? A recent study by Schenker *et al* that used a Positron Emission Tomography (PET) scan radioactive perfusion technique to examine the extent of coronary blockage and a different CT scan technique than electron beam tomography for measuring coronary calcium found a much greater event rate for those with zero CAC than had been found in numerous previous studies.⁷ In an editorial, Greenland and Bonow⁸ provide an interesting summary of the earlier studies done with conventional electron beam tomography. For a calcium score of zero, the annual event rate per 100 people ranged from 0 to 0.63, i.e. very low rates, with an average of 0.094, including 4 of the 13 studies that found a zero rate. Follow-up ranged from 2.7 to 7 years. The study with the anomalous result yielded an annual event rate of 3.5 per 100 on a follow-up of only 1.4 years. Whether or not this anomalous result can be ascribed to differences in the technology is unclear but it seems that it should not significantly influence the generalization based on 13 other studies that individuals with no detectable coronary calcium appear to be at very low risk. Also, the study by Schenker *et al* found the frequency of evidence of blockage based on perfusion studies to be 16% for individuals with a CACS of zero which was much higher than found in other studies⁹.

These recent studies reinforce the earlier work in this area and the resultant picture overall appears to provide compelling evidence of the utility of the calcium score in assessing both the presence of coronary atherosclerosis and the risk of adverse events especially in asymptomatic individuals with no known coronary heart disease. A distinguishing feature of these studies was that CAC was an independent risk factor. Thus there is an ongoing debate as to who should be screened for coronary calcium. Knowledge of enhanced risk can lead to action to halt or reverse the process but there is little evidence-based data regarding the long-term success of such interventions. The reader is referred to the recent Research Review concerning CHD for a detailed discussion of dietary and other interventions that may influence the development

and progression of atherosclerosis—interventions mainly targeted at inflammation and insulin resistance. A high calcium score, for example over 100 and certainly ≥ 400 should provide encouragement for aggressively addressing

important issues such as hypertension, smoking, inflammation, insulin resistance, omega-3 status, abdominal fat, fibrinogen levels and chronic psychological stress and depression.¹⁰

IMPACT OF PREVENTION ON CARDIOVASCULAR DISEASE

A new study shows that aggressive application of nationally recommended activities could prevent a high proportion of coronary artery disease events and strokes. The activities most important were smoking cessation, aspirin for high risk individuals, controlling prediabetes, weight loss for the obese,

lowering blood pressure in individuals with diabetes, and lowering LDL cholesterol in people with existing coronary artery disease. It was suggested that these should be the primary focus in terms of prevention.¹¹

VITAMIN D AND HEART ATTACKS IN MEN

A study published in *the Archives of Internal Medicine* in June described a 10-year study which was part of the Health Professionals Follow-up Study. Over 18,000 men were involved, aged 40-75 who were free of diagnosed cardiovascular disease at baseline when blood was collected. At the end of the follow-up, there were 454 fatal heart attacks (MIs) or fatal coronary heart disease. A comparison was then made with 900 controls matched for age, date of blood collection and smoking status. At issue in this particular study was the connection between vitamin D status as measured by serum

levels of 25-hydroxyvitamin D (25-OH D), with deficiency defined as ≤ 15 ng/mL and sufficiency ≥ 30 ng/mL (to get nmol/L, multiply by 2.5). Men who were deficient were at a 2.45 fold increased risk of MI. Correction for family history of MI, body mass index, alcohol consumption, physical activity, history of type 2 diabetes, hypertension, omega-3 intake, cholesterol, and triglycerides reduced the risk only to 2 fold. Both results were statistically significant. Even men with intermediate 25-OH D levels were at elevated risk providing an indication of a graded risk associated with vitamin D status.¹²

VITAMIN D AND ALL-CAUSE AND CARDIOVASCULAR MORTALITY

In this study, over 3000 men and women, mean age 62, scheduled for coronary angiography at a single center provided blood samples from which their vitamin D status could be determined. During a follow-up of almost 8 years, 737 patients died, including 463 from cardiovascular causes. Those in the lower two 25-OH D quartiles (median 7.6 and 13.3 ng/mL) had a 2-fold higher all-cause mortality compared to patients in the highest quartile (median 24.4 ng/mL). This enhanced risk was independent

of coronary artery disease, physical activity level, comorbidities and functionality. Low vitamin D status was correlated with inflammation markers (c-reactive protein and interleukin-6), oxidative burden, and cell adhesion. Vitamin D(25-OH D) levels were consistently higher in patients without significant coronary artery disease and low vitamin D status seemed to be an important mediator of mortality even in the absence of overt vascular disease.¹³

CIRCULATING VITAMIN D AND 25-HYDROXYVITAMIN D

An interesting and important question regarding vitamin D therapy is the conversion of vitamin D3 to 25-hydroxyvitamin D (25-OH D). A recent study has provided considerable insight. It was found that the concentration of 25-OH D in response to input

vitamin D3 was biphasic, i.e. a rapid increase occurs at low vitamin D concentration and a slower response occurs at higher concentrations. Thus, if one starts with a low level of 25-OH D, almost all the input vitamin D was converted and there was

little storage. Once the turning point is reached, the 25-OH D continues to rise, but now the level of vitamin D also increases, with the vitamin level increasing faster than the product molecule. This turning point is produced by an intake of roughly 2000 IU. Thus below the turning point, the 25-OH D product is the major storage molecule for vitamin D. Above this point, the conversion in the liver appears to saturate and the vitamin itself is stored, most likely in the fat. The authors postulate that the point

where the conversion in the liver saturates may be considered optimal for health. Their results suggest a value of 35 ng/mL or 88 nmol/L. They point out that this value is close to that obtained in attempts to define the lower end of normal from the relationship of 25-OH D to calcium absorption and to serum parathyroid hormone concentrations (75-85 nmol/L). Parathyroid concentrations are inversely related to 25-OH D levels but level off at 75-100 nmol/L of serum 25-OH D.¹⁴

VITAMIN D AND AUTISM

In an earlier issue, the hypothesis advanced by Dr. John Cannell regarding a possible connection between vitamin D deficiency and autism was presented. Thanks to one of the readers of this Newsletter, I was alerted to an interesting commentary by Dr. Cannell on this subject in the form a record of email exchanges with the mother of an autistic child (Google Cannell vitamin D newsletter June). This exchange discusses the improvement in the child's autistic symptoms with vitamin D supplementation. There is also an interesting discussion of genetic polymorphisms. But of even more interest, it would appear, is the point Dr. Cannell makes concerning the adverse influence on the benefits from vitamin D caused by vitamin A. In his advice to the mother, he makes a very strong point that all supplemental vitamin A including cod liver oil and vitamin A from multivitamin preparations must be eliminated if her son is to get maximum benefit from vitamin D therapy. He provides five references to back up this

assertion, and it appears to be a significant and perhaps generally unrecognized issue. As a substitute, he recommends colored fruits and vegetables. When the exchange of emails ends, the dose which started at 5000 IU/day had been reduced to 2000 IU/day which appears to be the maintenance dose Cannell favours. The boy continued to show improvement in a number of areas including speech and various activities. His mother was also prompted by this experience to recall seasonal variations in behavior which correspond to seasonal variations in vitamin D status in the absence of supplements or intentional UV exposure. This exchange of emails should be of considerable interest to any parent of an autistic child. Hopefully Dr. Cannell's article in *Medical Hypotheses*¹⁵ will stimulate research into this interesting aspect of vitamin D. The 2008 Vitamin D Newsletter cited above also has an interesting and lengthy Q & A section on autism—see the sidebar "autism" link.

DIETARY PATTERNS AND MORTALITY IN WOMEN

Readers of this Newsletter and the associated Research Reviews will be aware of dietary patterns as a tool for acquiring information regarding optimizing health through dietary choices. A recently reported study followed over 72,000 women for 18 years and identified a beneficial and a harmful dietary pattern, the prudent pattern and the Western Pattern. The former represented high intakes of vegetables, fruit, legumes, fish, poultry and whole grains. The latter reflected high intakes of red meat, processed meat, refined grains, French fries, and

sweets/deserts. After accounting for confounding, the prudent diet was associated with a 28% lower risk of cardiovascular mortality and a 17% lower all-cause mortality when the highest vs. the lowest quintiles of adherence were compared. In sharp contrast, the Western pattern increased cardiovascular risk by 22%, cancer by 16% and all-cause mortality by 21%.¹⁶ The consistency with earlier studies appears to make the evidence for the Prudent Diet Pattern compelling.

GARLIC AND BLOOD PRESSURE

Historically, a number of health benefits have been attributed to garlic and a number of preparations are available in health food stores. Garlic has been shown to have constituents that possess angiotensin II inhibiting properties and vasodilating effects. An attempt to clarify the benefits of garlic in blood pressure reduction has recently been reported with the publication of a meta-analysis of studies from 1994 to late 2007.¹⁷ Eleven studies were found suitable for analysis and showed a mean decrease of 4.6 mm Hg for systolic blood pressure (SBP) in the garlic group as compared to a placebo. When a hypertensive subgroup (SPB \geq 140 mm Hg) was analyzed, the mean decrease in SBP was considerably larger, 8.4 mm Hg and 7.3 mm Hg for the diastolic pressure (DBP). These blood pressure changes were achieved on average with 12 weeks supplementation. The authors comment that these SBP/DBP changes brought about by garlic are comparable to the hypotensive effects of commonly-prescribed prescription drugs, e.g. beta-blockers, ACE inhibitors, and angiotensin II type 1 receptor antagonists. They also comment

that a reduction of 4-5 mm Hg in SBP and 2-3 mm Hg in DBP has been estimated to reduce cardiovascular mortality and morbidity by 8-10%.

Most studies included in this meta-analysis used garlic powder at an intake level of 600-900 mg/day which would provide potentially 3.6-5.4 mg of allicin, the presumed active ingredient. Fresh garlic cloves yield 5-9 mg of allicin, but aged garlic extracts and heat-treated garlic may have lower levels and be less effective. Also, garlic supplements have the advantage over raw or cooked garlic in that the user avoids garlic breath and body odour and as well, such preparations avoid the potential destructive aspect of the cooking process. They suggest that garlic supplements may provide an acceptable and well-tolerated alternative to prescription drug therapy for hypertension. Since home blood pressure monitoring is now very common, it is easy for an individual to see if garlic does indeed work for them. Inexpensive, certified, automated home monitoring devices are now readily available

PYCNOGENOL FOR KNEE OSTEOARTHRITIS

Non-steroidal antiinflammatory drugs (NSAIDs) are the standard approach to the treatment of the pain associated with osteoarthritis. However, these drugs have a propensity to cause stomach ulcers, and GI bleeding and perforations, the latter being a surgical emergency. The specific COX-2 inhibitors, which were promoted as having fewer side effects, have been plagued by concerns that long-term use increases the risk of heart attack and stroke. A recent study has examined Pycnogenol as an alternative. This is a standardized extract from the French maritime pine and has been found to have analgesic properties. In a randomized, placebo controlled study just published, Pycnogenol was

studied for the relief of osteoarthritic knee pain. Patients were given 500 mg three times a day with meals or a placebo. Standard questionnaire-based measures of discomfort and functionality were used and as well, participants were asked to keep track of NSAID intake. The Pycnogenol group reported an improvement in pain, stiffness and the impact of the arthritis on daily activities whereas the placebo group reported no effect. In the treatment group, there was a 38% reduction in the use of analgesics vs. an 8% increase in the placebo group. The investigators report that the pycnogenol was well tolerated.¹⁸

WHOLE GRAINS AND CARDIOVASCULAR DISEASE

The merits of whole grains turn up repeatedly in dietary studies and the benefits as compared to refined grains seems hardly debatable. Refining whole grains removes most of the micronutrients and fiber and leaves rapidly digested carbohydrate of little nutritional value aside from calories. Yet decades ago refined grains became the grain product of choice for those who could afford it, and

then evolved to become a universal staple. Whole grain consumption has been associated with reduced cardiovascular risk. A recent meta-analysis confirms this view. Seven prospective cohort studies with quantitative measures of whole grain intake and cardiovascular outcomes involving almost 300,000 participants of both genders were analyzed. Outcomes included CHD, CHD death,

CVD death, and stroke. Greater intake (2.5 servings/day vs. 0.2 servings/day) was associated with a 21% lower risk of CVD events with similar results for different CVD outcomes (heart disease, stroke, fatal CVD). The authors conclude that clinicians should make a greater effort to promote whole grains into public health and clinical practice endeavours.¹⁹ This is a complex issue since foods

such as whole wheat bread generally do not contain whole grains as the name suggests and great attention needs to be paid to label reading.

Examples of whole grains include amaranth, barley, buckwheat, corn, millet, oats, quinoa, brown rice, rye, sorghum, various varieties of wheat with forms including bulgur, cracked wheat and wheat berries.

GREEN TEA AND ENDOTHELIAL FUNCTION

Flow-mediated dilation (FMD) of the brachial artery (in the arm) is related to coronary endothelial function and is an independent predictor of the risk of cardiovascular disease. Black tea has a beneficial effect on FMD and recently the role of green tea has been investigated in this context since there is evidence that green tea decreases cardiovascular risk.²⁰ Fourteen healthy individuals in their early thirties were on three occasions given 6 grams of green tea added to 450 mL of boiled water for 5 minutes, or 125 mg of caffeine (the amount of caffeine in the green tea) or hot water. FMD was

measured several times over 2 hours. As well, blood was collected and assayed for a variety of markers including CRP, interleukins and total plasma oxidative capacity. Green tea was observed to have an acute beneficial effect on endothelial function as assessed by FMD and this was not due to caffeine, nor was there any effect on CRP, interleukins, or total plasma antioxidative capacity or oxidative status. It was concluded that the impact on endothelial function may explain the beneficial effects of this form of tea on cardiovascular risk.

COFFEE AND MORTALITY

A study based on data collected over the years in the Nurses' Health Study and the Health Professionals Follow-up Study, which involved about 42,000 men and 86,000 women, has reported on the relationship between coffee consumption and mortality.²¹ A large range of intake from < 1 cup per month, to ≥ 6 cups per day was considered. It was found that regular consumption over this entire range was not associated with increased mortality rate in either men or women. In fact, a modest

inverse association between coffee and all-cause mortality was found in both men and women, an association which was mainly explained by a reduction in cardiovascular deaths. The researchers also found that the benefits of coffee consumption were associated with components other than caffeine. The results were consistent with the possible beneficial effects of coffee on inflammation, endothelial function and the risk of type 2 diabetes.

ANTIDEPRESSANTS AND CANCER

It is just been reported that there may be a connection between taking antidepressants and the risk of non-Hodgkin Lymphoma.²² The research, reported in the latest issue of *Epidemiology*, is based on data from the Danish Cancer Registry and a prescription database. Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI) and "other" antidepressants were examined. They calculated an adjusted incidence ratio by comparison with over 3.6 million unexposed individuals. It was found that the use of tricyclic antidepressants carried an overall 1.53 fold increase in incidence of non-Hodgkin Lymphoma

and the risk increased to 2.5 fold for users of ≥ 10 prescriptions and 5 or more years of follow-up. An important finding was that the tricyclic class was the only one to exhibit this increased risk. It is important to mention that these results are based on a limited number of cases and little opportunity to correct for confounding. The tricyclic antidepressants were first used in the 1950s. An analysis published in 2003 by the well-known Cochrane organization concluded that their effectiveness was only slightly greater than a placebo. Tricyclics have been increasingly replaced by SSRIs. However, in the past 6 months the effectiveness of the SSRI antidepressants has

also been called into question.^{23,24} In this case, investigative research revealed that the data submitted for US FDA approval was biased by the omission of negative results. When the total body of evidence from clinical trials was analyzed, it turned out that the SSRIs were only slightly more effective than a placebo except for the treatment of advanced depression, but even for the treatment of severely depressed patients, the efficacy was relatively small.

For readers interested in a general discussion of serious problems in drug trials, a recent paper in the

journal *Philosophy, Ethics, and Humanities in Medicine* should be of interest.²⁵ It was inspired by the antidepressant matter. The author discusses how the use of many small randomized trials with clinically non-relevant outcomes, improper interpretation of statistical significance, manipulated study design, biased selection of study populations, short follow-up, and selective and distorted reporting of results can yield a seemingly evidence-based conclusion or consensus that is in fact a myth (his term). This paper is available without subscription from the journal website.

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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>

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