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With the advent of the new year, it is perhaps useful to examine some aspects of the state of medicine. Medicine is of course a complex, multifaceted endeavour involving stressful intellectual and emotional challenges for practitioners, and the impact of huge financial interests, many not benign. The pace of research is staggering and keeping up is becoming difficult or impossible. Physician dissatisfaction appears to be growing, driven by reimbursement problems including a huge paperwork load, restrictions on how to practice medicine, bureaucratic interference and a less than satisfying success rate in the treatment and prevention of chronic disease which, with an aging population, has become central to the practice of medicine.

In the past year, the pharmaceutical industry has experienced increased high profile criticism. Accepted or approved therapies in the new era of evidence-based medicine depend on clinical trials which are terribly expensive and thus most frequently sponsored by the pharmaceutical industry. In some instances, the industry designs the study, recruits the subjects and collects the data. Today it is not uncommon to find that industry farms out these activities to private companies, many offshore. The results of the clinical trials form most of the basis for regulatory approval and treatment guidelines. The selection of subjects, the pre-trial screening and the statistical treatment of dropouts offer the opportunity for bias. The industry has historically conducted more trials than it submits to apply for approval, concealing some unfavourable to their product. Quantification and reporting of adverse side effects is also notorious for being subject to bias, and the duration and small number of subjects precludes the identification of some problems, which turn up in the post introduction period when a drug is suddenly being prescribed to tens or hundreds of thousands of patients rather than a few thousand participants. Thus the physician, attempting to practice evidence-based medicine, is faced with practice guidelines based on potentially inaccurate, incomplete, fraudulent or corrupted evidence. After all, for over 10 years treating to LDL targets was approved or even required evidence-based medicine and the standard of practice. Now physicians are told there was no acceptable evidence. Forget about targets.

Clinical studies are rather like a game with scores and winning or losing. The stakes can be high, involving where the study can be published, the professional benefit to the authors (promotion, ease of getting research support, prestige, potential for invitation to drug company speaker's bureaus, etc.), and the financial benefit to the sponsors if they have a financial interest, which of course is always present with industry sponsored studies. Clinical studies generally have clinical endpoints and the goal is either to demonstrate benefit or harm or superiority. The scoring system of this game is generally based on odds or hazard ratios, frequently produced through extensive statistical manipulation to adjust for real, suspected, or cherry picked confounders. These odds ratios or hazard ratios must be statistically significant. There must be less than a 5% chance of the result being due to pure chance, the so-called 95% confidence interval. This interval, the range of statistically acceptable ratios, must not include the null result, which for these measures is 1.00. As long as the ratio meets this statistical test, then for risk reduction, the smaller the better. While intervals including 1.00 are dreadful news, ratio ranges corresponding to this so-called 95% limit, such as for example 0.75—0.99 or 1.01—1.25 (for increased risk) represent winning the game. The 0.01 to get to 1.00 is like winning by a nose in a horse race. This ratio is also a

relative risk reduction (benefit) or a relative risk enhancement (harm). What is critical is the term relative. A large relative risk reduction or an identification of a large relative indication of harm will frequently be picked up by medical journalists and even may make the evening news. Large effects are professionally very good for the researchers and represent a powerful and effective marketing tool. Doctors sold on the notion that a drug reduces the relative risk by 40% may meet little scepticism from patients when told this impressive figure. Patients view their chances of being in this favoured 40% as good enough. But this is highly deceptive and perhaps even unethical since there is a failure to fully disclose information needed for a patient to make an informed decision.

This deception, an unfortunate aspect of the game and its accepted scoring system, is that the relative risk reduction does not inform as to the percentage of treated individuals who actually benefit or are harmed. These numbers may be buried in tables or difficult to calculate from the given data, or occasionally some may be given in the text but rarely in the abstract. In general the percentage of those treated that do or do not benefit is a taboo subject, a subject not productive to explore in the presentation of the results of a clinical study, and not a factor in determining winners or losers. The point is that one can have a 40-50% relative risk reduction and yet for example 99% of those treated have no benefit in terms of the problem or disorder at issue. The number of patients who must be treated to achieve one beneficial result is in this case 100, i.e. 1/0.01 where the denominator is merely 100%--99% = 1% expressed as a probability, i.e. by diving by 100. If a patient thinks this still OK, fine, but some doctors have reported as commenting that if they tell patients such numbers, the patients generally refuse treatment. Thus the taboo surrounding presenting clinical results in absolute terms. However, this is changing, albeit slowly.

And finally, 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 publication of IHN. You can find the store at http://www.yourhealthbase.com/vitamins.htm.

Wishing you and your family good health,

William R. Ware, PhD, Editor

Highlights

WINTER CAMPAIGN IN WAR ON SUPPLEMENTS. MULTIVITAMIN-MINERAL SUPPLEMENTATION

This war has been going on for a long time. The soldiers are mainly recruited from the many medical professionals who firmly believe that in the developed countries people get all the vitamins and minerals they need from food and that supplementation is unnecessary, can be dangerous and a waste of money. For prevention, one must look to the pharmaceutical industry and lifestyle. There is no shortage of studies to pick from if one is trying to make an evidence-based anti-vitamin argument, but most involve one or several vitamins or minerals or both, tested in isolation for a limited number of endpoints. In some cases, the use of low doses or the study design provide bias for a null result. There are actually very few multivitamin-mineral studies. Vitamin D is the classical example where low doses confused the picture for several decades. However, that is changing rapidly with growing awareness of the importance of having sufficient levels of this remarkable vitamin.

Even the die-hard fan of Big Pharma can no longer ignore the avalanche of vitamin D studies.

The winter campaign started with a report from the famous U.S. Preventive Services Task Force.[1] They concluded after conducting a systematic review that there was only limited evidence supporting any benefit from vitamin or mineral supplementation. Our concern here is with multivitamin-mineral supplements. Only one long-term multivitamin study was reviewed which included all the three endpoints, all-cause mortality, cardiovascular disease and cancer, the Physicians Health Study II. Aside from fatal heart attack, only null results were found in this study, and the statistical significant heart attack result had a negligible absolute risk reduction. However, it is hard to take this study seriously since the multivitamin was a commercial product containing very small amounts of most components which was augmented by modest amounts of vitamin E and vitamin C. For example, the supplement had 500 IU of vitamin D, an amount today considered borderline insignificant. The B vitamins, selenium and zinc were also very low compared, for example, to the one-a-day preparation sold by Life Extension Foundation or other high potency products.

The next study appeared in late 2013. The issue was the effect of long-term multivitamin-mineral supplementation on cognitive function in men.[2] It also was part of the Physicians Health Study and used the same low-potency multivitamin. The conclusion was that for male physicians over 65, long-term use of a multivitamin did not provide cognitive benefit. Again, dose is a critical issue.

The third study also has just appeared and was part of the Trial to Assess Chelation Therapy (TACT).[3] One arm involved the comparison between a multivitamin-mineral and a placebo, but both groups also received 30-40 IV infusions of saline and were the control for the chelation infusion. In this arm the drop-out rate was very high, raising questions concerning validity of the null results. However, the event-rate vs. time for primary endpoint of time to all-cause death, recurrent MI, stroke, coronary revascularization or hospitalization for angina diverged to show modest benefit which was not statistically significant. The cohort all had a history of heart attack and a significant number had diabetes.

Thus we have three studies, two using very low doses of vitamins and minerals and restricted to older male physicians and one restricted to hearts attack victims, many with a serious comorbidity. These cohorts can hardly be described as representative of the general population. Nevertheless, in editorials and media coverage, the above were taken as the final nails in the coffin and supplementation with multivitamins was declared worthless. One editorialist used the phrase, “Enough is enough.”[4] A more realistic position would seem to be that the question remains open because of the great difficulty in conducting studies, the dose issue, the compliance issue, and personal variations. There are those who eat mostly junk food or emphasize the worst aspects of the Standard American Diet. They would be good candidates for a long-term primary prevention study. They would certainly represent a different cohort than those in the studies discussed above. The acceptance of the null results in vitamin and mineral studies as applicable to the general population reflects the remarkably low standards that actually exist in so-called evidence-based recommendations.

Vitamins and minerals are essential cofactors for innumerable biochemical processes and a specific need for a certain level of one in an individual may be addressed and provide a huge benefit, but this is difficult to demonstrate in large studies. For some, very large doses are needed short-term. Human variability is the key problem. The multivitamin-mineral is like an insurance policy. The reader is referred to the Research Report regarding the “Metabolic Tune-up” which appeared in the October 2004 IHN and as well landmark paper by Bruce Ames[5] for a detailed discussion of vitamin and mineral enzyme cofactor problems and human individuality.

Even a high-potency multivitamin-mineral may not in general address a severe deficiency. This requires baseline and follow-up measurements. For example, deficiencies of vitamin D, potassium, sodium, magnesium, vitamin B12, selenium zinc and iodine are frequently discovered by integrative physicians and treated, generally with great benefit to the patient after conventional medicine has failed.

There is no easily identified optimum intake since there is too much personal variability regarding both baseline levels and needs. Comprehensive screening is for most only a dream of utopia, given the anti-supplement milieu.

VITAMIN D AND HEALTH. A SIGNIFICANT ATTACK

The connection between sun exposure and various health issues suggested that vitamin D sufficiency offered protection for a number of disorders. This hypothesis was supported by most but not all prospective cohort studies. Disorders included cardiovascular disease incidence and mortality, obesity, the metabolic syndrome, all-cause mortality, infectious disease incidence and severity, neurological and psychiatric disorders, and physical performance of the elderly. In many studies vitamin D status was judged by serum 25-hydroxyvitamin D (25(OH)D) which is much more reliable than food frequency questionnaires and permits judgement regarding sufficiency. Thus studies must be examined carefully with regard to the actual initial and long-term vitamin D levels.

However, with prospective studies there is the nagging uncertainty that the relationship between 25(OH)D and disorders is the result of confounding or physiologic events involving the disorders in question which might lower vitamin D levels. This issue can theoretically be resolved by a properly designed and conducted randomized, controlled intervention trials involving vitamin D supplementation. Most of the disorders addressed in the prospective studies that were also the subject of the randomized trials. Trials and especially randomized trials are not cheap and the large number of trials completed is quite remarkable considering that 5000 IU vitamin D capsules cost about 20 cents apiece and thus studies of this substance are of little or no interest to the pharmaceutical industry, except that they would benefit from false negative studies which motivate individuals to abandon supplementation and thus might need more pharmaceutical drugs, preferably patented.

A recent systematic review identified 172 randomized trials (RTCs) and 290 prospective studies from which studies were selected for review.[6] The issue was major health concerns. The prospective studies found moderate to strong protective (inverse) associations between 25(OH)D levels and cardiovascular disease, serum lipid concentrations, inflammation, glucose metabolism disorders, weight gain, infectious diseases, multiple sclerosis, mood disorders, declining cognitive function, impaired physical functioning and all-cause mortality. However, randomized, controlled intervention studies with vitamin D supplementation failed to find benefit in most studies, leading the investigators to conclude that low 25(OH)D is a marker for ill health, implying that supplementation is useless.

A number of possible explanations exist. In some cases the discrepancy between RCTs and prospective studies may indeed be due to confounding or the impact of underlying illness. Other explanations include subject groups with significant numbers with 25(OH)D levels above the threshold for the disorders in question, making it impossible to find significant effect for the sample size. Some studies with positive results may not have been included for invalid reasons. Other issues include inadequate supplementation, incorrect formulation of the supplement, insufficient follow-up or studies that were underpowered to detect a significant effect size. Dose in the reviewed studies covered a wide range including what today are considered insignificant amounts. 25(OH)D levels also ranged from very low to not very high. Some randomized trials may have been biased.

Among the large number of randomized trials, the investigators were able to identify only 34 studies where the subjects had baseline 25(OH)D levels < 50 nmol/L (20 ng/dL) and employed supplementation of more than 2500 IU/day. The endpoints involved were vascular endothelial function, blood pressure, C-reactive protein, interleukin 6 or tumor necrosis factor alpha, glucose metabolism markers, and infectious disease. This list omits most of the disorders listed above found in prospective studies to be associated with vitamin D deficiency, and are mostly markers rather than clinical endpoints. Included in main the analysis were 51 RCTs for cardiovascular disease, 24 for physical functioning, and 135 for all-cause mortality, none of which met the criteria for low 25(OH)D with interventions of ≥ 2500 IU/day. This strengthens the argument that many randomized trials used insufficient doses. The negative view of vitamin D supplementation appears to lack justification.

A fundamental problem involves drawing conclusions from combining large numbers of studies for a given endpoint and obtaining odds ratios and confidence intervals without regard for dose, the characteristics of the various cohorts, achieved or baseline 25(OH)D levels, variable study quality, etc.

VITAMIN D, AN EARLY PREDICTOR OF MULTIPLE SCLEROSIS ACTIVITY AND PROGRESSION

It was first pointed out in 1977 that the incidence of multiple sclerosis (MS) is low in the tropics and increases with distance from the equator in both hemispheres. This has become a hallmark of the association between disease risk and vitamin D levels. The first large prospective study concerning the hypothetical connection between MS and vitamin D deficiency was published in 2004 and based on data collected in the famous Nurses' Health Studies (NHS and NHS II).[7] This study found a 40% reduction in risk of MS among vitamin D supplement users, even when the doses were low (no supplementation vs. ≥ 400 IU). More recent studies which provided additional support for the positive connection between MS risk and vitamin D levels were based on the serum marker 25-hydroxyvitamin D (25(OH)D),[8] and a study published in 2013 was prefaced by the statement "Growing evidence suggests that vitamin D deficiency may be one of the most important environmental factors for the development of MS."[9]

A study has just appeared which addresses the question of the impact of vitamin D insufficiency on disease activity and progression in patients with a first event suggestive of MS but not diagnostic (a so-called clinically isolated syndrome--CIS).[10] This was part of a study where patients were treated with an interferon after a first CIS and had vitamin D status data. New active lesions, increased lesion volume and brain volume were determined by MRI, and MS relapses and MS related disability were also observed. Based on vitamin D levels at one year after the CIS event, higher levels of 25(OH)D (≥ 50 nmol/L vs. < 50 nmol/L, i.e. 20 ng/mL) predicted reduced MS activity and a slower rate of progression in a subsequent 4-year period. By the end of the follow-up, those patients with vitamin D levels ≥ 50 nmol/L had a 4 times lower change in lesion volume, a 2-fold lower rate of brain atrophy, and lower disability than those below 50 nmol/L. The analysis, which had a one-year lag between the last serum 25(OH)D measurement and the 4-year follow-up assessment of MS outcomes, was viewed by the researchers as evidence that low vitamin D levels were not a consequence of the disease process itself but rather a predictor. They also comment on the consistency between these results and previous epidemiological and biological evidence supporting the protective effect of vitamin D on the disease process underlying MS and the importance of correcting insufficiency, which they point out exists in about 50% of European MS patients and 20% of those in the US.

In comments to *medpagetoday.com* (January 20), a daily medical newsletter, Lawrence Steinman, MD, of Stanford University, who was not involved in the study, indicated that in his opinion the study was of great importance and supported a causal relation between higher vitamin D levels and reduced MS disease activity. He added that vitamin D regulates expression of interleukin-17, one of the key mediators of MS. He also suggested that these results might explain the progressive *decrease* in relapse rate in the placebo arm of clinical trials of MS over the past 10 years, i.e. more and more individuals become aware of vitamin D and started supplements, lowering the relapse rate.

ARE THERE HEALTHY OBESE INDIVIDUALS?

The headline in one of your editor's morning papers (National Post) read "There's no such thing as healthy obesity." The article went on to discuss the report which had just appeared in *Annals of Internal Medicine* involving a meta-analysis of studies comparing metabolically healthy overweight or obese individuals with metabolically healthy normal weight subjects.[11] Normal weight was defined as BMI ≥ 18 to ≤ 25, overweight ≥25 to < 30, and obese as > 30. BMI is defined as weight in kg divided by the square of height in meters. The endpoints were combined all-cause mortality and cardiovascular events. The events included in the non-fatal cardiovascular events included unstable angina, coronary angioplasty, coronary bypass surgery, congestive heart failure, stroke, heart attack, transient ischemic attack and claudication. Presence of the metabolic syndrome was used to distinguish metabolically healthy from unhealthy.

The title of the paper suggested that the issue was obesity being a benign condition in the metabolically healthy. The authors presented their meta-analyses by figures showing results from each study included in their analysis and then the final results. Included were the incidence rates summed over the included studies for each comparison. Consider the question of all-cause mortality and/or cardiovascular events. The table below compares those deemed metabolically healthy but either overweight or obese vs. those deemed metabolically healthy and of normal weight. The data are from the meta-analysis summaries and the table provides the number of studies included, and the absolute difference in event rate for the indicated weight comparisons, the odds ratios the investigators calculated when statistically significant, and the stratification according to any follow-up or ≥ 10 year follow-up. ARI is the absolute risk increase for all-cause mortality or cardiovascular events associated with being overweight or obese compared to having normal weight.

WEIGHT COMPARISON	STUDIES	ARI	ODDS RATIO	FOLLOW-UP YEARS
Healthy Overweight vs. Healthy Normal	6	2.8%	NS	ANY
Healthy Overweight vs. Healthy Normal	3	1.4%	NS	≥ 10
Healthy Obese vs. Healthy Normal	7	0.81%	NS	ANY
Healthy Obese vs. Healthy Normal	4	0.86%	1.24	≥ 10

These data indicate that independent of follow-up time, 97.2% *or more* of the subjects in these studies showed no difference in the combined endpoints, whether they were overweight or obese or were of normal weight, provided they did not have the metabolic

syndrome, i.e. for this study, they were deemed healthy. In fact, the obese did better than the overweight, where for 99.2%, being obese rather than overweight made no difference compared to being of normal weight. In the abstract conclusions the authors emphasize the significant odds ratio for healthy obese vs. healthy normal weight, even though the increased absolute risk was less than 1%. The 24% relative risk increase indicated by the OR is enough for the media to make a big deal out of this study, even though significant increased relative risk only appeared after stratifying for study duration and required obesity, not being overweight. As usual, the absolute risk increase was ignored. There is also a problem with the large number of endpoints combined to yield the published results. Some of these endpoints are considered soft, since judgment calls and potential bias are involved. By comparison, hard endpoints like verified stroke, heart attack or death are subject to much less potential bias since, for example, it is exceedingly rare to incorrectly pronounce one dead (it does happen, but the error is generally quickly corrected!). Thus if only hard cardiovascular events had been included, the differences might have even been smaller.

When the comparison was made between metabolically healthy normal weight individuals and metabolically *unhealthy* overweight or obese individuals, there was an increase in risk of adverse long-term outcomes, which is in fact expected and not surprising, and which appears to add little to the existing literature regarding the health risks of metabolic syndrome.[12] However, the study specifically addressed the title question discussed above by focusing on the metabolically healthy.

In a piece in the January 9 *New England Journal of Medicine* online *Journal Watch*, the headline read “Is Metabolically Healthy Overweight or Obesity a myth?” The answer was yes based on the odds ratio given in the above table of 1.24, only seen after ≥ 10 years follow-up, and with less about 1% difference in observed risks between the obese and normal weight individuals. Also Ignored were the three non-significant results for the same endpoints. Modern medicine appears to be satisfied with very small absolute effects when they correspond to the conventional wisdom.

ATHEROSCLEROSIS AND THE ANCIENT MUMMIES

Life expectancy in the developed world doubled between 1800 and 2000 and vascular disease attributed to atherosclerosis replaced infectious diseases as the leading cause of death. It is a common assumption that atherosclerosis is related to lifestyle and if modern humans could emulate preindustrial or pre-agricultural lifestyles, atherosclerosis and its clinical manifestations would be significantly decreased.

This view is challenged by recent studies of the prevalence of atherosclerosis in mummified remains of individuals who died between about 2000 BC (the modern designation is BCE, before the common era) to around 300 AD (300 CE). The mummies were examined by CT scans and evidence of arterial calcification sought and successfully found. The first published report from this project (the Horus Study) appeared in 2011 and involved 52 Egyptian mummies.[13] Forty-four of 52 mummies had identifiable cardiovascular structures and 20 had either definite or probable atherosclerosis in a variety of vascular beds. This study was expanded to include 137 mummies from for different geographical regions or populations from ancient Egypt, ancient Peru, the Ancestral Pueblos of southwest America, and the Unangan of the Aleutian Islands.[14] All but the Egyptian examples had undergone natural mummification which helped eliminate confounding including the high social class represented by the Egyptian mummies. In the expanded study, 47 mummies from all four geographical populations had probable or definite atherosclerosis. Calcification was evident in all the vascular beds which included aorta, coronary, carotid or peripheral (pelvic or leg). Age of estimated time of death correlated with the presence of atherosclerosis. Thus arterial

atherosclerosis was a common phenomenon in diverse populations over a period up to over 4000 years in the past.

The Egyptians were upper class who presumably ate what was available in the markets including farm products and fruits, and as well consumed beer and wine. Peruvians were farmers who domesticated animals, the Pueblos were forager-farmers and the Unangans/Aleuts were classical hunter gatherers who ate a diet high in fish. Thus diet varied considerably for the four groups. Meat came from domesticated or hunted animals.

Two not mutually exclusive theories have been offered to explain the widespread prevalence of atherosclerosis which in fact appears not that different from modern populations. One involves exposure to smoke from heating and cooking, generated frequently but not always in confined spaces. This may be equivalent to tobacco smoking as a large risk factor. The other involves infections and the associated acute response which included high levels of inflammation. In fact, Caleb Finch from the University of California, Los Angeles, had by 2010 described an evolutionary pattern predating these populations wherein increased inflammatory response to infections added to early to midlife survival, but then due to the promotion of atherosclerosis and other inflammation disorders of aging, proved to be an ever increasing risk factor.[15] It is interesting in this context that for the populations in the mummy studies, survival to about age 30 added about 30 additional years of life.

The infection theory of atherosclerosis is not new but has never been seriously considered. In 2012 Ravnskov and McCully[16] expanded on an earlier hypothesis[17] for the pathophysiology of atherosclerosis by dealing in detail with infections. The earlier hypothesis attributed arterial plaque as originating from obstruction of the vasa vasorum by oxidized and homocysteinylated lipoprotein aggregates complexed with microbial remnants and LDL antibodies. The vasa vasorum provides the blood supply to the arterial tissue from the outside of the artery and they proposed a mechanism which involved immune response within the arterial wall and the adverse effects of restricted blood supply and oxygen. This recent theory nicely complements the view of Finch regarding infection derived inflammation effects which was repeated in the discussion section of 2012 mummy study report with Finch as one of the authors. An excellent review of this theory recently appeared in *Scientific American.*[18] Together these studies are also consistent with the observations cited by Ravnskov and McCully that autopsies on victims of the WW II concentration camp in Dachau found extensive atherosclerosis in individuals younger than 35, many of whom had evidence of severe infections but none of the traditional risk factors such as dietary cholesterol, dietary saturated fat, or smoking and there was no lack of exercise and no obesity, They also cite evidence that atherosclerosis starts in childhood and appears associated with infectious diseases. The theory promoted by Ravnskov and McCully has been almost totally ignored. It challenges the official dogma.

The results of the mummy studies suggest that important factors associated with the development of atherosclerosis and its progression remain to elucidate. The groups studied included one with a diet pattern grossly different from the other three. Three of the four groups appeared to have been physically very active. There were no synthetic food additives, no *trans*-fats except for the small amounts that occur naturally, no tobacco, and only wood or coal fires. While it would be dangerous to conclude that lifestyle and diet are of no consequence, the mummy studies can be regarded as weakening the hypothesis considerably.

It thus appears unfortunate that mainstream medicine is still focused on cholesterol and saturated fat even though the fat-heart hypothesis was falsified 15 years ago and there is compelling evidence that total or LDL cholesterol levels do not correlate at all with either the prevalence or progression of coronary atherosclerosis and statin treatment has no impact on progression.[19] If the very small absolute benefit seen with statins in primary prevention is in

fact an anti-inflammatory effect, these observations obviously point to a potentially fruitful direction for research. The infection theory is an integral part of this different view.

There is at least one notable exception where a large percentage of a population does not experience significant or progressive atherosclerosis. It is Okinawa where longevity, even extreme longevity, is common and coronary heart disease is rare. The elderly typically have the arteries common of young persons. Okinawan longevity is an interesting story described in the book *The Okinawa Program* by the medical scientists involved in studying this unique population. The resultant peer reviewed literature will perhaps be reviewed in a future issue of IHN.

INCREASED RISK OF DIABETES ASSOCIATED WITH STATINS

There have not been enough studies with results suggesting that statins increase the risk of diabetes that the issue is being taken seriously. The mainstream response has been that the benefits of statins outweigh the risks of diabetes, and frequently the argument is based on numbers needed to treat for cardiovascular benefit exceeding the numbers need to harm for increased incidence of diabetes.

In this context, a very interesting study has just appeared in the *British Medical Journal* based on a reanalysis of data from a large trial.[20] The investigators identified subjects who had never taken statins or antihypertensive and then followed those who started one or the other with the incidence of diabetes determined by periodic laboratory measurements (rather than crude methods such as phone calls). The study cohort was restricted to individuals with impaired glucose tolerance, i.e. prediabetic, and is the first study to examine such a cohort for the impact of statins on the progression to diabetes. In addition, the question of the impact of beta-blockers and diuretics was examined, using those on calcium channel blockers as a reference. The authors cite the following strengths of the study. Firstly, it was large, and largest of its kind to date. Secondly, it used standard methods for diagnosing diabetes, with pre-specified serial glucose assessments and laboratory confirmation for all patients. Thirdly, the study population was treatment naïve. Also, the statistical analysis of the results was done by an independent academic group and all the investigators had access to all the data.

The authors provided relative risk increases and numbers needed to harm. Regarding the latter, which are of course vastly less misleading, 12 patients had to take a statin over 5 years to generate one case of diabetes. To put the statin number in perspective, for primary prevention of coronary heart disease related events, the number need to treat to prevent one event is somewhere around 50 to 100 depending on the level of risk in the cohort. For secondary prevention, the number is 25 to 50. Thus a number needed to harm of 12 has a significant effect on the risk/benefit ratio in the case of prediabetics initially statin naïve.

The world is full of prediabetics, 80 million over 20 in the US, and it is not uncommon for them to be unaware of this condition. For those on statins, their risk of developing diabetes appears significantly enhanced and overwhelms the small benefits for many that accrue from statin treatment. In addition, the risk/benefit assessment for statins is made almost impossible because of significant underreporting of other adverse side effects and studies that are biased by design and execution to have low side effects.

NEWS BRIEFS

ADHD EPIDEMIC KEEPS ROLLING ALONG

In November the U.S. Center for Disease Control (CDC) presented a report available form their website which has been widely discussed and described in the media. It provided an update on the statistics regarding Attention-Deficit/Hyperactivity Disorder (ADHD). We have reached the amazing point where more than 20% (one in five) 14 year-old boys have been diagnosed with a problem officially deemed a mental disorder. In addition, 13.3 % of American 11-year-old boys are being medicated for ADHD. New information also indicates the mental disorder is diagnosed on average at age 7 with about half of the victims diagnosed by age 6. This is not due to the definitions in the new *Diagnostic and Statistical Manual of Mental Diseases* (DSM V) which recently created so much controversy. It has not been out long enough. It appears in part the fulfillment of the nightmare created by DSM IV used for over a decade. Fear of this outcome and remorse was "confessed" publically several years ago, first in the *Los Angeles Times*, by the director of the DSM IV writing group, Dr. Allen Francis, then Department of Psychiatry chair at Duke University.

While the mainstream view is no doubt satisfaction that so many of these unfortunate children who are mentally ill are being identified and many provided with the most up-to-date medical interventions, mostly using highly restricted substances such as amphetamines of high street-drug value per pill, something that has not gone unobserved by children. However, there are certainly those who view this as a horrible example of reckless overdiagnosis. Justification of this view was discussed in IHN where a study revealed that within a given school year ADHD diagnosis was much higher among the youngest vs. the oldest members in each of a number of grades. This study was in jurisdictions where there was always a guaranteed one-year spread in age in each class.

CURCUMIN SUCCESSFULLY TREATS RHEUMATOID ARTHRITIS

A pilot randomized study has reported comparing the turmeric-derived spice curcumin alone (500 mg/day) to the non-steroidal anti-inflammatory diclofenac sodium (Voltaren) 20 mg/day, alone or in combination for the treatment of rheumatoid arthritis. It was found that curcumin alone was equal or better than the pharmaceutical alone.[21] The curcumin preparation used was reported to have six- to eight-fold enhanced bioavailability over ordinary preparations (curcumin with enhanced bioavailability is available from Life Extension). Curcumin performed best when judged by most of the components of the American College of Rheumatology assessment criteria such as total painful or swollen joints, patient or physician global assessment or a disability measure. Curcumin was also better than diclofenac in decreasing erythrocyte sedimentation rates, a measure of systemic inflammation. There was little to recommend the combined therapy, and the pharmaceutical approach had a number of unpleasant side effects which were absent with curcumin. Curcumin has been studied extensively over the years and toxicity even at high doses has not been reported. The dose used in this study may have been unnecessarily conservative since much higher doses have been used in clinical trials for other disorders.

LIFESTYLE AND PREVENTION OF CARDIOVASCULAR DIABETIC COMPLICATIONS. ANOTHER FAILURE

A study with a median follow-up of 9.6 years randomized type 2 diabetics to either a rather intensive lifestyle intervention or the usual diabetes care.[22] The intervention involved a calorie intake goal of 1200 to 1800 cal/day, < 30% of energy from fat and > 15% from protein. Thus the diet was in practice probably a moderately low fat—high carbohydrate diet. Approximately three hours of moderate-intensity physical activity per week was the other major component. Meetings were periodically held during the first 4 years to provide encouragement to the intervention group.

The subjects were obese and the diet initially resulted in an 8.6% weight loss which quickly reversed such that there was only a small weight difference between the controls and the intervention group at the study end. In the intervention group, HbA1c dropped below the diabetes threshold at year one but after 3 years, the group returned to being diagnosable as diabetes and the difference between control and intervention A1c at study end was insignificant. Furthermore, all were on diabetes medication and around 10% were on insulin during the study. Benefit in terms of glucose metabolism would require decrease or discontinuation of medications.

No effect was found on cardiovascular mortality or morbidity, the primary endpoint, and the trial was stopped early for reasons of futility. This does not appear surprising since weight loss was temporary and the excursion into the high end of the prediabetic state transient. This study merely showed that lifestyle intervention goals such as weight loss or improved glycemic control are not sustainable under the circumstances of this type of study and emphasizes the need for something better.

In the December 2013 IHN an approach to completely reversing type 2 diabetes with an eight-week abrupt and severe calorie restriction program (600 cal/day) was described which in a small study in the UK was very successful. The contrast with the above study is clear. However the impact of totally reversing diabetes (normal glycemia, no drugs or insulin) on the complications associated with having had this disease remain to be elucidated, as this is obviously and sadly completely uncharted territory. However, not needing medication and the favourable changes observed in the pancreas and liver from MRI scans (return to normal) suggest that there may be a very significant impact on complications due to the prior disease.

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