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***Nature**, born in 1869, is a famous and prestigious journal that, for example, published the discovery of the double helix by James Watson and Francis Crick, and the first suggestion, made by physicists Lise Meitner and her nephew Otto Frisch, incidentally while in exile in Sweden at the start of WWII, that neutron bombardment split the uranium atom. This journal has just published a paper promoting the proposal that large numbers if not almost all men, women and children will benefit by lifelong cognitive enhancement brought about by taking prescription stimulants like Ritalin or Adderall. We are told that schools will be happy to see all their students well behaved and "smartened up" and as well, employers will benefit greatly by a "smartened-up" workforce. To quote a famous humorist, "I'm not making this up." While there is certainly evidence from current events that at least part of the world's population needs to "smarten-up," it seems go against common sense that this should be accomplished with a life-long use of prescription drugs. However, this suggestion is in keeping with the trend to medicate everyone including the healthy who are the principal target of this proposal (by some measures the industry is already half way there), but the article does not seem to be consistent with what one might have naively assumed to be the mission and standards of a journal such as **Nature**.*

Closely related to the above is a review of recent articles concerning the debate over the attention-deficit hyperactive disorder. The wide acceptance of ADHD as a disease and the use of antipsychotic drugs on young children and adolescents has been a subject of debate for decades and remains an important issue.

While the basic philosophy of this newsletter is that natural approaches to prevention and disease should come before drug intervention, recent studies from the University of Southern California Medical School of an off-label use of a rheumatoid arthritis drug for patients with Alzheimer's disease seemed sufficiently important to deserve coverage, given the prevalence of the disease, its devastating nature and the toll it takes on those who end up being the care-givers. The two critical papers are in the public domain, i.e. there is free access to full text via the journal websites.

The remainder of this issue is devoted to subjects related to cardiovascular disease and, in particular, its primary prevention as distinguished from the treatment of individuals who have experienced acute coronary events. This focus was in part inspired by the publication in November of the JUPITER trial which demonstrated that a high dose of a statin lowered various adverse cardiovascular events in a population that was described as healthy with normal or low cholesterol but had quite high levels of the inflammatory marker C-reactive protein. This was a big event in 2008 in cardiology and the detailed discussion provided in the Perspective at the end of this issue was deemed warranted. The implications of this study and the issues it raises are numerous and judged important in the context of primary prevention and the role of statins vs. non-statin approaches when significant levels of inflammation are present.

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Wishing you good health for the new year,

William R. Ware, PhD, Editor

Highlights

COGNITIVE ENHANCEMENT FOR EVERYONE

The respected and high-profile journal *Nature* published a commentary online December 7 concerning cognitive enhancing drug use which gives the reader a glimpse of what the future of medicine may hold.[1] The title more or less states the thesis: *Towards Responsible Use of Cognitive Enhancing Drugs by the Healthy.*

The authors start by pointing out that the use of cognitive enhancing drugs is already common and give as an example that in US, universities estimate that up to 25% of students have used them in the past year. These drugs are termed "enhancers" and their use "enhancement." The stated purpose of the *Nature* article is to propose actions what will "...help society accept the benefits of enhancement, given appropriate research and evolved regulation." After pointing out that prescription drugs are regulated primarily for safety and potential abuse, they go on to say "…cognitive enhancement has much to offer individuals and society, and a proper societal response will involve making enhancements available while managing their risks."

The authors "call" for a number of actions or changes which in fact describe a rather different world than one in which we now live, although the symptoms of change have been around for some time. Here are the author's "calls" quoted verbatim

- *Based on our considerations, we call for a presumption that mentally competent adults should be able to engage in cognitive enhancement using drugs.*
- *We call for an evidence-based approach to the evaluation of the risks and benefits of cognitive enhancement.*
- *We call for enforceable policies concerning the use of cognitive-enhancing drugs to support fairness, protect individuals from coercion and minimize enhancement-related socioeconomic disparities.*
- *We call for a programme of research into the use and impacts of cognitive-enhancing drugs by healthy individuals.*
- *We call for information to be broadly disseminated concerning the risks, benefits and alternatives to pharmaceutical enhancement.*
- *We call for careful and limited legislative action to channel cognitive-enhancement technologies into useful paths.*

If the above quote leaves any doubt as to the agenda being promoted, consider this statement: "..liberal use of cognitive enhancers would be expected to encourage classroom order and raise standardized measures of student achievement, both of which are in the interests of schools: it would also be expected to promote workplace productivity, which is of interest to employers." It is curious and perhaps inconsistent that the authors appear to feel that performance-enhancing drugs in sports should still not be permitted. The authors dodge the troublesome issue of long term (life-long!) risks by taking the position that the same standards should be applied to enhancing drugs as are already generally applied to pharmaceuticals. It is well known that the pharmaceutical industry could not function with anything but rather short term testing of adverse effects. The commentary is appropriately illustrated with pictures of Adderall and Ritalin pills, two obvious choices. But there is the little problem that the Food and Drug Administration requires a warning with prescriptions of these two drugs advising of enhanced risk of cardiovascular problems. (http://www.fda.gov/bbs/topics/news/2007/new01568.html) While it is true that many already use an enhancement drug in the form of caffeine, it can be argued that there is a difference between caffeine and prescription drugs that carry a FDA warning concerning serious dangers. Also, caffeine is a natural product rather than a patented drug, although it may be hard to argue against a proposal that a sophisticated "scientific" enhancement program is just what we all need since in fact that we already manipulate ourselves with stimulants and alcohol. But this proposal places pharmaceutical enhancers almost in the same class as food.

This commentary is particularly interesting in view of what appears to be a trend in the pharmaceutical industry and mainstream medicine to aggressively

broaden the "patient" base for prescription drugs. Incidentally, two of the authors of this proposal declared financial ties to the pharmaceutical industry in the form of research grants or work as consultants. Critics suggest that disorders are being invented that do not actually exist, especially in the field of psychiatry, and thresholds are being lowered for various markers and age ranges expanded in order to achieve a larger market for certain drugs and to in fact medicate more of the healthy, the ultimate untapped resource of revenue. It is being argued in the medical literature that everyone should have an LDL of about 70 mg/dL which for most can only be achieved by lifelong statin therapy and now every student and the whole work force should be "smartened up" with prescriptions written by prudent health providers. Perhaps it is time to reread *Alice in Wonderland*, *Nineteen Eighty Four,* and *Brave New World* in order to gain added perspective. To this could be added any of a number of recent books authored by MDs with impeccable credentials that document the overmedication and overtreatment of North Americans.

ATTENTION-DEFICIT HYPERACTIVE DISORDER (ADHD)—IS IT A REAL DISORDER?

The above commentary, which suggests that vast numbers of humans would benefit from "enhancement," motivates one to look at one of the applications of the drugs being promoted, ADHD. From the first introduction of the idea that this was a real disorder, there were vocal dissenters. A recent review by Lydia Furman[2] and recent studies address this important issue. ADHA is now almost universally recognized at home, in schools, and in the practice of medicine. It is estimated that anywhere from 2.4 to 4.4 million children aged 4 to 17 meet the published criteria for ADHD, and yet this disease has no established biological cause nor an objective diagnostic test.[2] It is also estimated that one in 25 children in the US has been prescribed a remedy, i.e. paradoxically a stimulant such as Ritalin. The rapidly rising rate of diagnosis and stimulant drug use in children have prompted a public debate over the validity of the diagnosis and treatment of ADHD and the ethics of exposing children to psychotropic drugs.[3,4]

In a long-term study almost 600 ADHD-diagnosed children were followed and the latest report indicates that over 36 months, both the treatment and non-treatment groups did not significantly differ in any measure of outcome, and that children receiving the stimulant medication showed significant symptom *increases* during the period from 24 to 36 months and as well there were higher delinquency rates compared to those not receiving medication.[5,6] In addition in large randomized trials, psycho stimulants were found to suppress growth rates during treatment as measured by both height and weight.[7] Furthermore, as Furman points out, the psychometric properties widely used in ADHD rating scales do not meet the standards expected for disease identification. The author concludes that ADHD is unlikely to actually exist as an identifiable disease and that inattention, hyperactivity and impulsivity are symptoms of many underlying treatable medical, environmental and psychosocial conditions.

The National Institute for Health and Clinical Excellence (NICE) has just published ADHD guidelines in the European setting.[8] The guidelines recommend drug treatment only for school age and young people with moderate ADHD if they have refused non-drug interventions or if their symptoms have not responded sufficiently. Otherwise, drug treatment is recommended only for those with severe ADHD. It was quickly pointed out in letters to the editor (British Medical Journal) that the only evidence presented by the NICE group for the use of drugs for severe ADHD was the study cited above which found that after 36 months of treatment, no long-term benefits were observed in comparison with non-drug behavioural therapy, even in those with more severe symptoms.[8]

It can be argued that guidelines in the case of behavioural problems have a low level of impact. The driving force for drug treatment of ADHD comes from teachers and principals and from parents. The morning Ritalin pill is much easier than lengthy sessions with behavioural specialists and psychologists or a revised approach to parenting. It is also interesting that the NICE guidelines do not just ignore the potential role of food additives, food allergies and diet, they explicitly indicate that this area of intervention is not recommended.[8]
In a recent review titled *Child Psychiatry: Does Modern Psychiatry Treat or Abuse?*, Dr. Abram Hoffer discusses the diagnosis and treatment of not only ADHD but also bipolar disorders.[4] He

comments on the rapid increase in the diagnosis of children with psychiatric problems and the use of antipsychotic drugs. He suggests that this is a so-called *Cascade Phenomenon* and the end result is bandwagon diseases and over treatment. Hoffer's review includes several very interesting case histories which illustrate the success that is possible with non-drug treatments based on diet and vitamin therapy. Particularly significant is the effectiveness in some cases of high dose niacin or niacin combined with vitamin B6. Hoffer has authored a number of books that describe his approach to a variety of psychiatric problems (see Amazon.com).

In the context of the two above reviews, readers may find the book by Eric R. Braverman, M.D. titled *The Edge Effect* (Sterling Publishing Co, New York 2004) to be of interest. Braverman provides a very accessible discussion of brain function and the important biochemicals involved. His approach to optimizing brain function and dealing with brain associated health problems emphasizes diet and supplements and employs drugs only when these interventions fail to suffice or when the condition is of sufficient seriousness to warrant immediate pharmaceutical intervention. He discusses the various aspects of ADHD in several sections of the book. This philosophy of diet first, supplements containing only substances present in human biochemistry, food or normally consumed fluids next, and then chemicals foreign to human biochemistry only as a last resort would seem to make great sense. We evolved quite nicely in the absence of pharmacies and organic chemists.

SLEEP DURATION AND INCIDENCE OF CORONARY CALCIFICATION

While there is some evidence in the literature that sleep patterns and duration influence the risk of coronary heart disease, the validity of the studies has been questioned. Thus King *et al* organized a study to examine over a 5-year period the relationship between sleep duration and the development of coronary calcification in young adults 35-47 years of age.[9] Sleep duration was measured by a wrist-watch like device which had been demonstrated to provide excellent correlation with directly observed sleep duration. Coronary calcification was measured at baseline and at 5 years and sleep data was collected twice starting about 3 years after enrolment. Data was also obtained regarding potential confounders.

The five--year calcification incidence was about 12%. Longer measured sleep duration was significantly associated with reduced calcification incidence with an adjusted odds ratio of 0.67 per hour of additional sleep. This result was maintained after adjusting for a very large number of factors including smoking, apnea risk, blood pressure, body mass index and diabetes. Those with less than four hours of sleep per night had a calcification incidence over 9 per 100 person-years whereas for sleep duration between 7 and 8 hours, the number dropped to less than 2 per 100 person-years. The study provided little guidance as to potential mechanisms since there was incomplete inflammation marker data nor was there information available on the 24 hour variation in blood pressure or blood glucose. Nevertheless, the bottom line appears valid—sleep deprivation increases the risk of CHD at least in part by increasing the risk of atherosclerosis which is indicated by an increase in coronary calcification. This makes one wonder about the adverse effects of 6-8 years of medical education which is traditionally characterized by severe sleep deprivation.

OFF-LABEL USE OF ETANERCEPT FOR ALZHEIMER'S DISEASE

A standard characteristic of the brain pathology present in individuals with Alzheimer's disease is neuroinflammation with overexpression of cytokines such as tumor necrosis factor-alpha (TNF-alpha). In 1998 a potent anti-TNF-alpha drug was approved for human use with rheumatoid arthritis as the indication. The drug, etanercept, binds to TNF-alpha and blocks its interaction with cell surface TNF-alpha receptors, and thus reduces the effect of excess TNF-alpha. There are more than 1 million patient-years of experience with this drug for the treatment of inflammatory disorders in which TNF-alpha is implicated.

In a recent case study reported in the January 2008 issue of the *Journal of Neuroinflammation,* Tobinick and Gross describe the action of this drug in achieving a rapid cognitive improvement in an individual with Alzheimer's disease. The justification for the intervention was a pilot study reported in

2006,[10] which was an un-blinded study of 15 patients where etanercept was injected in the vicinity of the spine (perispinal) in an attempt to improve the delivery of the drug to the brain. The objective was to examine the impact on Alzheimer's disease. Patients were treated weekly for a period of 6 months. It was found that this treatment protocol resulted in sustained cognitive improvement in this cohort of patients with probable Alzheimer's disease (Alzheimer's disease cannot be definitively diagnosed except at autopsy!). The recently reported case study expands on the earlier "proof of principle" and concerns the cognitive improvement in a patient with late-onset Alzheimer's disease. The patient was a physician, 81 years old, who had either not tolerated or not benefited from various attempts to medicate his disease. At issue was the speed with which the drug affected cognitive change.

The cognitive status was evaluated just before treatment with etanercept, shortly after the injection, and at just over 7 weeks later. The injection was repeated once a week for 6 weeks The paper presents the graphical results of the Montréal Cognitive Assessment which included drawing a clock, connecting a sequence of dots designated both by sequential numbers and letters, and making a copy of a cube depicting 3 dimension. Prior to the injection, the patient was totally unable to even draw a clock face on a blank piece of paper after being given the time it had to display. He also failed the dot-connecting test although the cube was OK. Nor was he able to give neither the current year nor his state of residence. Ten minutes after the injection he was much more attentive and able to identify the year and the state in which he lived. Two hours after the injection he was able to approximate the clock and do the dot connection test correctly, and after 7 weeks the he was able to correctly put the numbers on the clock face and came close with the hand positions. At his visit for the second injection he correctly identified the year, month, season, day of the week and state of residence. A variety of other cognitive tests showed remarkable improvement over 2 hours and after 7 weeks. His wife also confirmed that his remarkable clinical improvement was sustained.

The hypothesis advanced by the authors to explain the rapid clinical improvement involved the emerging evidence that TNF-alpha is of critical importance in the regulation of synaptic transmission in the brain, and that etanercept is both potent and selective in its anti-TNF-alpha activity. The results are also consistent with evidence suggesting that synaptic dysfunction may be of central importance in the pathogenesis of Alzheimer's disease and that TNF-alpha regulates synaptic transmission in the brain. While a placebo effect could not be excluded due to the design of the experiment, it is noteworthy that the clinical, cognitive and behavioural improvement in the patient was observed by his family, family friends and both investigators and confirmed by the use of several objective tests. This rapid improvement was not an isolated event but had been commonly observed by the authors in multiple patients during the more than three years clinical experience utilizing perispinal etanercept for the treatment of probable Alzheimer's disease. The authors suggest that their experience thus far suggests that the maintenance of anti-TNF--alpha therapy may have prolonged beneficial effects.

Drs. Tobinick and Gross are associated with a private neurological research institute and as well the Department of Neurology, University of Southern California School of Medicine in Los Angeles. The perispinal injection technique was described in the pilot study[10] and the treatment method also described in a review article by Tobinick in *Current Alzheimer Research.*[11] Full text of the two studies cited is available free from the journal websites. This can be useful for caregivers of Alzheimer patients who wish to discuss this novel off-label approach to therapy with the patient's physician. The typical and inevitable downward spiral of Alzheimer patients and the long history of the use of etanercept for rheumatoid arthritis would suggest that the risk-benefit equation is tilted in favour of benefit even though this is not an FDA approved use the drug.

CHOLESTEROL LOWERING AND MORTALITY

An invited article by M. de Lorgeril and P. Salen has just appeared in the *Scandinavian Cardiovascular Journal*[12] which raises again some disturbing (some would say inconvenient) facts regarding cholesterol levels, cholesterol lowering and all-cause mortality. De Lorgeril and Salen achieved a high profile in heart disease prevention research through their involvement in the famous Lyon Diet Heart Study which dramatically reduced the recurrence of heart attacks by diet in a cohort where the cholesterol

levels were largely unchanged over the course of the study. In this paper the authors make the following points

- In the US about 65% of cardiac deaths among adults aged > 35 years were due to sudden cardiac deaths (SCD). SCD was defined as death occurring out of the hospital, in the ER or as dead on arrival with the underlying cause reported as cardiac disease. For the age group between 35 and 55, 75% of the cardiac deaths were SCDs.
- Studies that have investigated the risk factors for SCD fail to find a correlation with either total or LDL cholesterol. Thus while high blood cholesterol does not appear to be a risk factor for SCD in the general population, SCD appears to be the main cause of death from coronary heart disease (CHD).
- In the primary prevention setting, of the four major studies reporting in 2002-2003, three found no statistically significant effect of cholesterol lowering on overall mortality and the one study finding an benefit yielded an absolute risk reduction of only 1.8%, which the authors regard as not being important in terms of public health.
- A meta-analysis of primary prevention trials of cholesterol lowering found a risk ratio for mortality of 1.02 with the 95% confidence intervals 0.89 and 1.15, which translates into no effect at all.
- In the four recent secondary prevention trials, the effect of cholesterol lowering on overall mortality was either very small or insignificant. In the TNT trial which enrolled over 10,000 participants, during a median follow-up of almost 5 years there were 284 deaths in the intensive statin treatment group and 282 in the low-dose treatment group.
- Most trials and all recent trials which test the effects of cholesterol lowering drugs do not report SCD as a separate category. If cholesterol lowering had a significant impact of this endpoint, then it would surely be discussed if not emphasized, given the importance of SCD in terms of the overall picture of cardiac death.
- There is an urgent need for a scientific explanation as to why secondary prevention trials with statin drugs reduce the risk of non-fatal complications but have no significant effect on overall mortality.

The authors conclude by emphasizing that one might expect a big problem associated with motivating patients to take anti-cholesterol drugs over a long period when they cannot be reassured that this will improve their life expectancy, and that a new paradigm is needed both to explain CHD epidemics and organize prevention in the general population. What they do not point out is that probably most patients are unaware of the facts enumerated above. Also, as discussed in the Perspective at the end of this Newsletter, in the very recent JUPITER trial, the absolute reduction in overall mortality was 0.6% which is equivalent to needing to treat 166 individuals with a high dose of Crestor to prevent one fatality. Also, the graph of cumulative overall mortality vs. time appeared to be converging to yield no difference at all when the study was prematurely terminated.

THE RUSH TO DO PERCUTANEOUS CORONARY INTERVENTIONS

Most clinical practice guidelines strongly recommend the documentation of moderate-to-severe coronary blockage through stress testing before the invasive procedure termed percutaneous coronary intervention (PCI) is suggested, recommended, or vigorously promoted. A recent study examined the prevalence of the practice of ignoring the guidelines.[13] The researchers reviewed the records of over 23,000 Medicare patients aged 65 or greater who underwent elective PCI for stable coronary heart disease. Only 44.5% of these patients received pre-PCI stress testing. The rates of stress testing varied by geographical area and ranged from 22% to 74%. At issue here is the possibility that some who were rushed into PCI might not benefit from the procedure because for some patients with stable CHD, the COURAGE trial showed that PCI is not superior to optimal medical therapy in lowering the excess risk of cardiovascular death or future heart attacks.[14,15] The authors note that their results are not necessarily indicative of misutilization since the data sources used did not include a variety of clinical factors that might explain the observed patterns. However, as pointed out by

editorialists, the analysis of the data provides a clear impression that referral for PCI was influenced less by objective evidence of ischemia than by incidental factors, a conclusion supported by the wide geographical variation observed. As the editorialists point out, despite the increasing evidence supporting plaque instability as the proximate cause of adverse events attributable to atherosclerosis, treatment strategies continue to focus on arterial blockage and the identification of flow-limiting lesions, even among asymptomatic patients, and this leads to mechanical or surgical interventions. It was also pointed out that the COURAGE trial provided good evidence in support of the guideline recommendations to the effect that the majority of patients should be treated medically and that revascularization is best reserved for patients with objective evidence of ischemia despite ongoing intensive medical (non-interventional) therapy.

The subject of the overuse of PCI is discussed at length in Shannon Brownlee's fascinating book *Overtreated. Why Too Much Medicine Is Making Us Sicker and Poorer (*Bloomsbury, New York, 2007). Her discussion is both enlightening and disturbing and relates directly to the above issues. It is also significant that an increasing number of hospitals are creating an expressway from the ER entrance to the so-called *cath lab*, and while the decrease in time between the appearance of symptoms and mechanical or surgical intervention is being dramatically shortened, the problem of unnecessary treatment is obviously present.

SMOKING ORDINANCES REALLY DO WORK

There is little debate that smoking as a strong risk factor for cardiovascular disease. Probably not enough emphasis is placed on discouraging smoking when a program of prevention is being suggested to patients although there has periodically been talk of physicians refusing to take or treat patients who smoke which would certainly be a potentially effective way of making the point. Over the last decade there has been growing evidence that second-hand smoke also poses considerable risk and in a number of jurisdictions ordinances have been passed banning smoking in public places and/or the workplace. The impact of one such ordinance followed over 36 months has just been reported in the Center for Disease Control's journal *Mortality and Morbidity Weekly Report*.[16] This report supplements an earlier report covering 18 months published in C*irculation* in 2006.[17] The setting is Pueblo, Colorado which is a blue-color community with a higher percentage of smokers than the state-wide average (22.6% vs. 18.6%). The ordinance passed in 2003 prohibited smoking inside the workplace and in all buildings open to the public including restaurants, bars, bowling alleys and other business establishments. Vigorous enforcement began in July 2003 and continues.

The study involved examining the incidence of acute myocardial infarctions (AMI--heart attacks) in Pueblo using as an external control a nearby city and its surrounding area, El Paso County, which had a smoking rate of 17.7% as well as Pueblo County outside the Pueblo city limits where there was no smoking ban. The goal was to assess the impact of the smoke-free ordinance on the incidence of hospitalization for AMI. This endpoint was evaluated over a period of 18 months prior to the ordinance, and 18 (Phase I) and then an additional 18 months after its implementation (Phase II). Compared to the rate of AMI prior to implementation, there was a 27% drop in hospital admissions during the first 18 months and a 41% drop during the second 18-month interval. In the control areas there was no significant change. It is also of interest that the benefit found from the smoke-free ordinance occurred rapidly, increased significantly with time and produced a very important and significant drop in the AMI patient load in the hospitals serving the smoke-free area.

Earlier studies have suggested that the reduction in AMI hospitalizations is more pronounced among non-smokers than smokers. One study found that the decrease in hospitalizations among non-smokers accounted for 67% of the total observed decrease in incidence after a ban came into effect. This should reinforce the view that second-hand smoke is by itself dangerous.

SMOKING CESSATION DRAMATICALLY REDUCES INCIDENCE OF BOTH STROKE AND HEART ATTACK

Closely related to the above investigation, a large study from Korea has just reported where almost 500,000 Korean men aged 30 to 58 were followed from 1992 to 2001 for the occurrence of stroke or heart attack (MI).[18] While other studies have looked at the impact of smoking cessation on heart attacks, this appears to be the first to also study the impact of stopping smoking on the incidence of all types of stroke. Compared to heavy smokers who did not reduce their usage of cigarettes, those who quit had significant reductions in risk of occlusive stroke and MI with risk reductions of 34%, and 57% respectively. These reductions were statistically significant. The risk of hemorrhagic stroke was also reduced but the result failed to achieve statistical significance. When smoking reduction rather than total cessation was examined, the risk of all strokes and MI showed trends towards reduction but the results were not statistically significant. This latter result, while surprising, could be due, according to the investigators, to more intense inhaling among those reducing the number of cigarettes smoked daily. They also point out that smoking is more strongly associated with the precipitation of acute events than with the promotion of the underlying atherosclerosis and suggest that even low levels of tobacco consumption or smoke exposure can increase the risk of MI and cardiovascular events and mortality.

Thus the bottom line appears to be that smokers should strongly consider the merits of total cessation, and in particular taking advantage of the assistance that is available from their physician if their will power fails to break the addiction. It should be remembered that smoking is one of the strongest risk factors for CHD.

VITAMIN C REDUCES ELEVATED C-REACTIVE PROTEIN

Elevated C-reactive protein (CRP), a marker for the presence of inflammation, is a well-established independent risk factor for cardiovascular disease (CVD). Interest in CRP reduction in the context of CVD prevention was recently strongly stimulated by the results of the JUPITER trial which used a high dose of a strong statin drug which dramatically reduced elevated CRP levels (see the Perspective in this issue of the Newsletter). Therefore the results of a recent study which accomplished a similar reduction in CRP with vitamin C is of considerable interest.[19] Healthy non-smokers (396) were randomized to either 1000 mg/day of vitamin C, 800 IU/day of vitamin E added to the vitamin C, or placebo. The trial lasted 2 months and the endpoint was CRP change. The median CRP at the start of the study was low (0.85 mg/L) and no treatment effects were found when the results for the entire cohort were examined. However, among participants with CRP ≥ 1mg/L, there was a reduction in the median CRP of over 25% vs. the placebo with a 16.7% reduction in the vitamin C group and an 8.75% increase in the placebo group. The authors point out that these results are similar to that obtained with statin drug therapy. Vitamin E also reduced CRP but the effect was not as large nor statistically significant. In the cohort studied, the baseline plasma levels of vitamin C indicated that the subjects were will nourished. Supplementation with 1000 mg/day increased serum vitamin C levels by about 50%.

As the authors point out, it makes sense that inflammatory biomarkers are likely to be reduced only if they are not already low. In the JUPITER trial the mean level was over 4 mg/L whereas in this study, for those with CRP ≥ 1 mg/L the mean was 2.7 mg/L. It was also found that there was a strong correlation between BMI and CRP levels. Among those judged obese, 75% had CRP ≥ 1 mg/L. In the JUPITER trial, Crestor at 20 mg/day reduced CRP levels by 37%.

It is unfortunate that the dose dependence of the CRP lowering attributed to vitamin C was not investigated since it is of course possible that higher intakes would have produced results even closer to those found in JUPITER.

DENTAL HYGIENE, INFLAMMATION AND HEART DISEASE

Individuals who expect advice on preventing heart disease from their physicians should be disappointed if they are not advised, among other things, to be sure they visit their dentist regularly. Someone should do a study to see how common this advice is. Probably not very common. Yet periodontal disease is very common, easily treated, and easily prevented by regular visits to the dentist. It is estimated that the prevalence of severe periodontal disease is 20-30% and that mild forms of the disease affect the majority of the population.[20] It is also an inflammatory condition that carries an increased risk of CVD. In fact, the severity of periodontitis appears correlated with the risk of CVD independent of the conventional risk factors including smoking, diabetes and body mass index. A study has just been published that addresses the effect of treatment of periodontal disease on measures of atherosclerosis. Thirty-five healthy subjects (15 men, 20 women) of mean age 46 who were affected by mild to moderate periodontal disease were enrolled in this study done in Milan, Italy. It was found that inflammation biomarkers were abnormally increased at baseline. Of particular interest was CRP at 1.35 mg/L which falls into the moderate risk of CVD range, and fibrinogen which was above the upper limit of the standard reference range. The treatment, as described by the principal author to *theheart.org* was "totally simple…it involved removal of tartar and cleaning the gums, that is…just your basic dental hygiene." One month after dental treatment CRP had dropped to 0.66 mg/L, i.e. into the low-risk range, and at 3 months and 6 months it was 0.30 and 0.42 mg/L, fibrinogen also dropped into the normal range. The study also involved following the so-called intima-media thickness (IMT) measured using echo-Doppler ultrasound at several locations in the carotid arteries. This is a widely used measure of the presence, progression and regression of atherosclerosis. In this study IMT was significantly diminished after treatment. The authors remark that these results, which shed light on the pathogenesis of atherosclerosis, should be examined further in a larger study and could have practical implications for public health. This appears to be an understatement. It seems clear that questions about regular dental hygiene should be an essential part of every physical examination, and that anyone concerned about their cardiovascular health should religiously have dental hygiene done regularly. Flossing regularly is probably also worth mentioning. This paper relates directly to the subject of the Perspective on JUPITER contained in this issue.

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PERSPECTIVE

The JUPITER Crestor Heart Disease Prevention Trial

William R. Ware, Ph.D.

INTRODUCTION

Early in November, 2008, the results of the JUPITER trial were announced which indicated treatment with a statin drug lowered the risk of cardiovascular events in what was described as a healthy cohort. The subjects had low or normal LDL cholesterol but elevated levels of the inflammation marker C-reactive protein (CRP). The relative risk reduction for adverse cardiovascular events was large, and there is sure to be vastly increased interest among physicians in using elevated CRP levels as a guide or argument for recommending statin therapy. Thus readers of this Newsletter need to be aware of many important aspects of JUPITER and their implications. If the same CRP threshold (2 mg/L) for recommending statins to individuals with elevated CRP is used as was used for eligibility in the JUPITER trial, there would be a significant increase in the number of adults meeting the criteria and thus eligible for statin intervention. In the U.S. adult population, 44% of men and 60% of women have a CRP level ≥ 2.0mg/L and 30% of men and 44% of women have levels exceeding 3.0 mg/L.[1] Thus it is quite likely that many readers will find a CRP number on the lab results the next time they have "blood work" done, and they may be pressured to start taking statins. They need to be aware of the relevant facts concerning the motivation for this potential change in the prescribing practices. It turns out that this is far from a simple matter.

Randomized trials of statins fall into two general categories, primary and secondary prevention. In the former, the subjects should have no symptoms or evidence of vascular disease such as angina or peripheral artery disease, but they can be of either low, intermediate or even high risk by some measure or other. It is not uncommon that a trial described as primary will in fact include many high-risk subjects. Secondary prevention involves subjects that have cardiovascular disease, e.g. history of a heart attack or severe angina or so-called revascularization (coronary artery bypass or angioplasty with or without stents). Other factors that strongly impact the nature and outcome of the studies are gender and age distribution. Most statin studies have focused

on secondary prevention since the inherent risk in the subjects is much higher, thus providing more events and smaller required enrolment to achieve acceptable statistics Primary prevention, where the cohort is at low risk has not been a popular area for investigation, and women have been underrepresented in primary prevention studies. Their event rate is generally much lower than found for men. In primary prevention studies the absolute risk reduction is small—some would say insignificant, with large numbers of individuals (e.g. 75-250) needed to be treated over a long period to prevent one event. Secondary prevention trials yield larger rates of adverse events and higher absolute risk reductions, and there is little debate over using statins if a patient has had a heart attack or has evidence of severe heart disease. However, there is growing evidence that some of the benefits seen in secondary prevention are due to statin action that is not related to lipid lowering.

Conventional wisdom holds that diabetes should be considered equivalent to existing heart disease when determining the level of risk of future CDH events. However, this view has been challenged.[2] In addition, a very recent meta-analysis showed that the benefits of statin therapy on major vascular events in diabetic populations (mostly type 2) were similar to those patients without diabetes. It was concluded that statin therapy should be considered for diabetic individuals who are at sufficiently high risk of vascular events. However, the magnitude or threshold of elevated risk, even for CVD-free non-diabetics, which merits statin treatment, continues to be debated since not everyone agrees with the current guidelines. For primary prevention in the absence of vascular disease, the meta analysis found that the absolute rate reduction for diabetics was small (2.6%) and similar to that for patients without either diabetes or vascular disease (1.6%).[3]

The drug industry elects to promote statin drugs by emphasizing relative risk reductions since they typically range from 25-40%, and absolute benefits and the so-called number needed to treat are downplayed. Frequently no distinction is made between the results of primary and secondary prevention results. Randomized trials yield guidelines which strongly influence practice. In the field of CHD-CVD disease prevention, the guidelines as well as reviews and commentaries are frequently written by academic medical scientists, many of whom have strong financial ties to the companies that make statin drugs. Unfortunately, not all journals require conflict of interest declarations, but when present they can be revealing. These trials also provide the justification for regulatory approval.

THE JUPITER TRIAL

JUPITER is a randomized, drug company sponsored trial that was not named after the god of sky and thunder from Roman mythology. Instead, the translation is *Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin.* The other name for rosuvastatin is Crestor. But there was a considerable amount of thunder involved in the announcement of the results and the reaction of the media and the cardiology community to what is being described as a potential landmark study. The results were announced November 9 at the American Heart Association 2008 Scientific Sessions and published at the same time in the *New England Journal of Medicine*.[4] This perspective examines the study because it is bound to have an influence on how physicians view prescribing statin drugs to healthy individuals with low or normal cholesterol, and in addition brings to center stage the well known marker of inflammation, C-reactive protein.

JUPITER examined the hypothesis that reducing C-reactive protein, now generally designated as high sensitivity C-reactive protein because of the nature of the current test, would reduce cardiovascular events. The link between CRP and cardiovascular disease (CVD) starts at much lower levels of CRP than traditionally measured during the course of monitoring acute infections with older assays. This Perspective will use CRP to indicate high sensitivity CRP. The class of drug chosen to reduce CRP levels was a statin. This choice was based in part on the fact that several studies had demonstrated that statins appear to function as anti-inflammatory agents and indeed significantly reduce CRP. Subjects at low or moderate risk of CVD with normal or low LDL cholesterol levels were selected to participate. They were required to have a CRP level > 2 mg/L and in fact the mean was over 4 mg/L. These CRP levels are in the range found to increase substantially the risk of adverse CVD events. The enrolment criterion for LDL was < 130 mg/dL. The primary endpoint consisted of a number of adverse cardiovascular outcomes and subjects were followed for a mean of almost 2 years. This was a randomized, placebo controlled study paid for by AstraZeneca, the company that makes and already aggressively markets the drug used in the trial. Some of the academic investigators also declared financial and research support from pharmaceutical companies that market statins. The principal investigator is listed as a co-inventor on patents held by Brigham and Woman's Hospital that relate to the use of inflammatory biomarkers including CRP. The patents are licensed to two drug companies, one of which was the sponsor of this trial. However, the

Independent Data and Safety Monitoring Board and the Clinical Endpoint Committee were composed of individuals with no declared conflicts of interest.

Crestor reduced LDL levels by 50% and CRP levels by 37%. The primary endpoint—a composite of nonfatal heart attack or stroke, hospitalization for unstable angina, revascularization (angioplasty or a coronary bypass) and death from CVD causes was reduced by 44% in those on 20 mg/day of Crestor as compared to the placebo. The trial was stopped 1.9 years into its planned 4-year duration because it was considered unethical to deprive the placebo group of the option of availing themselves of the perceived benefits of the treatment. For those who prefer absolute risk reduction numbers, the results based on events per 100 individuals rather than 100 person-years were 1.2% for the composite endpoint and 0.9% for the so-called hard cardiac events, i.e. cardiovascular death, heart attack or stroke. Corresponding event reductions based on a per 100 person-years basis were 0.6% and 0.4%. The media and the drug company focused on the relative risk reduction which of course looks spectacular. But an absolute risk reduction of 0.9% equates to needing to treat 111 individuals over the mean length of the trial (2 years) to prevent one hard cardiac event, i.e. 110 out of 111 fail to benefit. When the trial was halted, the cumulative overall mortality for the drug and placebo groups was converging with the number needed to treat to prevent one death from any cause increasing rapidly.

There are some who regard the small absolute differences observed in JUPITER as clinically meaningless even though they are statistically significant. Mortin Hadler, M.D., professor of medicine at the University of North Carolina states in his book *The Last Well Person* that his cut-off for clinical credibility is an absolute benefit of 2% and his comfort zone starts at 5% for meaningful "hard" outcomes. For what he calls "soft" outcomes such as angina or need for revascularization, he is not comfortable until the absolute difference between the intervention and control approaches 20%. Thus he would presumably not find the JUPITER results convincing. In fact, one of the criticisms of almost all of the statin trials over the years has been the very low absolute benefit in the primary prevention setting. Historically, the presence of statistical significance was enough for the drug companies and the FDA, and looked good when converted into relative risk reduction, but nevertheless troubled many who had no vested interest in the results and disliked thinking in terms of relative risk reduction.

The cohort used in JUPITER, while described as healthy, included approximately 41% with metabolic syndrome. The median systolic blood pressure was 134 mm Hg, and the median BMI was about 28, i.e. overweight, with some obese. The median age was 66 and about 38% were female. To get even a small number of events, it was necessary to enroll almost 18,000 individuals (out of about 90,000 who attended a screening clinic) which in this study were from all over the world at 1315 sites. The study was criticized for not using as a control group individuals with low CRP. However, the frequency of CVD events in the control group would then have been so low that a very large and unrealistic number of subjects would have been required to produce a statistically significant comparison.

If one reads the reaction to the results which appeared in a forum set up by the *New England Journal of Medicine* for readers to record their answer to the question, "will this change your practice?" it is clear from the comments submitted that some physicians are utterly convinced that this is the way to go and are all set to order CRP tests for their patients. The enthusiasm reported by *the heart.org,* an online newsletter for the cardiology community, was what one might term "unbridled." Submissions to the forum also commented on the early termination of the trial which limited the potential yield of information, the inconsistency with earlier rosuvastatin trials where no effect on mortality was found, the fact that healthy individuals do not have the metabolic syndrome which was the case with 41% of the subjects, and that no data was provided regarding the relationship between the extent of CRP lowering and events. Lower than expected muscle problems were noted with suspicion. Also there was concern regarding the role the drug company played in collecting and storing the data. Critics also pointed out that that the JUPITER cohort was in fact a mix of low- to high moderate-risk individuals based on Framingham score and the presence of the metabolic syndrome, and that most of the events occurred in the higher risk groups. Thus treatment decisions made on the basis of "old fashioned" risk estimates by traditional methods rather than CRP might have produced similar results.[5]

The principal issue here is clearly the wisdom of treating more or less healthy individuals having low or normal LDL cholesterol with a drug which presumably would be taken indefinitely simply because they initially had an elevated CRP, i.e. a CRP level that exceeded some arbitrary threshold (yet to be established). If the dose of Crestor used in the study were to be employed, many individuals would achieve a LDL level of 50 mg/dl or less.

No one has ever studied the effect of such low LDL levels artificially maintained over long periods, i.e. years or a lifetime. But this would be one of the results of the approach some would consider justified by JUPITER, and even this huge and significant uncertainty has not dampened the enthusiasm of some high profile representatives of mainstream medicine.

IS CRP A GOOD INDICATOR FOR TREATMENT?

A significant problem is associated with the use of CRP as a guide for therapy in this context. CRP is a non-specific indicator of inflammation or the presence of stimuli of the so-called acute-phase reaction, the normal reaction for example to infection. CRP levels can be elevated for numerous trivial, serious or transitory conditions. Furthermore, there is considerable intra-individual variation over periods such as a few months. These variations are large enough to make the use of a threshold for treatment of dubious value if applied after only one or even two measurements.

Campbell *et al*[6] pointed out that an individual's CRP would have to change by 118% before one could be confident that the change was not just due to intra-individual variations. They also show plots of individual measurements made on samples from healthy subjects where repeated measurements were obtained over a 6-month period. In one study cited 9/26 and in another 9/20 individuals had variations such that one or more result was during the 6 months either above or below the JUPITER enrolment cut-off of 2 mg/L. There was also a large variation in the intra-individual range. The 6-month study of 26 healthy individuals found an intra-individual variation average range of 2 mg/L and a maximum range of 5 mg/L, ignoring one outlier.[7]

Similar results were reported by Ockene *et al*.[8] They suggest that since CRP is an acute phase reactant, it could be argued that the lowest of several measurements should be used as the predictive value but point out that adequate data is unavailable. The suggestion that CRP has the same variability as total cholesterol[8] has been challenged and in fact appears to be 4-8 times greater.[9] The Centers for Disease Control and the American Heart Association recommend two CRP measurements two weeks apart.[10] In view of the above quoted studies, this would not appear to tell one much.

While it is widely assumed that the enhanced CVD risk indicated by an elevated CRP is associated in part with inflammation within atheromatous lesions, chronic systemic nonvascular inflammation is known to in general also be proatherogenic.[11] Thus the implied presence of inflammation or acute-phase stimuli based on the observation of an elevated CRP which may be relevant to CVD risk can have a large number of potential causes, both chronic and transitory. The list includes diet, sleep disorders and sleep apnea, depression, alcoholism, periodontal disease, gastrointestinal disease, rheumatoid arthritis, obesity, insulin resistance, the metabolic syndrome, diabetes and transitory and chronic infections[12-19] and additional inflammatory conditions.[11] Pepys points out that CRP values can be usefully interpreted only with comprehensive information about the individual patient at the time of sampling.[20] Such a comprehensive understanding may be difficult to achieve in a 10-minute office visit.

It is well known that most of the above listed causes of elevated CRP, some of which are common, can be treated with curative intent using exercise, diet, non-statin drugs or other interventions, and that this has the potential to permanently reduce CRP to normal levels. The effect of diet on inflammation has recently been reviewed.[14] Five dietary studies over the past few years yielded decreases in CRP between 28% and 44%,[21-25] reductions similar to those achieved with statins in JUPITER. Furthermore, it has been shown that CRP levels frequently increase to baseline when statin therapy is terminated, in fact in a manner uncorrelated with the increase in LDL.[26] The root cause of inflammation is not necessarily being addressed by statin therapy. Indeed, in JUPITER for those followed for 48 months the mean CRP was 1.8 mg/L, which is still in the moderate risk range according to the commonly used level for low risk of < 1.0 mg/L

The waters are further muddied when one considers the fact that there appear to be four CRP polymorphisms (genetic variations) that are associated with increased CRP levels of up to 64%.[27] Other studies have found similar results.[28] This magnitude of CRP elevation theoretically predicts an increase in the risk of CVD in these individuals. But it was found that the polymorphisms were not in themselves associated with an increased risk of CVD events[27] This result is consistent with most other studies[29] and would suggest that CRP itself plays little or no causal role in CVD. But it also means that a fraction of individuals with elevated CRP would theoretically not benefit from CRP lowering in the context of CVD risk.

Now that CRP testing may become as routine as measuring the blood lipid profile, it would seem reasonable for patients to expect physicians identifying an elevated CRP to first attempt to diagnose and deal with the underlying problem responsible, and as well, to investigate the possibility that elevated values are transitory before committing a patient to life-long statin therapy, especially when the long-term effects of very low LDL levels are unknown and statins have side effects. But given the multiplicity of causes for an elevated CRP and the potential for multiple causes in a single individual, this approach presents a diagnostic challenge that may be inconsistent with some primary care cultures and fee schemes.

Thus one can imagine the scenario where someone with an elevated CRP due to a transitory problem is tested twice over a period of several weeks and found to exceed the threshold for statin therapy. The therapy is started and the CRP level drops. This drop might have occurred without statin treatment, but this has now become more difficult to determine given confounding by therapy. It is entirely possible that some may take the drug for years when in fact the cause of the elevated CRP resolved after a few months or so and thus placed them is such a low risk category that no one would ethically prescribe the drug. This merely illustrates the fundamental problem with CRP as a marker and a generator of a treatment threshold. It is worth repeating that in one study where statin therapy was stopped, CRP levels returned to baseline, i.e. elevated.[26] It is hard to imagine valid arguments against the proposition that the first objective of treating elevated CRP should be to affect a *permanent* return to normal that does not require continuous drug therapy. After all, decreases in CRP equivalent to those found in JUPITER can even be achieved by diet alone even in the absence of significant weight loss.

THE JUPITER RESULTS FOR WOMEN

Now we come to the really interesting aspect of the study. JUPITER is the first study to show statistically significant evidence that statin treatment is beneficial to women in the context of primary prevention, *but this result applies only to women with elevated CRP*. The absence in general of benefit for women at moderate risk in the context of primary prevention has been pointed out repeatedly in the literature but falls on deaf ears. Two recent meta-analyses speak directly to this issue.

One analysis by Eisenberg and Wells has just appeared in an unlikely place, the *Journal of Empirical Legal Studies*.[30] The authors both hold “named chairs” at Cornell, one in the law school, the other in the medical school. The legal aspects of the paper involve questions concerning the advertising of statin drugs without indicating that they are not effective for most women. The meta-analysis of primary prevention trials provides the evidence. Only 4 primary prevention trials using statin drugs were available where data on female participants was given or could be obtained from the investigators and where the primary prevention group could be positively identified. Participants were at moderate risk of adverse CVD events. Mean baseline LDL levels in the 4 trials were from 132 to 155 mg/dL. In two of the trials, the combination of hypertension and one or more additional risk factors put the participants at the high end of moderate risk. These trials individually and when combined yielded null results. The only trial with an odds ratio suggestive of benefit was also of no statistical significance with a huge 95% confidence interval from 0.23 to 1.33 (1.00 indicates a null result).

The result obtained by Eisenberg and Wells was consistent with an earlier meta-analysis by Walsh and Pignone who also found no evidence of benefit for women if statin treatment was used for primary prevention.[31] However, in the trials subjected to these meta-analyses, the number of events was small which may have impacted the ability to detect benefit. Walsh and Pignone conclude that for women without CVD, lipid lowering does not affect total or CHD mortality and while it may reduce CHD events, the current evidence is insufficient to determine this conclusively. Thus the assertion stands that no evidence exists of benefit to women. The problem is that before JUPITER, the belief that statins provided benefit to women free of heart disease but at moderate risk was widely held to be an absolute truth even in the absence of any evidence. JUPITER will probably reinforce this notion once it is forgotten that the benefit to women was only found only in a select group with a rather high CRP.

THE NON-LIPID LOWERING EFFECTS OF STATINS

JUPITER is of course of considerable interest because it highlights the CRP lowering power of statins and the importance of inflammation. The authors of the paper announcing the results comment that a major study had already shown “extremely low event rates and no evidence that statin therapy lowered vascular risk among patients who had neither hyperlipidemia nor elevated CRP.” If one looks at the paper in question[32] the group that had no benefit from cholesterol lowering with statin therapy had an LDL < 149 mg/dL and a CRP lower than 1.9 mg/L. In JUPITER the only thing that was changed was the selection of a cohort with elevated CRP which the

drug therapy reduced. The mean LDL level at baseline in Jupiter was only 108 mg/dL. Nevertheless, from the comments in the *New England Journal of Medicine* forum, it is clear that many believe that it was the lowering of both LDL and CRP that produced the benefit. Obviously the results are open to a different interpretation, that is that the statin may have achieved the beneficial effect acting only as an anti-inflammatory and the concomitant decrease in LDL was irrelevant, The principal investigator, Paul Ridker refers to this possibility, stating in a just published editorial "...because JUPITER is testing an agent that markedly lowers LDL-C as well as hsCRP, this trial cannot directly address whether lowering inflammation alone lowers vascular risk."[33]

The notion that in the case of LDL, the lower the better has a significant following which this trial may increase since Crestor reduced LDL levels on average from 108 to 53-55 mg/dL. But it is important to recognize that the beneficial results found in JUPITER pertain to a special group with low LDL and elevated CRP, in this case with a rather high mean CRP of over 4 mg/L and a rather low baseline LDL. The investigator's comments concerning the failure to include a control group with low LDL and low CRP seems worth quoting. "…we did not include people with low levels of high-sensitivity C-reactive protein in our trial, since our hypothesis generating analysis of high-sensitivity C-reactive protein in the Air force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCaps) showed extremely low event rates and no evidence that statin therapy lowered vascular risk among persons who had neither hyperlipidemia nor elevated C-reactive protein levels. Thus, a trial of statin therapy involving people free from heart disease with both low cholesterol and low high-sensitivity C-reactive protein levels would have been not only infeasible in terms of statistical power and sample size but also highly unlikely to show benefit." The JUPITER investigators do not seem to endorse the hypothesis that we all should have LDL levels 70 to 50 mg/dL based on data from extrapolations of questionable validity and from modern hunter gatherers, wild primates such as baboons and monkeys, and wild mammals such as horses, rhinoceroses and elephants.[34]

One of the post-JUPITER reactions has been that there is now a need for randomized trials of an agent which will inhibit the production and thus lower the levels of CRP in order to test the causative role of this acute-phase protein in CVD.[29] This downplays the importance of the above mentioned genetic studies, ignores the dangers inherent in meddling with the immune system and also ignores the following:

- A recent study found that the levels of five different inflammation-sensitive plasma proteins (ISPs) were related to the incidence of heart attacks in men without any traditional risk factors if followed for more than 10 years. Furthermore, for men with at least two risk factors such as smoking, diabetes, hypertension, or dyslipidemia, the impact of having elevated ISPs appeared much earlier. CRP was not included in the ISPs studied. The relative risks associated with elevated ISPs were similar to those for the traditional risk factors such as those used in the Framingham assessment. Thus CRP is not the only relevant inflammation marker and its selective inhibition would probably not be a definitive experiment.
- The evidence that statins possess anti-inflammatory action is well established from numerous cell, animal and human studies.[35]. *A large number of different factors (biomarkers) are reduced, not just CRP.* Statins also appear to provide beneficial therapy for a number of disease processes where the effects appear unrelated to lipid lowering.[35]
- The questionable validity of the notion that that a causal relationship can be demonstrated by using some agent in a randomized controlled trial to lower a biomarker or chemical substance which then produces clinical benefit. For this to make any sense, it must be demonstrated that the agent has no other biochemical actions that might be partly or entirely responsible for the clinical benefit. Given the complexity of human biochemistry and microbiology, this is impossible to demonstrate for many agents that are foreign to human biochemistry (i.e. almost all "drugs") and to think otherwise implies a dangerous level of arrogance. In the case of statins, whole books could be written on their non-lipid lowering actions, more examples are being discovered all the time, and to quantitatively sort out the importance of the lipid lowering action as compared to all the other potential actions is probably impossible. Nevertheless, it is widely believed that this has been successfully accomplished.

Thus, while JUPITER has focused attention on CRP, the appropriate focal point appears to be inflammation in general.

The JUPITER results can be viewed as an example of a so-called *pleiotropic effect* of statins, i.e. an effect independent of what is identified as the principal action but produces benefit. This is strongly reinforced by the

fact that LDL lowering as seen in the trial was not, according to the investigators, expected to produce any observable benefit. Suggestions to the contrary involved data from secondary prevention trials which appear irrelevant. Periodically there are efforts, mainly by medical scientists who receive financial support and remuneration from the statin makers that attempt to demonstrate that the pleiotropic effects of statins are insignificant. A recent attempts to prove this was with a meta-analysis of a number of cholesterol lowering studies that involved diet, non-statin drugs, surgery (ileal bypass) and statins. The basis of the demonstration involved the hypothesis that if non-statin trials produced benefits proportional to the LDL lowering to the same extent that statin trials did for patients with stable CHD, the pleiotropic effects were to be judged as minor. However, this study seems flawed for three reasons: (a) that in spite of LDL lowering by non-statin treatments such as diet, other drugs and surgery, these interventions act on the risk of CHD events in a variety of ways, some of which are probably proportional to the LDL lowering; (b) but what is more important, in sharp contrast to all but one of the statin trials, the non-statin trials used in the analysis produced relative reductions in non-fatal MI or CHD death that were not of statistical significance with 95% confidence intervals spanning *negative to positive* reductions; (c) the scatter in the data graphically presented is more impressive than the weak correlations. Thus the central aspect of the comparison was with meaningless studies.[36] This study received a strong editorial stamp of approval from a high profile academic who indicated he was a consultant for companies that make statins.[37] The subject of statins, cholesterol and heart disease in fact strongly resembles a jungle, an observation that is supported by two Research Reviews that recently appeared in this Newsletter.

TARGET INFLAMMATION IN GENERAL, NOT JUST CRP?

Paul Ridker, the principal investigator in JUPITER, in the above mentioned editorial[33] calls for inflammation reduction trials that address the question of the effectiveness of non-lipid lowering interventions (what he terms therapies beyond statins), and that an appropriate target for therapy might prove to be inflammation in general rather than CRP in particular, i.e. broader agents that also target for example interleukin-6 or tumor necrosis factor. He also mentions low-dose methotrexate (LDM) which has been shown to reduce several inflammatory biomarkers in patients with both rheumatoid arthritis and psoriasis. LDM has also been associated with reductions in cardiovascular mortality and morbidity and the drug has a 2-decade track record for the treatment of rheumatoid arthritis. But, as he points out, LDM is now a generic product and it is unlikely that the drug industry would support clinical trials.

While JUPITER suggests inflammation as indicated by elevated CRP might be a target for therapy, it also reinforces the school of thought that wishes to add CRP to risk factor algorithms such as the Framingham Risk Score. This is a complex matter that in part involves debates as to the proper statistical criteria for such additions. Thus far, the evidence appears to favour the conclusion that CRP does not perform better than Framingham for risk discrimination and the improvement in risk stratification or reclassification with regard to risk categories from the addition of CRP to models based on established risk factors is both small and inconsistent.[38] However, this should not diminish the importance of dealing with chronic inflammation in the context of CVD risk since interventions to reduce CRP will in many cases beneficially impact other risk factors.

In the January 2009 issue of *Health and Healing* Dr. Julian Whitaker offers his recommendations for CRP lowering. At his clinic they have been measuring CRP for a number of years and treating elevated levels naturally. The recommendations include at least 2000 mg of vitamin C a day, to which he adds 1-3 g krill oil, 2-8 g of fish oil, 2000-4000 IU vitamin D, and 500 mg magnesium. Other suggestions include phytosterols, curcumin, ginger, and proteolytic enzymes such as Wobenzyme-N. To these supplements he adds 30 minutes of moderate exercise daily and a Mediterranean diet rich in plant foods and lean protein.

CONCLUSIONS

Thus we come back to a topic discussed above. If individuals with low or normal LDL levels have elevated CRP, doesn't it make sense to attempt with diet, weight loss, exercise or other non-drug interventions to reduce the CRP to below 2 mg/L or better still to near 1 mg/L at which point statin therapy has been demonstrated to be irrelevant in the context of primary prevention? But one wonders how many physicians even are going to suggest a visit to a dentist before starting statin therapy [39] (see the study on CRP and periodontal disease discussed in this issue of the Newsletter). In other words, target the root causes of inflammation and if possible eliminate them. This seems preferable to the life-long use of an anti-inflammatory drug with a growing number of documented side effects which was originally designed to reduce cholesterol levels by enzyme inhibition, but turned out to influence a large number of biochemical processes and pathways, with many consequences that

are ignored, a others presumably still imperfectly understood and some still to be recognized above the noise created by various diseases.

Perhaps the most important thing to be learned from JUPITER is that it is time to pay attention to the non-cholesterol lowering action of statins, and to approach the primary prevention of heart disease and atherosclerosis by aggressively addressing issues such as excess abdominal fat, insulin resistance, hyperglycemia, hypertension, periodontal disease, psychological stress and the omega-3 status as individual problems deserving of treatment, something which can not be accomplished simply by giving people a statin pill, even though it may be an anti-inflammatory.[40] One can now add vitamin D deficiency to the list. The potential for a feeling of false security regarding CVD risk associated with popping the daily statin pill for the purpose of primary prevention appears unjustified as indicated by the low to nearly insignificant absolute risk reductions accomplished by this almost universally promoted therapy. In fact, it now appears that there is growing interest in re-examining the lipid management approach to reducing CVD risk.[41] For individuals with heart disease however, many of the issues raised concerning JUPITER and statin therapy do not apply. Stephen Sinatra, a cardiologist and well know author of books on heart disease states that "Patients with the most to gain and the least to lose (from statin therapy) are men, aged forty-five to sixty-five, with proven coronary artery disease."[42] He adds that he and the coauthor of the book cited do not prescribe statin drugs to lower cholesterol. They selectively use statins to improve outcome in patients with risk markers known to respond well to this drug intervention.

A number of the issues raised in this Perspective have been discussed in some detail in two Research Reviews, one on cholesterol and one on coronary heart disease, which recently appeared in this Newsletter.

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