INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

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*This issue features recent research reports concerning the remarkable antioxidant **alpha lipoic acid**. Readers who find this topic interesting should consider the books by Bert Berkson, Julian Whitaker and Lester Packer. They come up at the top of the list when using alpha lipoic acid as the search item in www.Amazon.com.*

Also included is a discussion of the risks of cancer associated with CT scans. This should not be interpreted as a condemnation of this valuable diagnostic and screening tool, but merely make readers aware of the potential harm that might arise from overuse. Thus the question "Is this scan really necessary?" should come to mind whenever one is ordered and patients may want to explore with their physician alternative procedures and the risk vs. benefit question.

Finally, mention is made of an article in the "New York Times". While this is not a normal source of information for this newsletter, in this case your editor regards the article by Gary Taubes as important in the context of preventive medicine and public health and highly recommends downloading and reading it. Taubes is of course a journalist specializing in scientific and medical subjects, but sometimes journalists have a clearer insight into some aspects of medical matters than those professionally associated with the field. Next month we will review an exciting new book by Taubes titled "Good Calories, Bad Calories. Challenging the Conventional Wisdom on Diet, Weight Control and Disease".

Included in this issue is the last part of the review on cholesterol. There remain a number of important issues which will be the subject of a future Research Report.

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Wishing you good health,

William R. Ware, PhD, Editor

Highlights

WHAT'S NEW FOR ALPHA LIPOIC ACID?

Lester Packer, Ph.D., for many years head of the Packer Laboratory at the University of California, Berkeley, calls alpha lipoic acid (ALA) a super-antioxidant that breaks many of the rules regarding antioxidant behaviour. He comments that if he were to invent the ideal antioxidant, it would closely resemble ALA (*The Antioxidant Miracle, L. Packer and C. Colman*, John Wiley 1999). He lists the following general attributes:

- Offers powerful protection against stroke, heart disease and cataracts.
- Strengthens memory and prevents brain aging.
- Boosts the entire antioxidant defence network since it functions in part to increase levels of vitamin E and C, glutathione, and Coenzyme Q-10.
- Has been used safely and effectively in Europe for more than two decades to prevent and relieve the complications of diabetes
- Turns off bad genes that can accelerate aging and cause cancer
- Reverses mushroom poisoning of the liver which is generally fatal and has been used to treat other liver diseases such as hepatitis C.

Research on both humans and animals continues to reinforce and expand on these benefits.

In connection with mushroom poisoning, Berkson, in his book *The Alpha Lipoic Acid Breakthrough,* describes one of the first successes of ALA. When he was a medical resident he treated a couple suffering form this problem with a sample of the chemical he had couriered to him by a University researcher who had demonstrated its efficacy and safety in this context and published the results. Berkson remembered seeing the paper! Treatment with ALA rapidly cured both patients. He was nearly fired from his residency for this breach of the rules related to using only hospital approved medications, but if he had not had the courage to do this, both of these individuals would have almost certainly died. He was told that if he ever did such a thing again his career was over. This "culture" is probably still alive and well in some hospitals today.

ALA exists in two forms called R- and S-alpha lipoic acid. Naturally occurring ALA is in the R-form whereas the synthetic version is a 50-50 mix. The R-form is currently being promoted as more biologically active but there are synergistic actions between the two forms. In addition, only the synthetic mixture has a long track record of apparent benefit. In addition, Canada, for example, currently forbids the importation of the R-form. Wisdom might dictate using the tried and true form until sufficient human studies report on the R-form. We are after all, somewhat different in many respects from laboratory animals and cell-culture studies are never 100% transferable from the lab to the so-called bedside. Nevertheless, because there are potential pro-oxidant possibilities with both ALA and its reduced form (*Medical Hypotheses*, 2006;66:110), some would argue that it is prudent to avoid doses larger than generally used in clinical studies, i.e. about 600 mg/day. There follows a discussion of several recent papers on ALA, although they will not be as entertaining as Berkson's story.

ALA and Diabetic Polyneuropathy – Dose Dependence

Up to 50% of diabetics will develop polyneuropathy in their extremities, generally the feet and lower limbs. Diabetic neuropathy may arise when metabolic changes in patients result in structural and functional deficits in the vascular system, and particularly endothelial dysfunction. The resultant blood flow changes are accompanied by oxygen deprivation which contributes to neuronal damage. The resultant pain and discomfort can exert a significant deleterious impact on the quality of life. Tang *et al* engaged in a critical appraisal of this topic which involved three academic institutions. They focused on a randomized controlled trial which used oral doses of 600, 1200 and 1800 mg/day of alpha lipoic acid with efficacy judged by a so-called Total Symptom Score which involved ≥ 50% reduction in symptoms. At 5 weeks, the number needed to treat to achieve this reduction was 2.7, 4.1 and 3.2 patients for the three above doses respectively. Numbers needed to treat that are this low are generally viewed as indicating a high level of merit for a treatment. Since adverse effects, which included nausea, vomiting and vertigo, were the lowest and generally minor with the 600 mg/day dose, the authors regarded this as an effective and well-tolerated dose.

A study from Korea that measured both Total Symptom Score and skin blood flow in response to ALA therapy has just reported. Reduced skin blood flow was used as a marker for vascular abnormalities. All patients were diabetics with a mean duration of 12.5 years. While the decreases in skin blood flow did not reach statistical significance, the neuropathic symptom score as assessed by the Total Symptom Score, a standard tool in this area, revealed a dramatic and statistically significant improvement in symptoms of diabetic polyneuropathy.

Tang, J, et al. Alpha-Lipoic Acid May Improve Symptomatic Diabetic Polyneuropathy. ***The Neurologist,*** *2007, Vol. 13, No. 3, pp. 164-167.*

Jin, H.Y. et al. The effect of Alpha-Lipoic Acid on Symptoms and Skin Blood Flow in Diabetic Neuropathy. ***Diabetes Medicine,*** *2007, Vol. 24, pp. 1034-8.*

Editor's comments: These results are consistent with a recent meta-analysis (study of studies aimed at improving statistics) by Ziegler *et al*, *Diabetic Medicine* 2004;21:114) where 600 mg/day resulted in improvement in the Total Symptom Score related to the feet, a score which included pain, burning, and numbness, when those treated were compared to patients taking a placebo. ALA has been used in Germany for over 30 years to treat diabetic neuropathy.

ALA, Peripheral Arterial Disease and Intermittent Claudication

Peripheral arterial disease (PAD) is a systemic atherosclerotic condition that causes impaired blood flow and what is termed claudication and is associated with limping and difficulty in walking due to pain. During exercise, PAD causes repeated intermittent blood flow interruption within active muscles thereby activating free radical formation and associated impaired vasodilation. Some studies have shown benefits from the intake of antioxidants other have not. Vincent *et al* have recently published a pilot study on the use of ALA in this context. A dose of 600 mg/day was compared with a placebo over a period of 3 months. Outcomes included the time during a brisk walk and the distance covered before pain became serious. The only significant results were obtained with patients who were regular exercisers and for this group the walking time to serious pain was significantly improved, as was the peak pain rating. The researchers were unable to detect significant changes in inflammatory markers. They considered the improvements in walking tolerance in the ALA group to be clinically significant.

Vincent, H.K. et al. Effects of Alpha-Lipoic Acid Supplementation in Peripheral Arterial Disease: A Pilot Study. ***Journal of Alternative and Complementary Medicine****, 2007, Vol. 13, No. 5, pp. 577-84.*

ALA Plus Acetyl-L-Carnitine – Influence on Vascular Function and Blood Pressure

In a study from Boston University School of Medicine and the Whitaker Cardiovascular Institute, researchers examined the effect of combined ALA/acetyl-L-carnitine treatment vs. a placebo on both blood pressure and vascular function, the latter measured by changes in the diameter of an artery in the arm. Treatment increased the arterial diameter significantly. In addition, patients with blood pressure above the median or those with the metabolic syndrome experienced significant reductions in blood pressure. The authors call for further studies to confirm the benefits of this combination as an antihypertensive therapy.

*McCackin, C.J. Effect of Combined Treatment with Alpha-Lipoic Acid and Acetyl-L-Carnitine on Vascular Function and Blood Pressure in Patients with Coronary Artery Disease****. Journal of Clinical Hypertension****, 2007, Vol. 9, No. 4, pp. 249-55.*

Possible but Rare Adverse Side Effect of ALA Supplementation

ALA is generally considered free from serious or dangerous side effects and has a long history of use, especially in Germany. However, recently reports have started to appear describing a disorder first reported in 1970 called insulin autoimmune syndrome (IAS). Involved is the production of antibodies to insulin. Patients present with problems associated with very low blood sugar (hypoglycemia) and extremely high levels of insulin. The hypoglycemia occurs in the late post-meal period and not during fasting. Most reported cases have occurred in Japan although a few have occurred outside Asia. Almost all Japanese IAS patients have a particular but rare gene mutation. The syndrome has been related to both the intake of sulphur containing antibiotics and most recently ALA, which is also a sulphur-containing compound. The syndrome appears to subside over time although residual antibodies may persist. Given the apparent benefits of ALA and the extreme rarity of IAS, especially outside of Japan, some may not consider this syndrome an issue, but it is important that users of ALA be aware of its existence and characteristic symptoms.

Yoshihiko, I. et al. Alpha-Lipoic Acid and Insulin Autoimmune Syndrome. 2007, Diabetes ***Care,*** *Vol. 30, No. 9, pp. 2240-1*

Cavaco, B. et al. Hypoglycaemia Due to Insulin Autoimmune Syndrome: Report of Two Cases with Characterisation of HLA alleles and Insulin Antibodies. ***European Journal of Endocrinology,*** *2001, Vol 145, pp. 311-16*

CT SCANS AND RISK OF CANCER

Periodically one sees or hears warnings about this problem in the papers or on TV. A recent article in the *New England Journal of Medicine* attempts to put this matter in perspective. The authors present a table comparing doses from various diagnostic radiological procedures. If we take the chest x-ray for comparison, then screening mammography provides 20 times the dose, adult abdominal CT scan of the stomach, 67 times, barium enema related scan of the colon, 100 times, and a neonatal abdominal CT of the stomach, 133 times. This of course does not take into account multiple scans indicated or required in some situations. In 1980 there were only a few million scans performed annually, partly because there were only a small number of scanners and the technique was just catching on. By 2005, the number reached about 62 million and will no doubt continue to increase.

At issue is the risk of cancer. The authors rely heavily on the studies made over many years of the survivors of the atomic bombing of Japan, where the follow-up has now been more than 50 years, and where there is consistency of risk estimates from this cohort with large-scale epidemiologic studies. In addition there is a reasonably good understanding of the biologic mechanism which involves the generation of free radicals by the absorption of the radiation followed by chemical attacks on surrounding molecules which includes DNA. While most damage is not permanent, some is indeed dangerous, and in particular the so-called double-strand chromosome breaks. Misrepair can lead to mutations, chromosomal translocations and gene fusions, all of which are linked to the induction of cancer.

Thus the question—how big really is the risk. The authors present graphical results of their estimates which illustrate the dramatically enhanced risks associated with exposures while young. For example, a single abdominal CT at age 5 carries approximately a 6 times greater lifetime risk of death from cancer attributable to this exposure than if the scan was done at age 35, and from age 35 to 75, the risk remains almost constant. Neonatal exposure is even worse, with 10 times the risk compared to exposure at age 35. However, the individual risk estimates are small with adult estimated attributable risks of death from cancer in the range of 0.01% to 0.02%. But the authors refer to estimates based on data on CT scans from 1991 to 1999 which may account for about 0.4% of all cancers in the US and they extrapolate, based on current use, that the figure may now be in the range of 1.5 to 2.0%.

Obviously this is a classic risk vs. benefit problem and one has little choice but to depend on the judgment of the clinicians involved. However, there is a growing enthusiasm for scans, and in particular scans covering a large percentage of the body that are done for screening in asymptomatic individuals concerned about early detection of disease and hope for the comfort and reassurance conferred by a totally negative result. Since such scans are expensive, the participants are generally restricted to those in the upper income classes. Here the risk vs. benefit question becomes much more complex since not only is there the cancer risk, albeit small, but what may be even more significant, there is the problem of false positives, where suspicious images are detected which prompt more diagnostic procedures, some invasive, some dangerous, a few fatal, and in many cases the end result is negative.

The authors conclude by pointing out that the estimates they present are not hypothetical nor are they based on large extrapolations of dose. They also point to a considerable literature questioning the unnecessary or overuse of CT scans and multiple CT scans, and they particularly point to questions associated with their use as a primary diagnostic tool for acute appendicitis in children. They refer to an informal study that indicated pediatric radiologists agreed that perhaps one third of CT studies on children could be replaced with alternative diagnostic approaches. Finally, they quote an interesting statistic that 53% of radiologists and 91% of emergency-room physicians did not (in 2003-4) believe that CT scans increased the lifetime risk of cancer.

Brenner, D.J. et al. Computed Tomography—An Increasing Source of Radiation Exposure. ***New England Journal of Medicine****, 2007, Vol. 357, No. 22, pp. 2277-84*

VITAMIN D AND CANCER MORTALITY IN THE US

A prospective follow-up study has just been reported which involved almost 17,000 participants from the Third National Health and Nutrition Examination Survey. Vitamin D status was determined by blood levels of 25-hydroxyvitamin D, the standard serum marker and cancer related mortality was ascertained from national death registers. The principal findings were (a) total cancer mortality was not associated with baseline vitamin D status. The range of 25(OH)D ran from < 50 to ≥ 100 nmol/L; (b) colorectal cancer mortality was significantly lower for individuals with 25(OH)D levels ≥ 80 nmol/L with a risk reduction of 72% when the reference comparison was with those with levels lower than 50 nmol/L. The authors list as limitations the fact that the study lacked the power to detect associations between cancer sites for which there were insufficient deaths, and it relied on a single measurement of vitamin D status.

Freedman, D. M. et al. Prospective study of Serum Vitamin D and Cancer Mortality in the United States. ***Journal of the National Cancer Institute****, 2007, Vol. 99, No. 21, pp.1594-602.*

Editor's comments: Readers should compare this study with that reported in the November issue of *International Health News* which involved a much larger group of participants and obtained significant evidence regarding mortality. If one is trying to establish the association between vitamin D status and some endpoint, what does one use as a 25(OH)D value, an average over the year, a peak value or just a more or less random value? In this study it is not possible to determine how close the values used were to either a maximum or minimum or average value. Furthermore, the subjects resided in both the southern latitudes and northern latitudes which could have accentuated the departures of single measurements from something more representative like an annual average. In addition, when only one measurement is made this opens up the possibility of the value being highly uncharacteristic of even the average for some individuals. Finally, for the breast cancer part of the study, only two ranges of 25(OH)D were used, < 62.5 and ≥ 62.5 nmol/L. In the low status group, there were 20 deaths from breast cancer whereas in the higher status group, the number was 8, resulting in a significant relative risk reduction of 72%. But these are very low numbers of events which highlights one of the serious problems with this study. In addition, an endpoint that would have been of great interest is site-specific incidence rather than mortality, given the rather long period cancers require to run their course and lead to death. The design of course precluded such analysis.

The results for colorectal cancer are impressive. Ralph Moss in *Cancer Decisions*, December 2 issue, calculates that preventing 72% of deaths from this cancer would translate into 37,570 lives saved each year, roughly the seating capacity of Fenway Park in Boston. But the numbers that would be really interesting would relate to the relative risk for various cancers, both for incidence and mortality, if levels of 25(OH)D were maintained roughly constant at some high value throughout the year, say >90 or > 100 nmol/L with a combination of supplementation and sun exposure. Considering the small number of cancer cases observed in a cohort of almost 18,000 individuals, it may be a long time before statistically significant data becomes available in what would have to be a long-term intervention study with frequent vitamin D status assessment. Given this, some may find it attractive to simply play it safe and take levels of supplementation that will assure such levels. This matter has been discussed in previous newsletters.

Vitamin D—The American Institute for Cancer Research Position

In an online position statement bearing a copyright date of 2007, this cancer research institute stated a number of points which included:

- "Children between six months and five years could benefit from taking drops containing vitamins A, C and D, although children with good appetite who eat a wide variety of foods may not need them."

- "Older people should consider taking a vitamin D supplement, as should: people who rarely go outdoors; people who cover up all their skin when outdoors; those who don't eat meat or oily fish."

One would think that when a recommendation is put out for a world-wide audience, it would provide accurate and useful information. Missing from the above statement are (a) the fact that in the northern latitudes, and this includes a significant portion of the US, exposure to the sun from October to March is a non-issue since no vitamin D is generated. The

AICR presumably does not think this is important information in spite of the fact that they mention being outdoors as a factor; (b) Food is a notoriously poor source of vitamin D unless one eats large amounts of oily fish. If we are to believe the current expert opinion that 2000 IU or more is needed in the winter in the northern latitudes, then food as a source is totally unrealistic, and certainly meat is also. 2000 IU/day from oily fish requires consuming about a pound per day. There are very few individuals who will eat a pound of salmon every day; (c) Why restrict the recommendations to older people. Is vitamin D deficiency, which is recognized to be widespread among all ages, to be ignored in favour of an age group where the problem is especially severe? (d) Given that this is such a critical issue—why do they not discuss supplement doses. Many who read this recommendation will look at their multivitamin bottle, see 400 IU and think all is OK when in fact this amount turns out to have almost no impact on achieving optimal vitamin D status; (e) they state clearly that children between six months and 5 years who have a "good appetite and eat a wide variety of foods" do not need vitamin D supplements but otherwise vitamin drops would be satisfactory. No mention is made of graduated dose per body weight and if children do not eat oily fish, about the only source left is fortified food which is generally inadequate, and simply eating a wide variety of food devoid of vitamin D has no bearing on the problem.

Incidentally, the title of the recommendation is "Don't Use Supplements to Protect Against Cancer." It is abstracted from an "Expert Report."

Source:
http://www.aicr.org/site/PageServer?pagename=dc_recs_08_no_supplements

DO WE REALLY KNOW WHAT MAKES US HEALTHY?

Readers of this newsletter may be familiar with the name Gary Taubes, author of two articles in the New York Times Magazine that attempted to get at the truth regarding the relationship between fat and cardiovascular disease. The most frequently quoted one had the catchy title "What If It Has All Been A Big Fat Lie." While Taubes' attack on the conventional wisdom was no doubt unpopular in many circles, it was nevertheless replete with quotations from highly respected experts. Now in the same newspaper magazine, he has presented an analysis of the problems and weaknesses of so-called observational studies on which are based many recommendations regarding the merits of actions or interventions involving drugs, lifestyle changes, supplements, etc. The unifying theme running through the article is the flip-flop on hormone replacement therapy which was initially justified on the basis of a large observational study (the famous Nurses' Study) but later advised against on the basis of two randomized trials. This flip-flop has had an impact on confidence in observational studies and public health recommendations. Again, many well-known epidemiologists are quoted in the course of the article. Taubes explores the impact of the media in this context and their thirst for stories which is in part satisfied by news releases from universities which prompt them publicize some alleged benefit just demonstrated. Taubes provides the reader with a valuable insight into the differences between association and causality, observational studies and randomized trials, and the major avenues by which bias can creep into studies undetected and consequently invalidate the results. He concludes with a section "What to Believe" with advice on how to react to studies reported by the media. First, be skeptical of the initial evidence, the first published evidence. If the association appears consistently in study after study but the effect small, doubt it since even if it is real it may have little effect on overall health or the risk of disease. If an association involves some aspect of human behaviour then question its validity since socioeconomic status, education, medical care, and healthy-user effects may make the association impossible to interpret reliably. When a result that is large, unexpected or a harmful effect is found when a beneficial effect was expected, the result may have some merit. He gives as examples cancer in children of women taking the drug DES and mesothelioma among asbestos workers. Finally, he discusses why randomized trials are in general more credible.

*Taubes, G. Do We Really Know What Makes Us Healthy**?*** ***New York Times Magazine**, Sept 16, 2007. Available from several of Internet sources. Google the author and title.*

Editor's comments: Attempts to answer many questions relevant to preventive medicine can only be done with observational studies, either for practical or ethical reasons, and even randomized trials have their problems. Effects are sometimes seen in placebo groups that reflect powerful placebo effect or serious bias or confounding. Also, the

accounts of study results in the media generally have only the spin introduced by the investigators or the author of the news release. Journalists generally do not look at the tables, study design and the statistics. If they did, the would find is some cases that the spin is far from justified by the actual numbers and that clinical significance is being attached to statistically significant but tiny differences. Furthermore, many randomized trials that are compared to observational studies are in fact not comparable since the study groups are fundamentally different. Yet one sees results from randomized trials that, for example, studied individuals who already had a disorder, found negative results for some intervention or factor, and these results are applied to discredit long-term follow-up observational studies done on individuals free of the disorder at the start. The cohorts are not comparable nor in general is the period in the natural history of the disorder being studied the same. One also repeatedly sees studies where correlations are sought and the results presented as so-called correlation coefficients. Perfect correlation is indicated by 1.00, none by a low number. Positive significant correlations are proclaimed based on coefficients of 0.2 to 0.3. Individuals trained in the physical sciences would ignore such correlations as virtually meaningless and graphs of the data generally look completely random—like what would be produced by a shotgun. Yet these results are published in peer-reviewed journals, held up to the reader as important and can even influence clinical practice. Each month your editor finds a number of studies that look very interesting and relevant to preventive medicine issues that should be of concern to readers. But careful examination of the actual data results in ignoring many for reasons that are enumerated above and in the article by Gary Taubes.

NEWS BRIEFS

CHEMOTHERAPY AND TAKING ANTIOXIDANTS

There has been considerable debate concerning the pros and cons of taking antioxidants during chemotherapy. One school of thought claims that doing this diminishes the effectiveness of treatment whereas others suggest a beneficial action regarding diminished side effects or synergistic effects and suggest that there even exists the potential for decreasing chemotherapy doses. A recently published systematic review of evidence from randomized trials attempts to put this matter in proper perspective. Of over 800 studies considered, 19 trials met the researcher's criteria for inclusion in the meta-analysis. Supplements evaluated included glutathione, melatonin, vitamin A, antioxidant mixtures, vitamin C, N-acetylcysteine, vitamin E, and ellagic acid (an antioxidant found in many fruits and vegetables). The investigators concluded that none of the trials reported a significant decrease in efficacy of chemotherapy due to antioxidants and in fact many studies found antioxidant supplementation resulted in increased survival times, increased tumor response, or both as well as fewer toxic effects, all these being relative to controls. They also comment on the prevalence of low statistical power and call for larger studies.

*Block, K.I., et al. Impact of Antioxidant Supplementation on Chemotherapeutic Efficacy: A Systematic Review of the Evidence from Randomized Controlled Trials**. Cancer Treatment Reviews**, 2007, Vol. 33, pp. 407-18.*

MORE GOOD NEWS FOR RED WINE LOVERS

A recent study from Australia, a country which now has a worldwide reputation for fine wines, examined the impact of consuming 400 mL/day (0.53 of a bottle) of red wine on antioxidant status and oxidative stress in the circulation. Twenty younger and 20 older subjects were recruited and randomly divided into the red wine and abstainer groups. After two weeks, the subjects crossed over into the other group. It was found that for both age groups the consumption of red wine significantly increased plasma total antioxidant status and significantly decreased oxidative stress in the circulation. These changes are in believed to be beneficial in the context of the pathogenesis of cardiovascular disease.

*Micallef, M. et al. Red Wine Consumption Increases Antioxidant Status and Decreases Oxidative Stress in the Circulation of Both Young and Old Humans. **Nutrition Journal,** 2007, published online ahead of print.*

Editor's comment: A half bottle of wine a day contains about 40 grams of alcohol. In most studies of the benefits of alcoholic beverages in the context of cardiovascular and other diseases, this represents the threshold where benefit turns into enhanced risk for men, and is considerably beyond

the recommended intake for women (one drink per day, or about 12-15 g of alcohol), mainly because of the suspected connection with breast cancer. Thus for both genders, moderation is the path of wisdom, but for women, moderation involves very limited consumption.

RESEARCH REPORT

Cholesterol – A Review: Part III

by William R. Ware, PhD

CHOLESTEROL AND STROKES: LIPID LOWERING

"When all think alike, no one is thinking very much." Walter Lippmann

STROKE RISK AND CHOLESTEROL

Epidemiologic studies have not shown a clear association between cholesterol levels and stroke. However, the subject is complicated by the presence of two distinct types of stroke, i.e. ischemic and hemorrhagic. The former involve occlusive interruption of blood flow while the latter are due to bleeding. In a number of studies and some meta-analyses, these have been lumped together. The problem that arises involves what appears to be an increase in hemorrhagic stroke at low cholesterol levels which would compensate for a decrease in ischemic strokes, drive the results toward the null and mask a positive association between stroke and serum cholesterol. The large meta-analysis of prospective studies which comprised 450,000 subjects with 13,000 strokes [1], and which found no association between incidence and cholesterol levels, has been questioned on these grounds by a number of observers. Law *et al* [2] attempted to resolve this question with a meta-analysis of observational studies where the ischemic and hemorrhagic strokes were reported separately. At issue were LDL levels. Seven studies reporting on ischemic stroke qualified, but one involved only smokers and is hardly representative of the general population. Furthermore, the paper referenced for the data on this particular study was not relevant because it did not stratify by LDL and in addition, the results for total cholesterol failed to yield statistically significant associations, whereas the LDL results used in the meta-analysis were given as significant. References to the other studies included in the analysis lead to papers that also did not measure LDL and the authors give no indication as to the source of the LDL data on which they base their analysis. Six of the seven studies found no significant association between LDL and stroke. All seven when subjected to a meta-analysis produced a statistically significant 15% decrease in risk of ischemic stroke for each 38-mg/dL decrease in LDL. The major goal of meta-analyses is to tighten up the statistics by reducing the uncertainty in the result through the use of a larger sample of subjects. The individual studies are generally weighted and this weighting process is arbitrary. In fact, there is in general a problem with the meta-analysis of observational studies. As Willett points out, issues of validity in observational or prospective studies are determined by confounding and bias, and this is not altered by the enhanced statistical power of a pooled data study or meta-analysis [3]. And it is the enhanced statistical power that produces a significant result from a set of studies that individually showed no statistically significant results. Law *et al* also found a 19% increase in hemorrhagic stroke for each 38% decrease

in LDL, but the same problems described above apply here as well. Thus this meta-analysis does not seem to resolve the issue in question.

Two studies were not considered by Law *et al*, in one case simply because the study came after their paper was prepared. One, the Eurostroke Study, which examined both ischemic and hemorrhagic strokes in the general population using a case-control model, found no significant association between cholesterol and either stroke type, fatal or non-fatal [4]. A very large prospective Korean study reported in 2006 [5]. Involved were over 787,000 individuals which provided a large number of strokes for analysis. Six ranges of total cholesterol were used, with < 130 mg/dL as a reference. When the results were adjusted for confounding, only cholesterol levels grater than 270 mg/dL were associated with increased risk of ischemic stroke, and only 0.9% of the subjects were in this category. For everyone else, there was no statistically significant association. For hemorrhagic stroke, total cholesterol levels above 160 mg/dL were protective when < 130 mg/dL was used as the reference, i.e. as cholesterol levels increased, the risk decreased. However, an interesting connection with alcohol consumption was made. By using a blood marker for alcohol consumption, it was found that when this marker was low, the association between low cholesterol and enhanced risk of hemorrhagic stroke disappeared. Thus in apparently healthy populations, the balance of evidence suggests that the incidence of stroke is unrelated to serum cholesterol levels but someone with a very high level may be at a modestly enhanced risk.

The absence of an association between cholesterol levels and the risk of ischemic stroke was termed a paradox by Matthias Enders in a review published in 2005 [6]. But he points to an additional paradox. Given that cholesterol does not appear associated with the incidence of ischemic stroke, it is then curious that treatment with statin drugs reduces the incidence of stroke, at least in patients with existing CHD or a history of stroke. Several studies have shown this. When data was combined from 9 trials including over 70,000 participants with established CHD or high risk of CHD, the relative risk reduction was 21% with an absolute risk reduction of 0.9% (number of individuals needed to treat to prevent one stroke—111) [7]. When intensive (higher dose) statin therapy was compared with therapy using usual doses, a pooled analysis of 4 trials yielded an additional 18% relative risk reduction but only a ½% absolute risk reduction [8]. In older studies statins were not found to reduce stroke risk in typical populations without known CHD, but in these primary prevention studies the age was rather low and thus so was the stroke incidence, and these trials lacked the statistical power to reliably detect a significant effect. For asymptomatic individuals not deemed high-risk, the benefits of statins for primary prevention is not clear. But there remains the problem of whether or not the primary action of the statin drug in this context is related to cholesterol lowering or some other anti-stroke action. Enders points out that the observed dose dependence relative to baseline cholesterol levels suggests that cholesterol lowering may not be the important factor, and this view is bolstered by studies of cholesterol lowering using non-statin drugs where there was no decrease in stroke incidence in spite of significant cholesterol lowering [6].

There is some evidence that low cholesterol levels induced by statins increase the risk of hemorrhagic strokes [9-12]. In the just published SPARCL trial it was found that treating 1000 ischemic stroke and transient ischemic attack patient with high-dose atorvastatin for over one year will avert 4.8 ischemic strokes while causing 1.9 additional hemorrhagic strokes [11,12]. It is also interesting that post-stroke mortality is inversely related to cholesterol levels because higher cholesterol levels are associated with less severe strokes [13]. Finally, in a study of diabetics, while statin treatment reduced non-hemorrhagic strokes by 50%, the benefit was independent of baseline cholesterol and the presence or absence of a first stroke [14].

Taken together, all this evidence strongly suggests that the benefits of statins in the context of stroke has little to do with cholesterol lowering and may be due to other actions of these drugs.

LIPID LOWERING TRIALS

Today statins are with rare exceptions the only drugs given to lower cholesterol levels. Worldwide sales of 55 billion U.S. dollars suggest widespread use. It is widely accepted that the success of statin drugs in decreasing the risk of cardiovascular events provides convincing proof of the role of cholesterol in the etiology of CHD. As discussed in Part I of this review on cholesterol, this argument is seriously flawed. Since the use of statins is so widespread, it is of interest to examine the relative and absolute benefits associated the use of these drugs in

both the primary and secondary setting and as well, the notion that when it comes to LDL, the lower the better and that almost everyone has elevated LDL and needs therapy.

Some lipid lowering trials were exclusively for primary prevention, some only for subjects with CHD, and some looked at both. There have been trials that exclusively enrolled men and those that had a mix of genders. In several studies, women have been seriously underrepresented. A number of different statins have been tested.

For primary prevention using statins the available studies are very limited. One is 100% male and the other two are 82-85% male. One [15] recruited only hypertensive individuals with at least three other CVD risk factors (ASCOT), and one [16] had a lower limit on baseline TC of 252 and a mean of 272 mg/dL, which translates into a significant percentage of individuals with family related high cholesterol (FH) (WOSCOPS). The one that came closest to reflecting characteristics of the general population was AFCAPS [17] where the mean TC was 221 and LDL ranged from 131 to 191, although this cohort had low HDL. Here are the results:

- WOSCOPS. 22% reduction in non-fatal CHD which was derived from a 1.9% absolute risk reduction. Thus the number needed to treat (NNT) to prevent one non-fatal CHD event was 53 and in the drug group 95.7% has no events compared to 93.8% in the placebo group during a 4.4 year follow-up. There was no significant benefit in terms of overall or CHD mortality. All the men had very high TC. The reduction of TC was 20% and LDL 26%.

- AFCAPS. The reduction in non-fatal CHD events was 38% but the absolute risk reduction was only 2%, yielding a NNT of 50 individuals. In the drug group, 96.5% experienced no adverse non-fatal CHD event whereas in the placebo group the number was 94.5%. There was no significant benefit in terms of overall mortality or CHD mortality. The cohort had average TC levels and was 85% male. The reduction of TC was 19% and LDL 26%.

- ASCOT. A 36% reduction in non-fatal heart attacks and fatal CHD was found. The absolute risk reduction was 1.1% giving a NNT of 91. No benefit was found in terms of overall mortality or cardiovascular mortality. In the treated group, 98.1% were free of non-fatal heart attacks or fatal CHD whereas for the placebo group the number was 97.0%. The cohort was comprised of hypertensive individuals with three other CHD risk factors and was 82% male. Reduction of TC was about 24% whereas LDL went down by about 32%.

A meta-analysis of seven primary prevention randomized controlled trials involving statins was published in 2006 which included the above three studies [18]. The results were as follows:

Outcome	Relative Risk Reduction (%)	Absolute Risk Reduction (%)	NNT
Major CHD events	29.2	1.66	60
Stroke	14.4	0.37	268
Non Fatal MI	31.7	1.65	61
Revascularizations	33.8	1.08	93

No significant effect of statin treatment on coronary heart disease mortality or overall mortality was found. For individuals in the Framingham low or intermediate risk categories, statin therapy was estimated to reduce the absolute risk of major coronary events by 0.75% and 1.63% respectively. Thus this analysis which involved almost 43,000 participants overall provides a similar picture to that for the three studies discussed in detail above. The absolute risk reduction is just slightly above negligible. However, from the public health point of view, even these small reductions would add up to a large number of events prevented in a large population such as the US, The benefit found for Framingham high-risk individuals was greater with a 2.51% absolute risk reduction, but the use of statins in this group is less contentious than for the low and intermediate risk groups.

It is not clear the extent to which these results apply to women since they were severely underrepresented. Also, the ASCOT trial does not apply to the general population, only a hypertensive population at high risk of CHD. Critics of the Cholesterol Hypothesis consider the small absolute risk reduction to be inconsistent with cholesterol being regarded as a large, significant and highly important risk factor. Believers say the above

studies prove that serum cholesterol and in particular LDL actually causes atherosclerosis and CHD and in addition, lowering TC or LDL by 20-30% reduces CHD events by 20-30%. As discussed below, when the primary prevention studies are stratified for women of all ages and the elderly, the risk reduction of statin treatment disappears leaving only young men as beneficiaries, and some would regard number of young men needed to treat of 50-70 to prevent one adverse event as suggestive of marginal benefit. Treatment is generally for life.

Most of the research in lipid lowering has centered on secondary prevention and the comparison between low and high dose protocols. Regarding the former, Costa *et al* have provided a meta-analysis of 7 studies [19]. The result was as 23% reduction in major coronary events and the absolute risk reduction was 5.1% with the NNT about 20. In the meta-analysis discussed above [18], for trials where secondary prevention was also involved, the relative risk reduction for major coronary events was 20.8% with an absolute reduction of 2.4% and the number needed to treat of 33. In this study of secondary prevention trials there was also no statistical significant association between statin treatment and coronary heart disease mortality or overall mortality.

Studies aimed at evaluating the benefits of high-dose statins vs. the usual dose have examined either individuals with stable CHD or those experiencing an acute coronary syndrome. Cannon *et al* have performed a pooled analysis of 4 studies [8]. When the two dose protocols were compared, the reduction in risk of CHD mortality or heart attacks achieved for high dose statins was 16% with an absolute risk reduction of 1.4% and the NNT was 71. The benefits should be viewed as in addition to those obtained with the standard statin therapy. In the pooled analysis the LDL reductions were from 130 to 101 mg/dL for the usual dose and from 130 to 75 mg/dL for the high dose, so-called intensive treatment. No significant differences were found between low and high dose treatment for CVD mortality or overall mortality. The analysis involved over 100,000 patient years of observation.

This then is a snapshot of the research behind the statement that for secondary prevention, statins offer benefit in terms of preventing additional adverse coronary events. Critics of the Cholesterol Hypothesis do not appear to dispute this conclusion. Where they part company with the conventional wisdom concerns the use of these results as proof of the Cholesterol Hypothesis, frequently with statements embellished with superlatives. As will be discussed below, the use of high statin doses, presumably for life, raises questions about side effects over and above those already associated with the standard dose protocol.

PRIMARY PREVENTION: THE SPECIAL CASE OF WOMEN OF ALL AGES AND THE ELDERLY

In the January 20th 2007 issue of the journal *Lancet,* two researchers, one from Harvard (J. Abramson) the other from the University of British Columbia (J. M. Wright) raised serious questions about the extent of the evidence supporting the use of statin drugs for true primary prevention of cardiovascular events or life extension [20]. The authors acknowledge that for individuals between 30 and 80 years of age with occlusive vascular disease, secondary prevention with statins confers benefit. What is at issue here are individuals who exhibit no evidence of disease. They point out that about 75% of those taking statins are in this category, i.e. pure primary prevention. On the basis of analysis of pooled data published earlier [21] and as well, reference to specific studies, they conclude that there is no statistically significant evidence favoring the use of statins for pure primary prevention for the following subsets: (a) women of any age; (b) men older than 69 years. The authors claim that in justifying primary prevention with statins in women and in people over 65 years of age, the U.S. guidelines for treatment cite 16 randomized trials and yet not one provides evidence of benefit from statin therapy for these two groups. In addition, they find that high-risk men between 30 and 69 with no apparent vascular disease should be advised that about 50 patients need to be treated for 5 years to prevent one adverse event.

The pooled studies used by Abramson and Wright consisted of five large trials of statins including the three discussed above, which mostly involved primary prevention (average percent primary prevention—83% of participants, range 56-100%). In the pooled studies, total mortality was not reduced by statins and while the 5-year frequency of total heart attacks and stroke was reduced (relative risk 0.84) the absolute risk reduction was only 1.4%. This is equivalent to needing to treat 71 individuals for 5 years to prevent one event. They also quote the results of the PROSPER randomized controlled trial which involved over 5800 men and women over 69 years of age [22]. In a subset of 3239 men and women in this trial with no evidence of previous vascular

disease and viewed at risk because of smoking, hypertension or diabetes, this study found that statins did not reduce total cardiovascular events. When the PROSPER results were stratified just by gender, among women there was no significant benefit from statin treatment and an unspecified number of the total female cohort actually had prior vascular disease. In the interpretation part of the abstract of the PROSPER paper no mention was made of the absence of benefit for primary prevention or for elderly women in general (primary or secondary prevention), but rather, it is simply stated that the statin in question given for 3 years reduced the risk of coronary disease in elderly individuals, thereby omitting an important result. This is in spite of the fact that of the 5804 individuals included in the analysis, about 56% were in the "no previous vascular disease" category, i.e. a significant fraction of the total study population. This data has been in the literature since 2002. Finally, the paper published in 2004 in the *Journal of the American Medical Association* to which Abramson and Wright make reference found for women without cardiovascular disease, cholesterol lowering with a statin drug did not affect total or coronary heart disease mortality. For fatal heart attacks, revascularization or coronary heart disease events, only one out of nine studies showed significant treatment benefit and this was just for one outcome of many reported in that study. Even for those with known cardiovascular disease, lipid lowering did not affect total mortality. This was a study of studies (meta-analysis) which included six trials involving 11435 women of various ages without cardiovascular disease [23]. Thus the evidence points to the conclusion that in the context of primary prevention for women of all ages and the elderly of either gender, cholesterol lowering is without benefit—a non-issue.

THE LOWER THE BETTER. WE ALL HAVE ELEVATED LDL

There is an interesting problem of why people with low as well as high LDL or TC get the same heart disease. One ad hoc hypothesis offered by those who defend the Cholesterol Hypothesis is that in fact in the Western world almost everyone has high cholesterol and therefore high LDL. The contention promoted by O'Keefe *et al* is that the optimal LDL for everyone is between 50 and 70 mg/dL [24]. For almost everyone, the only way to get LDL down to these levels would be lifelong use of drugs, currently statin drugs. This assertion regarding a universal syndrome of high LDL is based on the observation that the LDL range is 50-70 mg/dL in native hunter-gatherers, newborns, free-living primates and wild animals such as the baboon, howler monkey, horse, black rhinoceros, and African elephant. However, the hunter-gather societies looked at by the proponents of this theory all had very short life expectancies ranging from 17 years to 36 years. These individuals are hardly comparable to those residing in the developed part of the world. Also, it is debatable if newborns are a good standard. If we attempted to achieve the low blood pressures commonly seen in newborn children, we would probably in the process kill ourselves. The relevance of cholesterol levels in animals ranging in size from small to huge is also not obvious, especially since they are not carnivores. Thus there appear to be problems with this theory. In this context it is interesting that in Japan when cholesterol levels rose from 150 to 190, life expectancy increased and CVD fell dramatically. Also, as discussed at length in Part II, Cholesterol vs. mortality studies consistently show a J-shaped curve for men with mortality increasing as TC or LDL decrease to low values and a flat dependence for women as TC is decreased from high values until at low values the mortality also rises like that seen for men. Most of these studies are designed so that concurrent disease that might lower cholesterol is excluded. The 30-year report from the Framingham study also found that when cholesterol declined by itself rather than through the action of drugs, mortality increased rather than decreased. Thus even if one is convinced by blood cholesterol studies on new-born babies, modern-day hunter-gatherers and a marvelous assortment of animals, they still have to deal with this mortality issue in adult humans.

O'Keefe *et al* also attempt to justify their belief that every one should have an LDL level between 50 and 70 mg/dL by presenting some diagrams of CHD events vs. LDL and showing a linear correlations where CHD events go to zero in this LDL range. However, there are problems with this approach. Let's consider the correlation they obtained based on primary prevention trial data. Three studies were used. One involved only men with very high LDL and TC and one involved only hypertensives with three additional risk factors. The third looked at mostly men with average cholesterol levels. When the CHD event rates are plotted vs. the baseline average LDL and the average LDL achieved after statin treatment, a straight line results going to zero events at an LDL of 55 mg/dL. But these three populations are not comparable and this approach involved no corrections for confounding. The high cholesterol group probably included individuals with FH. And data from only three studies were used. If one wants to examine the correlation between cholesterol and CHD events, this highly limited data set uncorrected for confounding does not appear to be a very good way to do it. And this analysis

also ignores the great danger of extrapolating data. Finally, the many results discussed in Part I where no correlation was found among asymptomatic individuals between CAD events and TC (and thus LDL) except for young men argues against the validity of this or the other similar correlations used by O'Keefe *et al*.

The acceptance and implementation of the notion that only LDL in the range of 50-70 mg/dL is healthy and that if one does not meet this criterion, lipid lowering is in order, would put a significant fraction of the developed world and the rich and well-off elsewhere on statins for life since there is currently no other means of achieving these very low levels. Exercise and diet would for most not accomplish such reductions, given that such lifestyle interventions are already well known to produce only small changes in TC or LDL.

SIDE EFFECTS WITH STATIN THERAPY

It appears that mainstream medicine is moving toward lower and lower targets for optimal LDL and, as mentioned above is flirting with the notion that it should be as low or even lower than 70 mg/dL for everyone. What appear to be limited benefits only for a very small sup-population in the developed world and as well data suggesting higher mortality at low LDL levels seem to be ignored. But this is part of a larger question—the side effects in general of statin drugs. This is an issue when any risk-benefit analysis, formal or informal, is undertaken. What are the side effects, how serious are they, and are they significantly underreported and downplayed?

Before a drug is approved, drug companies must study adverse side effects. This is generally done with at most several thousand subjects over a fairly short period, a system that is bound to fail. If we had mandatory long-term (say 5-10 years) testing for side effects in a cohort of say 10 or 20 thousand subjects, the introduction of new drugs would decline precipitously. In fact, the industry would probably never allow this to happen. The point is that only the most prevalent side effects manage to surface. After the drug is approved, a mechanism exists for the reporting of adverse side effects, but it is well known that the compliance is negligible with only about 1% of the cases reported. When very serious side effects were just below the threshold of detectability during clinical trials but surfaced when several million prescriptions are written, it is not uncommon that the drug is recalled, although the period of denial can be considerable (e.g. the Vioxx incident). Side effects either ignored or missed in the clinical trials have to kill or disable enough patients for someone to notice. Numerous examples could be quoted. With the statin drugs, it is very easy for a physician to regard side effects as simply manifestations of aging or related to some comorbidity or lifestyle excess. There must also be an element of denial involved since statins are taken by millions worldwide every day, so how can there be any serious problems? It is interesting that in veterinarian medicine both alertness to adverse effects and a willingness to immediately take action appears much greater than in human medicine. Evidence—the very rapid recognition and equally rapid response to the recent contaminated pet food incident.

Comprehensive reviews of the side effects of statin drugs are mostly to be found outside mainstream medical literature and are thus easily dismissed or ignored by the establishment. But some of the voices have considerable credibility. For example, the author of *Statin Drugs--Side Effects and the Misguided War on Cholesterol* and *Lipitor--Thief of Memory* is Dr. Duane Graveline, M.D., a former astronaut, an aerospace medical research scientist, NASA flight surgeon. Another voice is that of Dr. Mary G. Enig, Ph.D., a well-known and respected authority on lipid biochemistry and the author of over 60 publications and presentations. She is the author of *Know your Fats: The complete Primer for Understanding the Nutrition of Fats, Oils and Cholesterol.*

Graveline's most recent book on Lipitor and memory provides an account of his shocking experiences with what is called *transient global amnesia* (TGA), a sudden temporary total loss of memory where one does not recognize anything or anybody and fails to have memory of past events going back decades. When his first incident occurred, no one was able identify a cause. After he recovered he reasoned that it might be medication related. He had been put on Lipitor and immediately discontinued it. No more episodes occurred until he resumed Lipitor under pressure from his physician. Then he had a second and more serious episode. This prompted him to set up a website and collect information on statin side effects and in particular TGA. Over several years he has collected enough data to convince himself that TGA is much more common than acknowledged. This is not a trivial matter since there are many occupations where such an episode could prove dangerous to others than the victim, e.g. an airline pilot at the controls during a final approach. In his book on

side effects Graveline provides a comprehensive review which should be of interest to anyone taking or contemplating taking statins. His website (www.spacedoc.com) updates his continuing research and data collection on adverse side effects and in particular what is reported to the government site (Medwatch).

Mary Enig and Sally Fallon have written a review of statin side effects which was published by the Weston A. Price foundation and can be found on its website (www.westonaprice.org). They point out what most scientists involved in cholesterol research know, statins not only interfere with cholesterol synthesis but also with a number of other biochemical pathways which generate substances of critical biological importance. The two most important are Co-Enzyme Q10, a critical cellular micronutrient present in all mitochondria, and a family of compounds call dolichols which in cell biochemistry direct manufactured proteins to their proper targets in response to DNA directives, ensuring that cells respond correctly to genetically programmed instructions. Also, squalene, an intermediate in the reaction chain that yields cholesterol, has anti-cancer properties.

But statins also reduce the synthesis of another compound, mevalonate, which among other things is involved in clotting mechanisms and thus might cause changes that are in a favorable direction. There are other potentially beneficial biochemical actions of statins that are under intense investigation by scientists impressed by the growing evidence that statins act by mechanisms independent of cholesterol lowering. Lipid lowering is also very effective in relieving anxiety about elevated cholesterol levels, and this may have significant health benefits.

But to return to adverse side effects, let it suffice to list them: (a) muscle pain and weakness including potentially fatal rhabdomyolysis; (b) peripheral neuropathy and nerve damage which can be permanent; (c) heart failure thought to be partly due to a deficiency of Co-Enzyme Q-10, a biochemical that incidentally is used in some countries as a prescription drug to treat heart failure; (d) dizziness and large drops in blood pressure; (e) cancer and the depression of the immune system. Statins have even been suggested for use with transplant patients as an anti-rejection drug; (f) depression linked to low cholesterol levels. This list comes from the review by Enig and Fallon cited above. More details can be found in Graveline's books, which also include some interesting case histories. It is probably safe to say nobody really knows the prevalence of the adverse side effects of this class of drug. This is also not a popular or prestigious area of research, nor one where it is easy to get funding.

In his book on side effects cited above, Graveline presents numerous anecdotal reports where the individuals involved though their problems were connected to statins, but their symptoms were attributed to Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, i.e. (Lou Gehrig's disease (ALS), or multiple sclerosis. This puts the problem in clear perspective. The incidence of such disorders increases with age and there are no widely recognized or accepted studies that directly relate statin use to these symptoms. Thus while physicians would not be surprised to see an increase in patients presenting with symptoms of these neurological disorders, in general they would not make any association with statins. Statins after all, except for what the industry describe as very rare muscle problems, are thought to be safe. The point is, while it may be true that statin users are putting themselves at increased risk of neurological disorders which may mimic the diseases listed above, it is unlikely that mainstream medicine will recognize the potential connection. The association if present may never be established to the satisfaction of those demanding evidence. The studies are too long, too difficult to organize, and too difficult to interpret, given that the incidence of the problems in question is rare, although certainly significant to those who experience the symptoms. And who is going to pay for them? What is really alarming about the anecdotal reports given by Graveline is that in most cases, while symptoms diminished after termination of statin use, in some individuals they did not completely resolve, leaving patients worried that the damage sustained, possibly by statin use, was permanent. No one appears to be seriously studying these issues. In the real world of evidence based medicine, anecdotal reports are easily dismissed. Finally, in this review evidence was presented that cholesterol was not an issue for women or the elderly provided they did not have CHD. Yet there are millions of women of all ages and as well elderly individuals who are on statins and yet to not have CHD. If indeed they do not need statins, then they are unnecessarily putting themselves at risk for serious side effects.

This is not just an issue that cholesterol critics have emphasized. There is a class action lawsuit before the courts in the US claiming damages from a drug company for encouraging the medical profession to prescribe statins to women and the elderly. According to the submission to the court, the case is based on the contention that there is no evidence from relevant studies indicating benefit and there is a risk of harm for the age-gender groups in question.

These then are some of the considerations that come into play when trying to weigh the risks and benefits of statin therapy. If one believes that cholesterol is not an issue for women or for the elderly who do not have CHD, then one side of the scale has nothing on it. For young men, this is an important issue given the large number of individuals needed to treat to prevent one adverse CHD incident.

STATINS FOR CHILDREN ???

The American Heart Association has just published its latest guidelines regarding drug therapy for high-risk lipid abnormalities in children and adolescents [25]. These represent modifications of the 1992 National Cholesterol Education Program guidelines. The main features of the older guidelines have been preserved, and merely modified on the basis of what the committee regards as the current situation with regard to other risk factors that might influence the decision for drug intervention. Thus the current guidelines are as follows.

1. Consider drug intervention in children age ≥ 10 (usually wait until menarche for females and after a 6-12 month trial of diet and exercise).
2. Consider drug therapy if LDL remains ≥ 190 mg/dL (4.90 mmol/L). If LDL remains > 160 mg/mL (4.1 mmole/LL) and (a) there is a positive family history of premature cardiovascular disease or (b) ≥ 2 other risk factors are present after vigorous attempts to control these factors, then drug intervention is also indicated.
3. Treatment goal: Minimal, LDL < 130 mg/mL (3.35 mmole/LL; ideal < 110 mg/mL (2.85 mmole/LL)

Risk factors and high-risk conditions: Male gender, low HDL, high triglycerides, small dense LDL, overweight or obese and other aspects of the metabolic syndrome, hypertension, smoking or exposure to passive smoke, and elevated lipoprotein(a), homocysteine, or c-reactive protein. Finally, there are medical conditions that increase the risk such as diabetes, HIV infection, systemic lupus erythematosus, organ transplantation or surviving childhood cancer and these also count as risk factors.

The authors comment that the evidence base underlying these recommendations including LDL targets is supported only by indirect evidence, evidence extrapolated from studies on adults, studies performed in the context of familial hypercholesterolemia and expert consensus. Furthermore, they caution that direct evidence of an impact of interventions during childhood and adolescence on later cardiovascular morbidity and mortality will likely always be lacking and that drug therapy should only be targeted toward individuals with high-risk lipid abnormalities or high-risk conditions who have not reached the target lipid levels with lifestyle modification.

First, how common are levels of 190 or 160 mg/dL? A recent study looked at averages from data collected between 1988 and 2002 [26]. For the age group from 12 to 20 years, mean LDL values were about 100 mg/dL. For men, the 98th percentile came in at about 155 mg/dL and for women the 95th percentile was about 135 mg/dL. Thus for this age group, LDL > 160 or especially ≥ 190 is rare and appears to truly represent an abnormality. But In the group of children with LDL > than 160 mg/dL, if only two of the above listed risk factors are necessary for triggering drug intervention, then this no doubt expands the eligible group considerably. Second, how successful are dietary interventions in correcting elevated LDL. In a study published in 2001, a conventional intervention involving reductions in total fat, saturated fat and dietary cholesterol over 5-8 years produced a 2.0 mg/dL drop in LDL when comparison was made with a control group. Furthermore, for this group which was initially 8-10 years old, *both the intervention and control groups experienced a drop in LDL from about 130 to 110 mg/dL on 5-8 years follow-up* [27]. Obviously, a 2 mg/dL decrease in LDL would seem to have little clinical significance, especially if one has an LDL over 160 and measurements in this age group may have little value anyway.

However, there are fundamental questions. We are dealing here with recommendations that are by and large not based on studies relevant to the age group in question nor to the intended long-term use of drug intervention. In a special article for the journal *Pediatrics,* Belay *et al* address these and related issues [28]. They make the following points: (a) Randomized clinical trials of statins in adults have been mostly for secondary prevention in older adults, and because even children considered at the highest risk rarely experience a cardiovascular event, the results of secondary prevention trials in adults should be cautiously applied to children;

(b) the translation of aggressive treatment targets based on secondary prevention trials from adults to children and adolescents is not justified for primary prevention; (c) primary prevention studies using statins with adults have not demonstrated any reduction in absolute risk for total mortality. They regard this as a crucial aspect since before statins are used for primary prevention in children and adolescents, they consider it critical to demonstrate that total mortality is reduced in later life with childhood statin therapy; (d) the anti-inflammatory benefits of statins on advanced atherosclerotic plaques may not be seen in children whose plaques are at a much different stage of development. They go so far as to suggest that the effect of statins seen in primary prevention relates to the subgroups of individuals who already have unstable plaques; (e) with regard to the safety issue, the AHA position which incidentally seems to downplay side effects, is based on trials with children that have lasted only from 6 months to 2 years and the clinical trials on adolescents and children have been underpowered (too few subjects) to detect infrequent or rare adverse effects. They also point to the problem that the intervention is during cognitive and endocrinologic maturation, skeletal growth, and bone mineral accretion and that there are no studies that directly address other statin safety issues in this age group.

Other problems need to be mentioned. Statins may be associated with central nervous system problems and limb anomalies in about 15% of exposed first-trimester pregnancies [29]. Therefore, statin therapy among female teenagers capable of reproduction may carry a very significant birth defect danger unless contraceptives are successfully employed. Also, girls have lower risk of developing cardiovascular disease than boys, and this must be taken into account in decisions about who to treat. There are also issues associated with breast cancer risk associated with use of oral contraceptives prior to about age 20 (see the recent review on primary prevention of breast cancer in the archives of IHN).

Finally, a study published in 1990 looked at cholesterol levels in children 8 to 18 years of age and then followed them for 20-30 years to see how many as adults developed cholesterol levels that would have merited continued surveillance and intervention [30]. The researchers found that screening for total cholesterol resulted in significant numbers of individuals being *incorrectly* classified with respect to future cholesterol level elevations. They point out that based on their results, many children with high cholesterol levels have normal levels in young adulthood without intervention.

While the above considerations seem to make it clear that the AHA recommendations are not, as the authors admit, really evidence based and that there are many important issues, it is however almost impossible to implement studies that start with very young children, put half of them on statins, and follow the cohort for 30-40 years to see if the childhood LDL levels and risk factors that would trigger this drug intervention in childhood really lead to cardiovascular problems in much later life which are significantly decreased in the treatment group. Early treatment vs. treatment of adult disease has never been carefully investigated. Thus the bottom line in the case of children deemed at risk appears to be very aggressive lifestyle intervention to correct childhood obesity and poor dietary habits. But the guidelines talk about diets low in cholesterol and saturated fat, and yet the studies they quote found this intervention had almost no effect on LDL levels. Other studies cited in the guidelines paper also were impractical (no meat or dairy products) or produced only small effects and these on children with normal LDL levels. They also are inconsistent in that they reference the AHA pediatric diet strategies which do not mention avoiding cholesterol containing foods and which appears more in tune with reality [31]. To get the diet plus exercise approach to really work will, it would seem, present a severe but obviously highly worthwhile challenge to parents with children who might be targeted for statin therapy.

In addition, guidelines, which severely restrict fat, will in this age group probably invariably result in a large increase in refined carbohydrate intake with an associated increase in triglycerides and HDL, an increase in the risk of insulin resistance and inflammation, and thus an increase in the risk of atherosclerosis. Just what is being targeted for prevention.

Given that (a) the indications for statin use in children are very far from securely evidence based and in fact mostly based on evidence from adult studies on individuals with heart disease; (b) that we are presumably talking about very long-term therapy; (c) that the long-term safety has not and may never be directly established for this age group; and (d) that the optimum age for pharmaceutical intervention has not been established, it would seem that parents need to be very concerned regarding the recommendation to proceed with childhood statin therapy. But it must also be acknowledged that children with a strong family history of premature heart disease who have very high cholesterol levels are a special case for which some of the objections and cautions

enumerated above may perhaps assume somewhat less important. But this does not minimize the problem of the absence of relevant evidence of benefit in this age group.

STATIN BENEFITS UNRELATED TO CHOLESTEROL LOWERING

In a recent review, Ray *et al* summarize the evidence suggesting that some of the benefits of statin drugs are independent of lipid lowering [32]. They include

- Benefits appear independent of baseline LDL level.
- Benefits exceed the benefit predicted by the change in LDL level.
- Rapid benefits of aggressive initiation of statin therapy which come long before there is a change in cholesterol levels.
- The different efficacy between statins is unrelated to their effects on cholesterol levels.

Studies have revealed that statin-mediated improvements in endothelial function (as for example measured by improved blood flow) occur within days in humans, even after a single dose and before any significant effects on lipids [33]. In fact, a recent study found that a non-statin cholesterol lowering drug (ezetimibe) which was effective in lowering LDL levels failed to improve endothelial function whereas equivalent lipid lowering with a statin produced the benefit [33]. These are called *pleiotropic* functions of a therapy, and at present this is a very active and expanding area of research.

These pleiotropic functions of statin drugs undermine the argument that is the cornerstone of the Cholesterol Hypothesis. This now appears to be gaining some recognition. For example, Brotman *et al* [34] state in a recent article that "*observing that statins reduce LDL cholesterol levels while reducing cardiovascular mortality does not prove that LDL causes CHD, since statins also affect other cardiovascular risk factors*." They continue, "*Since statins affect inflammation, endothelial function, oxidative stress, and coagulation, we cannot conclude that LDL cholesterol is atherogenic based on statin studies alone. This requires as convincing mechanistic explanation and an array of consistent evidence supporting it*." Also, in an editorial regarding the SPARCL study [9] which found 80 mg/day of atorvastatin reduced overall incidence of stroke and cardiovascular events, David Kent remarks that [10] "*However, the finding has not settled the controversy [cholesterol and stroke], since a strong correlation between the reduction of cholesterol level and stroke prevention would be expected regardless of the mechanism by which statins decrease risk, i.e. regardless of whether the cholesterol level is the actual mediator of the treatment effect or merely a marker of adequate therapy and adherence*."

SUMMARY

Ignoring the lipid lowering results, which we have dismissed as not proving the Hypothesis, the evidence that high total cholesterol or LDL cholesterol causes atherosclerosis and CHD appears limited to men under 50. An explanation for this exception was presented based on the hypothesis that this group may have on average a very high exposure to professional and domestic stress. In this age group there will be individuals who have exaggerated blood pressure response to stress and this is associated with high levels of cholesterol. Exaggerated blood pressure response is itself a risk factor for CHD, and thus the correlation with cholesterol. TC and LDL are bystanders, not causative agents in this view [35]. The arguments that family-related high cholesterol (FH) proves the Cholesterol Hypothesis is falsified if one accepts that atherosclerosis is different in young FH individuals, that FH has a number of other adverse aspects, and that in general, there is no evidence that FH on average reduces life expectancy. One has also to consider the large number of observations discussed in this review that tend to falsify the Cholesterol Hypothesis or weaken or destroy its foundations. In four books on this subject published since 2001, three by medical doctors, the phrase "The Cholesterol Myth" has set the tone. All four books essentially tell the same story as elaborated in this review. One has a nice cartoon showing spectators at a parade remarking the Cholesterol Hypothesis Emperor seated on his throne in a float has no clothes. But the Hypothesis is alive, well, thriving and in fact gaining momentum as more and more people become eligible for lipid lowering treatment under frequently revised guidelines, and this includes women of all ages and the elderly, both with no evidence of CHD, for whom there appears to be no significant evidence of benefit. Finally we have the now famous proposal of Wald and Law that *everyone over that age of 55* should

take the so-called Polypill since, in their opinion, it could largely prevent heart attacks and stroke [36]. This is not a joke but a serious proposal published in the *British Medical Journal*, a peer reviewed publication. The Polypill contains a statin, low-dose aspirin and a high blood pressure drug and would presumably be patentable. In the over-medicated developed world, this actually seems like a natural endpoint in the evolution of we have been witnessing in mainstream medicine's approach to health and disease.

This review has more or less ignored HDL cholesterol and the evidence that high levels are indeed protective. The subject of HDL is closely tied to triglycerides and to diet. A diet high in carbohydrates, and especially one with lots of refined carbohydrates such as refined starches and sugar, will in many individuals dramatically raise triglyceride levels and significantly lower HDL levels and at the same time increase the risk of developing insulin resistance and systemic inflammation which includes inflammation of arteries. This places one on the road to atherosclerosis, diabetes, obesity and CHD. These adverse blood lipid changes are accompanied by a shift in the LDL particle size in the direction of small, dense LDL particles thought to be the important fraction in the context of inflammation, atherosclerosis and CHD. In fact, high triglycerides and low HDL are considered to be a good surrogate marker for insulin resistance, and insulin resistance is definitely something to be avoided. Nevertheless, current guidelines include recommendations for low-fat diets and in some cases very low-fat diets and many individuals would find it very difficult to make up the calorie deficit with fruit and green vegetables and a minimum of protein, the latter being avoided because of the fat that many protein sources contain. They turn of necessity to refined carbohydrates in large amounts and thereby defeat the purpose of the dietary recommendation, i.e. reducing the risk of CVD, by raising their triglycerides, lowering their HDL and ultimately acquiring insulin resistance, changes which work in exactly the opposite direction from the goals envisioned by the guidelines. A review of this subject is planned for the near future. The next newsletter will also contain a book review of a just-published volume that addresses this subject in a very comprehensive but highly readable manner.

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The Prostate Monitor
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Reviews of recent studies from the peer-reviewed literature

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This issue features various aspects of the use of PSA measurements in the course of forming an opinion as to the presence or absence of prostate cancer. As discussed in our book "The Prostate and Its Problems" this is one of the most misunderstood aspects of prostate cancer with many individuals believing that they can go to the doctor to get a prostate cancer test, just as they would get a test for malaria or AIDS. In fact, every man has a PSA level, but the value varies dramatically from very low to very high and high values can be indicative of merely an enlarged prostate or in the worst case scenario when the value is very high, advanced metastatic cancer. The principal problem with the test is that individuals with either low or high PSA readings may or may not have prostate cancer. It is just that the probability is low if the PSA is low, and goes up from there with confounding along the way from an enlarged prostate, prostatitis, etc. Those concerned with this topic may find the articles reviewed to be of interest.

Another area of controversy involves the merits of prostate removal when there is evidence that the cancer has spread to one or more lymph nodes. Traditionally, a radical prostatectomy was not indicated when positive lymph nodes were present. The surgery was abandoned. This view is undergoing a significant change and the latest study, this one from the Mayo Clinic, finds very good results associated with a combination of radical prostatectomy and post-operative hormone treatment when positive lymph nodes were identified at the start of the surgery.

Finally, an up-date is provided on the so-called Expectant Management program at Johns Hopkins where patients enter into a program where definitive treatment is delayed until there is evidence that it will benefit the patient while at the same time taking care not to miss the window of opportunity where there is a high probability of a cure. This is a very interesting approach to treating prostate cancer in older patients who may not benefit from treatment and under this program may never need surgery or radiation therapy, thus avoiding side effects than can significantly diminish their quality of life. It is discussed at length in our book.

Wishing you continuing good health,

William R. Ware, PhD, Editor

NEW STUDIES ON PSA AND RISK OF PROSTATE CANCER

PSA velocity has been suggested and used for some time as an adjunct to PSA levels when the question of the need for a biopsy is at issue. The velocity is expressed as the change in PSA in ng/mL per year and the commonly used value of 0.75 ng/mL per year has been used to help distinguish men with prostate cancer from those with simply prostate enlargement (BPH—benign prostatic hyperplasia). In addition, a pre-treatment velocity greater than 2 ng/mL per year has been regarded as a bad omen since it is associated with advanced or aggressive cancer and an increased prostate cancer specific mortality rate subsequent to surgical or radiation therapy. In a recent paper, Loeb *et al* point out that these thresholds were determined mostly in groups of men with a PSA level greater than 4 ng/mL and that there was a need to examine the question of an appropriate threshold for biopsy recommendation in men who had PSA levels below this threshold, a common situation in the PSA era due to extensive screening. They report on a study of over 22,000 men with PSA levels less than 4 ng/mL. 501 were diagnosed with prostate cancer and had sufficient data to allow the calculation of a PSA velocity. It was found that a PSA velocity threshold of 0.4 ng/mL was the most useful for recommending a biopsy. Prostate cancer was diagnosed in 223 (2%) of men with a velocity less than this threshold, and in 278 (13%) of men with a velocity above this threshold. When a statistical analysis was conducted to compare the strength of various predictors, a PSA velocity > 0.4 ng/mL was a stronger independent predictor of prostate cancer diagnosis on subsequent biopsy than age, race or a family history of the disease for men with a PSA level < 4.0 ng/mL [1].

In the PSA era of extensive screening, it is not uncommon for asymptomatic men to have a pre-biopsy or so-called clinical stage T1c suspected cancer, which means that the digital rectal exam revealed no abnormalities and the only indication was an elevated PSA, which of course is merely an indication and not a diagnosis of cancer since that can only be accomplished with a biopsy. In fact, as is discussed at length in our book, even a single biopsy is not definitive and in fact misses a significant number of cancers, something that may not be understood by some patients when they agree to the procedure. In a landmark study which was based on the placebo arm of the Prostate Cancer Prevention Trial (PCPT) it was found that prostate cancer prevalence was a continuous function of PSA from very low values to the standard biopsy trigger of ≥ 4.0 ng/mL. Ahyai *et al* recently reported on a study that investigated this same question in a European cohort and obtained similar results based on total PSA. They found prostate cancer prevalence of 4% for PSA below 0.5 ng/mL which increased to 32% for those in the PSA range of 3.1 to 4.0 ng/mL. They also investigated the predictive power of both prostate volume and the % free PSA. The former is generally available from ultrasound data and the latter is now frequently measured along with total PSA in routine screening. They found that both were important parameters. For example, when a cut-off of 20% was used for % free PSA, 60% of those with a positive biopsy were below this cut-off whereas for those with a negative biopsy, the number was 31.5%. The rule of thumb has been that a low percent free PSA was indicative of cancer whereas a high value, typically above 25% suggests BPH [2].

The results of the PCPT trial mentioned above and discussed at length in our book *The Prostate and Its Problems* have been made the basis of an on-line calculator (Google *Prostate Cancer Prevention Trial calculator*) where age, PSA, family history and whether or not there has been a prior negative biopsy are entered into a form and the calculator displays the risk of prostate cancer and in addition the risk of high-grade disease. Reed *et al* have recently used this calculator to examine age and race specific prostate cancer ranges currently in use which provide an aid to judging prostate cancer risk. They found that on the basis of the PCPT data as embodied in the calculator algorithm, the current ranges are flawed and that many patients who would not be considered for biopsy based on these ranges are in fact at significant risk for high grade prostate cancer and that the risk is twice a great for black men as for white men. The only trouble with this approach, which is the same problem as with older approaches, is that now a percentage risk is being calculated but the threshold percentage risk for triggering a biopsy recommendation is of necessity arbitrary. The situation is similar to the Framingham risk factor calculation for coronary heart disease risk—is a 20% risk or a 25% risk or a 30% risk a reasonable threshold for recommending intervention. The choice is arbitrary [3].

Finally an interesting paper has appeared which addresses the issue of fluctuating PSA levels after an initial negative biopsy and poses the question, “should we be reassured?” Specifically, the question investigated was whether the risk of having a positive repeat biopsy was greater in patients with a steady or steadily rising PSA vs. one that fluctuated (up and down). Clearly this latter behavior makes it impossible to obtain a PSA velocity. It

was found that the risk of having a positive repeat biopsy was no lower with a fluctuating PSA than with a steady or steadily rising level, a result that the authors claim is in contrast with the common and yet unfounded view of clinicians [4].

Readers should recognize that the ongoing debate regarding identifying optimum thresholds for PSA parameters is simply a manifestation of the limitations of this blood marker. It reduces to a number's game, a matter of probabilities. The simple truth is that there is no definitive blood test for prostate cancer in clinical use at this time. One can have advanced prostate cancer and have a very low PSA. One can have an elevated PSA and be free of the disease. The elevated PSA merely indicates an increased probability. The % free PSA can help differentiate between prostate cancer and BPH, but again all one gets are probabilities. One frequently reads that testosterone replacement therapy would not be advisable for individuals with prostate cancer, but how is an asymptomatic man to know? As has been stated in the literature on a few occasions, the only way to answer the question is with a biopsy, and even that will have a have a false negative rate depending on the number of needles used and the skill of the individual conducting the biopsy. As discussed in our book, something close to certainty regarding not having prostate cancer can be achieved by two or three biopsies, or a saturation biopsy, but the patient still must be satisfied with a residual probability of a few percent that the cancer has been missed. But this is not to downplay the importance of PSA parameters in providing an alert signal, and of course, once prostate cancer has been diagnosed, it is an invaluable marker for judging the effectiveness of therapy as well as tracking the progression of recurrent disease.

MERITS OF RADICAL PROSTATECTOMY WHEN POSITIVE LYMPH NODES ARE PRESENT

Traditionally, finding that prostate cancer had spread to the lymph nodes during the initial phase of prostate surgery carried the indication the operation should be terminated and the patient treated with hormones alone. However, several studies have demonstrated improved survival for patients with positive lymph nodes treated with prostatectomy followed by hormone therapy as compared to patients receiving only the latter treatment. Another issue is the current relevance of PSA era patients in connection with this issue. Researchers from the Mayo Clinic have just published what they regard as the largest series to date of patients with lymph node positive disease treated during the PSA era. They reviewed records from their institution of over 10,000 consecutive patients who underwent radical prostatectomy and bilateral pelvic lymph node dissection. Patients with positive nodes were identified and patients who received hormonal or radiation therapy prior to surgery were excluded from the analysis. After five and ten years follow-up, the following results were obtained:

	% 5-yr survival	% 10-yr survival
Biochemical recurrence free	69.0	55.9
Local recurrence free	94.9	89.2
Systemic progression free	90.1	80.1
Cancer specific survival	94.2	85.8

Biochemical recurrence was defined as a PSA of ≥ 0.4 ng/mL. Local recurrence was defined as cancer on biopsy of the prostate bed or salvage radiation therapy to the prostate bed without evidence of metastasis. Systemic progression involved finding metastatic deposits during a bone scan or on biopsies of other than the prostatic bed. Most of the patients with positive nodes were staged T3 or T4 on pathological examination of the tumor, over 50% had a pathological Gleason score of 7, 67% had seminal vesicle invasion and 62% had a positive surgical margin (cancer cells left after surgery). When those without positive lymph nodes were compared to those with only one, the differences in outcome were small at five years follow-up, typically only a few percentage points. At 10 years the differences when two or more nodes were positive were much more pronounced in comparison with those having no lymph node involvement with a local recurrence free percentage difference of 5%, systemic progression free percentage 22%, and cancer specific survival percentage difference of 9%.

Almost 90% of patients received hormone therapy following surgery. It was found that this decreased the risk of biochemical recurrence and local recurrence but did not significantly impact systemic (metastatic) progression or the cancer free survival rate. No outcome comparisons were made between the patients in this combined radical

prostatectomy and hormone therapy and individuals who received only the latter. The authors merely conclude that radical prostatectomy may offer long-term survival to patients with lymph node positive cancer [5].

HORMONE THERAPY AND RISK OF CARDIOVASCULAR MORTALITY

This story might be filed under the heading "you can't win." The October 17 issue of the *Journal of the National Cancer Institute* includes a very interesting report on a study which examined the question of whether the use of hormone therapy (androgen deprivation therapy—ADT) in patients treated for localized prostate cancer results in an increased incidence of either cardiovascular or all-cause mortality compared to those who received just surgery or radiation as the primary treatment. Part of the motivation for the study was the fact that ADT is being used increasingly in combination with local therapy to treat patients with localized disease who exhibit adverse features and as well, reports in the literature that ADT increases the risk of developing diabetes and cardiovascular disease. The study involved a follow-up with a median time of about 4 years (range 0.1-11.3). The mean duration of ADT was 4.1 months (range 1.0-32.9) and 1015 patients were involved. After statistically controlling for age and available cardiovascular risk factors, it was found that treatment with ADT was associated with a significant increased risk of death from cardiovascular causes in patients treated with radical prostatectomy for localized prostate cancer. Patients 65 years of age or older had a 5-year cumulative incidence of cardiovascular disease death of 5.5% vs. 2.0% for those treated with surgery alone. For younger patients, the equivalent figures were 3.6% vs. 1.2%. This phenomenon simply complicates the risk-benefit analysis but the absolute risk is small. These results are consistent with studies that suggested ADT can lead to conditions associated with the metabolic syndrome which in turn increases the risk of coronary artery disease. The authors suggest careful cardiovascular evaluation and intervention are advisable before initiating ADT in patients with localized prostate cancer [6].

EXPECTANT MANAGEMENT OF PROSTATE CANCER WITH CURATIVE INTENT

Expectant management with curative intent is a relatively new approach to the persistent problem of over treating low-risk and indolent cancers and yet not missing the window of opportunity to achieve optimum treatment if the assessment appears wrong and the cancer is more aggressive than originally thought. Johns Hopkins and the Memorial Slone-Kettering Cancer Center have both developed programs and have been collecting data for some time. Now an update on the experience at Johns Hopkins has been published in the Journal of Urology. The Hopkins' criteria, which were found to be predictive of small volume, low-grade cancer, are as follows:

- Non-palpable prostate cancers (stage T1c)
- PSA density (PSA value divided by the prostate volume obtained from ultrasound) of 0.15 ng/mL/cm^3 or less
- Gleason score of 6 or less with no Gleason pattern grade of 4 or 5, no more than 2 cores positive for cancer, and no more than 50% of any 1 core involved with cancer.

Compared to other similar programs, the Hopkins program is viewed as conservative. Admission to the program obviously involves submitting to a biopsy. In addition, follow-up involves an annual surveillance prostate biopsy as well as semiannual measurements of free PSA and total PSA. However, curative intervention (surgery or radiation therapy) is triggered only by a failure to repeatedly meet the biopsy criteria given above, although the patient is always free to request a change in management. The protocol is interesting in that it does not depend on PSA parameters for an indication that curative treatment is desirable. This can be hard for some patients with rising PSA or even their primary care providers to accept.

A total of 407 men have been involved with the Hopkins Expectant Management program. Of these, 239 remained on active surveillance at a median follow-up of 3.4 years (range 0.43 to 12.5), 103 (25%) underwent curative intervention at a median of 2.2 years after diagnosis (range 0.2 to 7.39) and 65 (16%) were either lost to follow-up (12), withdrew from the program (45) or died of causes other than prostate cancer (8). Older age at diagnosis and an earlier date of diagnosis were associated with crossover to curative intervention. Two men were found to have lymph node involvement at surgery, 5 and 7 years after entering the program. Both had relatively high PSA density during follow-up but met the biopsy criteria for remaining under surveillance.

Finally, the authors reiterate the fundamental principle of their program. The majority of men diagnosed with prostate cancer today are older than 65 years, have low to intermediate disease risk but receive treatment. A substantial proportion of these men, according to this view, will gain no benefit from treatment in terms of additional years of life [7].

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