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William R. Ware, PhD - Editor

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This issue begins with what amounts to an editorial on so-called evidence-based medicine. The general public is led to believe that modern medicine is evidence based. The notion is even used in TV drug ads. Furthermore, mainstream medicine uses what they perceive as a lack of acceptable evidence to condemn many alternative therapies and the use of non-prescription substances for prevention. Thus one might expect that upon investigation, modern medicine would be found to operate within the bounds of solid evidence of effectiveness. As is discussed, first in general terms and then with two examples drawn from recent studies, this appears to be a myth.

Autism is on the increase and no one seems to have a good explanation. We look at a recent study from the University of California at Davis which attempts, with only partial success, to explain the well-documented increase in incidence between 1990 and 2006 in California. Some of the issues that come up in this discussion will be discussed in more detail in the May newsletter.

Other subjects examined include alcohol consumption and the risk of breast cancer where two very recent studies are reviewed. In addition, a potential mechanism for the cardioprotection afforded by moderate alcohol consumption is examined, and in addition, a study which found interesting results in connection with alcohol and heart failure. Finally, a study just published provides confirmation of the connection between vitamin D deficiency and influenza is reviewed.

This issue also contains a Research Review concerning the widely held hypothesis that cholesterol is the driving force behind atherosclerosis. This short review was prompted by seeing this notion used repeatedly in TV ads for statin drugs and by an editorial in a respected health magazine which accepted this connection as dogma. There is a strong connection between this review and the discussion of evidence-based medicine in this issue.

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Wishing you good health,

William R. Ware, PhD, Editor

Highlights

EVIDENCE-BASED MEDICINE—SOME OBSERVATIONS

Evidence-based medicine is well on its way to becoming the new religion of medicine. The standards the idealists would like to impose involve, whenever possible, randomized clinical trials, preferably controlled with a placebo. Gone are the good old days when if there was general agreement that if something worked, use it. While this approach worked well around the house and when repairing things, it became apparent that in the field of health, this approach was vulnerable to all sorts of bias, abuses and wishful thinking. The classical snake oil salesman was held up as a prime example, but those making this comparison fail to recognize the similarity to the drug detail troops who invade physicians offices on a regular basis and promote medications, some of which are later demonstrated to be as ineffective as snake oil and some even life threatening. It is of course evident that the principle of evidence-based medicine is a splendid thing, but it can also be argued that the evidence-based medicine is also, to a great extent, wishful thinking.

Evidence-based medicine depends on evidence, and by definition evidence involves experiments at the laboratory bench, all sorts of animal studies, mostly on rodents, and finally, the main and essential feature, humans studies that are free of all sorts of sources of bias and are adjusted for virtually all confounding. But the quality of what we are calling evidence is highly variable. For example, scientists who do the famous Cochrane Collaboration Studies rank studies in order to do meta-analyses, and they reject vast numbers as flawed or insignificant. So evidence-based medicine is only as good as the evidence, and this is a potential weak point in the concept. When an issue is viewed as really important, especially in the context of public health, committees of experts are assembled to examine the totality of the evidence and make expert pronouncements, generally referred to as guidelines. These of course have a profound influence on the practice of medicine. The publications that contain these pronouncements and the associated documentation are frequently lengthy and include some studies that go back before most medical literature in the form of full text was available online. Even for the documentation that is online, only readers with access to good medical libraries can, without going to a lot of trouble, actually look at critical parts of the evidence implied by citation that form part of the basis of the consensus. Lacking that access, something generally enjoyed only by academics, subscriptions are necessary but the literature is spread over dozens of journals, an impossible situation. For the older literature, a visit to library archives and their photocopier was required. Thus the profession is, for the most part, forced to accept consensus statements on face value and assume that the evidence cited is relevant, based on valid studies of statistical and clinical significance. When critics write letters to editors claiming that there are problems and that some or many of the references used to justify positions were irrelevant, these letters frequently appeared in journals that also were not so-called open access and thus the letters go unread by the vast majority of individuals being influenced by the guidelines.

The evolution of evidence-based medicine changed fundamentally during the last two decades with the widespread practice of forming consensus panels and guideline committees from individuals with direct conflicts of interest. These conflicts of interest involved relationships with the pharmaceutical industry and the device makers which ranged from research grant support to a variety of income enhancing mechanisms such as speaker's panels, consulting, involvement in continuing education and stock ownership. The analogy to prostitution has not been missed. Slowly, the better journals started requiring that these conflicts of interest be declared, generally in fine print at the end of the article, but in some cases the information was so complex and extensive that tables were required to display the full extent of the financial relationships between a group of authors and industry. Some argue that true expertise now comes out of necessity with this conflict of interest baggage, a point that can certainly be argued either way. While it is informative to know the full picture on those writing the guidelines or presenting consensus reports, the evidence they are using is coming from studies where, in many cases, the same conflicts of interest existed. Expert committees can also select the literature they consider important and supportive of their position, but critics have no trouble finding studies that present conflicting results which are not cited. Furthermore, papers describing the results of some studies are in fact ghost written to conceal the fact that the investigators were from industry. The task of obtaining the true picture is also obstructed by the fact that negative results are much less frequently reported in the literature than positive results, which provides an additional strong and unfortunate bias. Even the federal regulatory agencies have been misled by not seeing all the results of clinical studies, and in some cases only those that supported applications for approval of a drug, procedure or device.

There is also the matter of statistical vs. clinical significance, both in epidemiologic (observational) studies and clinical trials. We have reached the point today where no major study can get along without professional biostatisticians. Frequently their challenge, to quote Nortin Hadler from his book *Worried Sick*, "is to tease out minor exposures and minor health effects by observing all the glorious variability of humanity. Biases and confounders lie in wait for any epidemiologist trying to tease minor events and influences out of the complexity of life." The abstracts of papers presenting reasons to believe in some evidenced-based, beneficial effect may describe the result as statistically significant, but inspection of the tables, something generally denied to all but subscribers or those with library privileges, may reveal negligible absolute benefits that to critics appear to totally lack clinical relevance. If one goes back a decade or so, it was common practice to ignore what is today one of the key measures of statistical significance, the 95% confidence interval, which must, among other things, not contain the null result. Authors presented their results as important and meaningful even though today this description of the results would never pass peer review. The role of statistics must never be underestimated and it is considered old fashioned to demand effects big enough such that this, rather than the mere passing of some statistical test, is grounds for justification of a clinical application. Furthermore, studies find that many physicians do not feel comfortable evaluating the statistical aspects of studies reporting clinical results. When authors say two variables are correlated with a correlation coefficient of 0.2, some readers believe this is meaningful and even of clinical significance. It is to the credit of some authors that they accompany the announcement that such and such are correlated with a coefficient of 0.2 by showing a scatter plot of the two variables which would convince even an eighth-grader that there was in fact no correlation. Historically, there has also been the unfortunate practice of selecting data until the correlation corresponding to the belief that motivated the study is met in an adequately convincing manner. This seemingly dishonest approach was particularly evident in some older epidemiological studies where data was assemble from carefully selected countries while ignoring data from other countries that failed to agree with the preconceived theory. Older studies that would fail to get past peer review today are still to be found as key references in the documentation of positions in consensus reports and guidelines. If it is believed that no one is going to look at these papers, this is probably true. The activity of doing studies, getting statistically significant results that may be so small as to have no relevance to anything, is common today, and represents an important process along the road to academic success, promotion, grant support, and even a fruitful relationship with the drug industry.

What constitutes adequate evidence also seems somewhat arbitrary. It is not uncommon for recommendations concerned with primary prevention to be based on absolute benefits of less than 2%. A very recent example—a recommendation from two urology societies that men with PSA ≤ 3.0 ng/mL who are regularly screened with PSA may benefit from discussions of both the benefits and risks of 5-alpha reductase inhibitors (e.g. Proscar) in connection with the prevention of prostate cancer.[1] The absolute risk reduction is about 1.4% which translates to about 71 individuals needed to treat to prevent one cancer. Similar absolute risk reductions are seen in some statin primary prevention trials of very high-risk individuals. Thus the question, where does one draw the line regarding absolute benefit, and is there some level below which absolute risk reduction becomes meaningless to the individual unless the dangers presented by side effects are negligible? But side effects are rarely negligible and reliable information frequently nonexistent.

Today, we see considerable alarm emanating from the offices of editors of world-class journals. Readers are being told that they must be very careful believing what they read, especially with regard to clinical studies.[2] One journal now requires that all clinical studies sponsored by drug companies pass severe restrictions as to design and conduct and that the results must be examined by independent biostatisticians who are demonstrably free of bias. Otherwise, the manuscript describing the results will not be considered for publication.[2] But this is wishful thinking since some other journal will probably accept the paper and may not even require conflict of interest disclosure. A still unresolved problem that has also drawn sharp criticism from journal editors and editorialists is the growing practice of outsourcing clinical studies to countries where concerns for the safety of participants is lax and in some cases, the qualifications of those involved in the conduct of the study and the data collection might come under question.[3,4] If reports of studies are ghost-written to give them the credibility of academic institutions in the developed world, then this compounds the problem of judging credibility and explains why some journals are now on guard for ghost-written manuscripts.[5] Also, lawsuits against drug companies have forced vast numbers of industry documents into the public domain and provided the raw material for a few courageous academic medical scientists to write shocking exposés of the manner in which some companies conduct the clinical trials.[5,6] But the results of these trials are the fodder of evidence-based medicine and the feedstock for the regulatory agencies. An example just publicized by Bloomberg News (February 27, 2009) and

derived from e-mails unsealed in connection with litigation revealed that the manufacturer of Seroquel "buried" unfavourable studies. The London-based company faces about 9,000 lawsuits claiming it failed to warn users and physicians that Seroquel can cause diabetes. An article in *The Wall Street Journal* reported the same day that the company instructed U.S. sales reps to tell doctors that this powerful psychiatric drug did not cause diabetes. The landscape of the jungle is clearly being better defined.

In the past few years we have also seen a number of scholarly books written by medical doctors of impeccable credentials such as editorships of the world's leading medical journals, who have been motivated to expose what they view as serious problems confronting their profession and its interaction with the pharmaceutical industry, problems which of course ultimately and inevitably filter down to the consumers. Many of these books have been reviewed or recommended in this Newsletter. Reading them provides just about as depressing an experience as is currently available from the flurry of books describing the coming depression. So what to do? Profound skepticism regarding media treatment of drug company news releases as well as their advertising seems to be an indicated response. Limiting the intake of prescription drugs unless one is addressing a critical or crisis situation appears to be at least one option, but a difficult one for the elderly taking 10-20 prescription drugs per day. Some physicians suggest not taking a prescription drug until it has been out there for a number of years, given the magnitude of the recall rate and the time required to uncover side effects, some serious enough to get the black box in the package insert. But who reads the package insert? Do black boxes indicating serious risk really work? Rejecting the notion that in the past half-century we have all changed and now have an evidence-based need for and deficiency of prescription drugs would appear to help avoid some of the current hazards associated with the lack of real evidence and the now notorious flip-flops of mainstream recommendation.

The examples discussed above represent an attempt to point out that to some extent, evidence-based medicine is a fantasy and that it will be some time before this changes, given that the true picture of what goes on is merely a reflection of human nature, a comment that can also be made regarding the current financial meltdown. Thus skepticism is in order. After all, hormone replacement therapy was soundly grounded in evidence of benefit from observational studies and then turned out to be risky based on evidence from randomized clinical trials. But even this flip-flop is not black and white and what was really responsible for the discordant results continues to receive serious discussion in the literature.[7]

EXAMPLE: CARDIOLOGY GUIDELINES BASED ON WEAK EVIDENCE OR ONLY EXPERT OPINION

In the February 2009 issue of the *Journal of the American Medical Association,* Tricoci *et al* present extensive evidence showing that the recommendations of the American College of Cardiology/American Heart Association clinical practice guidelines are often based on weak evidence.[8] Two commonly used methods of classifying evidence were used. They found for 16 current guidelines reporting levels of evidence, only 11% were classified in the top category, i.e. based on evidence from multiple randomized trials or meta-analyses, and 48% were of the lowest class where the evidence was based on expert opinion, case studies or so-called standards of care. i.e. to quote from the paper "*indicating little to no objective empirical evidence for the recommended action*." They also found that the proportion of recommendations for which there is no conclusive evidence is growing with each revision. In an editorial, Shaneyfelt and Centor[9] discussed at length the aspect of bias and point out that guideline consumers can not fully adjust for this because the sources of information are "opaque." They state that guidelines often have become marketing tools for device and pharmaceutical companies, and cite one study of 44 guidelines which found that 87% of the authors had some industry tie. The editorialists also express concern that in spite of the problems with evidence quality, some of these consensus statements are being used as performance measures and as tools to judge the quality of physician care. They call for major changes, echoing another call for reform in guideline-making which appeared a month earlier in this same journal.[10]

Similar concerns were raised by Abramson and Wright in a short article in the *Lancet* titled *Are lipid-lowering guidelines evidence based?* They are particularly concerned with the extrapolation of evidence from secondary prevention trials to primary prevention and discussed problems with this approach which impacts current guidelines.[11]

EXAMPLE: PERCUTANEOUS CORONARY INTERVENTIONS IN NON-ACUTE PRESENTATIONS

This type of intervention involves balloon angioplasty (PTCA) with or without the insertion of stents. In the US, more than a million procedures are done each year, often for non-acute coronary artery disease. A recent study

just published in the March 14 *Lance*t examination of 61 trials has examined the extent to which this invasive procedure has better outcomes than non-invasive medical therapy in individuals with non-acute presentations, including unstable angina. In direct head-to-head comparisons, when PTCA was compared to medical treatment, no significant difference in outcomes was found for death, heart attack, need for bypass surgery, or revascularization. No study qualified for the analysis that compared head-to-head the insertion of drug eluting stents vs. medical treatment, but such a comparison with bare metal stents yielded no benefit for death, heart attack, need for bypass surgery or revascularization, and when drug eluting stents were compared with bare metal stents, they offered no additional benefit for preventing death or heart attack, although there was benefit in avoiding bypass surgery and revascularization. This seems to illustrate the very weak nature of the evidence base for a very common procedure, and one that is accompanied by risks of adverse events associated with the procedure. In fact, unless a drug eluting stent is included in the procedure, there was no difference in any endpoint, and the drug eluting stent failed to prevent either death or a heart attack.

AUTISM—IMPORTANT DEVELOPMENTS

The possible connection between autism and childhood vaccination has been studied and debated for a number of years. The *post hoc, ergo propter hoc* argument had and no doubt still has great appeal to parents who witness the development of autism shortly after a round of vaccinations. This as one might expect, ultimately leads to the courtroom and in fact, in the U.S., $2.5 billion in claims have been filed. This has been an issue extensively studied by epidemiologists who claim they cannot find a connection. On February 12, three so-called sentinel cases were decided in U.S. Federal court. The rulings were even reported in the *British Medical Journal*[12]. All three judges passed judgments that went against the plaintiffs, decisions that were based on considering expert testimony and a large number of medical articles. The reaction of the media seemed to be that now the matter could be laid to rest, although this supports the notion that the final decision on a question involving complex epidemiology can be evaluated by judges in civil courts. It would be surprising if these judges fully understood the more subtle points of biostatistics and epidemiology, but who else is going to decide in civil suits? However, it would be a mistake to consider that the science on this question is settled, as there are issues with data and the design of some studies. This will be discussed in subsequent newsletters.

An interesting twist to this matter involves the 1998 paper in the *Lancet*[13] by Wakefield *et al* which is credited with triggering fears that the MMR vaccine was linked to autism. According to a recent news item in the *London Times,* (February 8 and 9, 2009) the General Medical Council in England initiated an investigation, which is ongoing, into allegations of professional misconduct of Wakefield and two other authors of this *Lancet* paper. At issue, according to evidence presented to the General Medical Council, is the discrepancy between the data in the paper and the hospital and GP records of the cases used in the studies. It is alleged that results were changed and misreported. The three individuals under investigation deny any misconduct. An examination of the *Lancet* paper reveals that there were only 9 autistic children in this case study. Dr. Wakefield is quoted as currently taking the position that the connection between MMR and autism is not proven, nor has he ever claimed that it is. Subsequent to the 1998 paper, several large-scale studies involving millions of children have found no connection, but the debate continues.

At the same time a study appeared in the journal *Epidemiology* from researchers at the University of California at Davis which attempted to evaluate the various factors that might explain the huge increase in the incidence of autism in California between 1990 and 2006.[14] More than 3000 new cases of autism were reported in California in 2006 compared to 205 in 1990, and in 1990, 6.2 out of every 10,000 children born in this state were diagnosed with autism by the age of five, as compared to 42.5 per 10,000 born in 2001. Since 2001, the numbers have continued to rise. The annual rate increased exponentially between 1990 and 1998 doubling every 2.7 years, but there has been a slowing with the doubling time which is now about 8.7 years, based on a different but still exponential change between 2001 and 2006. Put another way, if one plots the logarithm of the rate data given by Hertz-Picciotto and Delwiche (Table 1) against time, there are two distinct straight-line portions, one from 1991 to 1998 and a second from 2001 to 2006 and the fit to the lines is near perfect. Had this abrupt change not occurred, the rate in

2006 would have been over three times that actually observed.

The investigators used government data to examine likely explanations for the increasing rates which included younger age at diagnosis, differential migration in and out of the state, changes in diagnostic criteria, and inclusion of milder cases as time progressed. When these factors were quantified they explained only about half the increase over the time period involved. Thus there remains a still large increase in incidence that begs for an explanation. In a commentary in *Scientific American* (January 9, 2009) Maria Cone provides some interesting insights based on interviews. Two factors frequently invoked in the context of causation are genetics and environmental toxins. One of the authors of the study, Dr. Hertz-Picciotto, commented that genetics do not change in such a short period of time and are unlikely to provide an explanation. But she pointed out that there are plenty of environmental candidates including mercury, polychlorinated biphenyls, lead, brominated flame-retardants and pesticides. High on current lists are flame-retardants used in furniture and electronics and pyrethroids found in insecticides. For example, according to an unpublished study, mothers of autistic children were twice as likely to use pet flea shampoos containing organophosphates or pyrethroids. But a broader view according to Hertz-Picciotto, would include both the "microbial and chemical world." She also pointed out that funding for genetic causes of autism is 10-20 times higher than funding to support studies of environmental causes—which she feels is "very off-balance."

While many parent groups believe that childhood vaccines are responsible for autism because they contained a mercury-based preservative, this chemical was removed from most vaccines between 1999 and 2001 (influenza vaccine is a notable exception). But it is curious that according to the data of Hertz-Picciotto and Delwiche, 1999 was the first year that there was a sharp change in the incidence curve. This change was rather dramatic leading to the establishment of a new exponential growth rate starting in 2001 with a doubling time of almost 9 years instead of about 3 years. Coincidence? Who knows? What is clear is that there has been significant progress in the past few years in justifying the potential importance of a number of causative agents other than mercury, and there also appears to have been really significant progress in treatments, mostly natural, that simultaneously approach a number of aspects of this disease. This subject will be revisited with a review of several studies in the May newsletter. Nevertheless, achieving a more or less chemical free environment seems like a good start for those planning a family or raising young children, and in fact probably for everyone. Accomplishing this is obviously far from simple. Just look under the sink, in the garage and in the medicine cabinet and start counting! Then consider all the other sources that do not come in bottles, cans, or applicators, such as chemicals in and on food, tap water, the out-gassing of building materials, furniture, electronics, and pollution in the outside air. It does not take much of a chemical substance to provide thousands of molecules for every cell in the body, estimated at about 10^{14} cells, when one considers Avogadro's number, the number of molecules in an amount with a weight equivalent to the molecular weight, i.e. 6X 10^{23} molecules. Three tablespoons of water contain about Avogadro's number of water molecules. Even a micromole of a toxin still offers about 10,000 molecules for every cell, and even very low concentrations toxic chemicals can be deadly if the chemical concentrates in certain tissues or organs.

Readers interested in autism should also look at the discussion of the use of vitamin D in treating autism which appeared in the September 2008 Newsletter. An interesting website that appears to have a high level of scientific credibility is *Defeat Autism Now* http://www.autism.com/index.asp, from the Autism Research Institute.

ALCOHOL CONSUMPTION, BREAST CANCER AND OTHER CANCERS IN WOMEN

A large follow-up study concerning the association between alcoholic beverages and cancer which involved over a million women in the UK (The Million women Study) has just reported results in the *Journal of the National Cancer Institute*.[15] In this study by Allen *et al,* a drink was defined as containing 10 g of alcohol. An 8 oz (1 cup or 250 mL) of red table wine containing 12-14% alcohol by volume contains 24-28 g of ethyl alcohol (ethanol density = 0.79 g/mL). Thus the typical red wine glass, if half-full, by this definition is equivalent to between two and three drinks. A regular can of beer

containing 355 mL and 5% alcohol contains about 14 g of alcohol or about a drink and a half. With this in mind, consider the following relative risks (RR) for breast cancer, adjusted for age, region of residence, socioeconomic status, body mass index, smoking, physical activity, use of oral contraceptives, and hormone replacement therapy.

CONSUMPTION	RR
Nondrinkers	1.00 (reference)
≤ 2 drinks per week	1.00
3-6 drinks per week	1.08
7-14 drinks per week	1.13
≥ 15 drinks per week	1.29

The last 3 relative risks were statistically significant with quite narrow 95% confidence intervals. Nondrinkers included never and former drinkers and as stated above, a drink was equivalent to 10 g of alcohol. Thus one glass per day of shiraz at 14% alcohol is equivalent to about 20 drinks per week by the definition used in this study (7X28/10) which increases the risk of breast cancer according to Allen *et al* by almost 30% compared to nondrinkers or those drinking less than 2 drinks per week, i.e. less than one glass of this wine per week. The same risk would be associated with drinking 2 cans of beer per day. Another way of analyzing the data yielded a 12% increase in the risk of breast cancer for an increase of 10 g/day of alcohol consumption. These are by some definitions moderate amounts of alcohol and if these numbers are taken at face value, for women drinking alcoholic beverages more than occasionally and in small amounts it appears to be a risky business. But the increased absolute risk is rather small. The investigators estimate that for every additional drink of 10 g of alcohol consumed per day the incidence up to age 75 years per 1000 women in developed countries is estimated to increase by about 11 breast cancer cases per 1000 women, i.e. a small change in absolute risk. The absolute risk of breast cancer in this cohort of middle-aged women followed for an average of 7.2 years was only about 2.2%.

When compared to epidemiologic studies worldwide, the authors admit that the increased risk they observe is almost twice what was found in a meta-analysis of 53 studies. In addition, no account was apparently taken of folic acid intake, which has been found to neutralize the breast cancer risk associated with alcohol consumption (see the Research Review on breast cancer prevention in the October, November and December, 2007 Newsletter).

This study also found that for an increase of 10g/day of alcohol consumption, the increased relative risk of cancer of the oral cavity and pharynx was 29%, esophagus 22%, larynx 44%, rectum 10% and liver 24%. But if expressed as the increase in incidence up to 75 years of age per 1000 women, the numbers per 1000 women were 1 for cancers of the oral cavity and pharynx, 1 for cancer of the rectum and 0.7 for each of cancers of the esophagus, larynx and liver, giving along with breast cancer a total of about 15 cancers per 1000 women.

In an accompanying editorial, Lauer and Sorlie attempt to put this study in perspective.[16] They point out that reported biological benefits and positive epidemiological studies have encouraged some medical organizations to state that low levels of alcohol consumption may be considered safe or may be a legitimate item of discussion between physician and patient. What they don't mention is that moderate alcohol consumption, frequently red wine, is almost always a component of the Mediterranean diet, the French lifestyle with its low risk of cardiovascular disease, and the practice is even recommended in Walter Willett's book *Eat, Drink and be Healthy*, which caries the imprimatur of the Harvard School of Medicine. At issue here are the benefits that have been observed in connection with cardiovascular health but as the editorialists point out, not everyone agrees that alcohol is cardioprotective and the evidence may be severely confounded. Thus at least for middle-aged women, the study by Allen *et al* should give one pause for reflection. The study had adequate power due to its enormous sample size and its message seems clear—no level of alcohol consumption can be considered completely safe for this cohort. They also point out that for women, cancer is the leading cause of death during the middle years and while it is true that cardiovascular disease is the leading cause of women overall, this primarily applies to women over 75 years. But one is again left with the problem of balancing risks vs. benefits and in addition, the small absolute increase in risk, but also perhaps a benefit of unknown actual magnitude.

WINE, LIQUOR AND BEER AND BREAST CANCER—ANOTHER STUDY

Another alcohol and breast cancer study has just reported. This was a large follow-up study of over 70,000 women who were members of a prepaid health care program in California.[17] Subjects were enrolled from 1978 to 1985 and followed until the end of 2004. Data was collected during examinations. 78% were below the age of 50 and there was a wide ethnic distribution including 53% white and 30% black. During the follow-up period, 2829 breasts cancer cases were identified (4% incidence rate). Alcohol consumption was defined in terms of drinks per day, and in the absence of detailed information, presumably they use the same definition as most studies in that a drink is about 15 g to 20 g of alcohol. Thus all the results are on the basis of drinks rather than grams of alcohol. The relative risks when adjusted for eight confounders were as follows

CONSUMPTION	RR
Abstainers (lifelong)	1.00 (reference)
< 1 drink per day	1.08 (not significant)
1-2 drinks per day	1.21
≥ 3 drinks per day	1.38

The last two results were statistically significant. Increased breast cancer risk was concentrated in women with estrogen positive receptor tumors and there was no major disparity related to the choice of wine, liquor, beer or the type of wine. The researchers concluded that there was a risk of breast cancer related to alcohol consumption with a threshold below 1-2 drinks per day which involved a hormone-mediated mechanism. In their opinion, the threshold could not be more exactly determined. They also point out that one meta-analysis of 38 case-control and cohort studies found increased breast cancer risk of 11%, 24% and 38% for 1, 2 and 3 drinks per day. They also refer to the analysis of 53 studies which found a 7% increase in risk per 10 g in all studies and 5% per 10 g in prospective studies, but studies have found increased risk at as low as 3% per 10 g of alcohol. While this study found a connection with hormone receptor status the results of other studies have been inconsistent in this regard. Assuming 15 g of alcohol per drink, then 2 drinks per day would correspond to about 20 drinks per week containing 10g which would in the study of Allen *et al* discussed above carry an enhanced risk of about 30% rather than the 21% found by the California study. Most studies found a lower risk per unit alcohol intake than Allen *et al*, and it may be that Allen *et al* have overestimated the risk. On the other hand, there is the potential for considerable under and over estimation of alcohol intake since it is not measured and subjects may be poor judges of just how much they drink.

Thus it appears that studies consistently find a connection which implies that it is real, but the magnitude of the risk is unclear as is the consumption threshold for significant risk, and the absolute increase appears small.

POTENTIAL MECHANISM FOR ALCOHOL-RELATED CARDIOPROTECTION

A recently reported study has provided potential mechanistic evidence of how alcohol might be cardioprotective. This study examined the association of alcohol consumption with the enhancement of the long-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in plasma and red blood cells.[18] For women, a fully adjusted multivariate analysis found that alcohol was positively associated with both plasma levels of EPA and DHA and as well, the EPA + DHA index (level) in red blood cells. Plasma and red blood cell levels of these so-called marine omega-3 fatty acids present in oily fish and fish oil have been found to be inversely associated with the risk of sudden cardiac death and one measure being recommended to measure risk is the EPA + DHA index which relates to the concentration of these two fatty acids in red blood cells. For men, only plasma and red blood cell levels of EPA were positively associated with alcohol intake. The authors comment that components of wine other than alcohol (such as polyphenols) might be involved in the elevation of plasma and red blood cell levels of the marine omega-3 fatty acids.

ALCOHOL CONSUMPTION AND HEART FAILURE

Data from the Physician's Health Study has recently been analyzed to examine the question of an association between alcohol consumption and heart failure among hypertensive U.S. male physicians.[19] The average age was 58 years and the subjects were free of stroke, heart attack or major cancers at baseline. Alcohol consumption was determined at baseline and repeated at the 84-month follow-up. The average follow-up was 18 years. Compared to subjects consuming < 1 drink per week, consumption of 1-4, 5-7 and ≥ 8 drinks per week afforded risk reductions of 11%, 28% and 62% respectively in heart failure in this group. The authors point out that this is the first study to report a beneficial association between light to moderate drinking and the risk of heart failure among hypertensive males.

The authors cite earlier reports of the beneficial effect of moderate alcohol consumption on heart failure risk factors. These include increased HDL, improved insulin sensitivity, lower risk of type 2 diabetes, decreased inflammatory markers, and increased plasma adiponectin, a substance shown to attenuate cardiac hypertrophy in response to pressure overload. Also, alcohol consumption has a diuretic effect.

ASSOCIATION BETWEEN VITAMIN D AND INFLUENZA CONFIRMED

In the April 2008 Newsletter a paper by Cannell *et al*[20] was reviewed which attempted to explain the seasonal variation of influenza, the mirror image of seasonal incidence in the southern hemisphere, and the absence of seasonal variation at latitudes close to the equator as an indication of a connection with sunlight generated vitamin D levels. Now a group of investigators have used the Third National Health and Nutrition Examination Survey database and examined the association between 25-hydroxyvitamin D (25(OH)D) blood levels and upper respiratory tract infections (URTI). Records of almost 19,000 participants 12 years and older were searched. Compared to individuals with 25(OH)D ≥ 30 ng/mL, those with levels < 10 ng/mL and between 10 and <30 ng/mL had increased risk of URTIs of 24% and 36%. For individuals with asthma or chronic obstructive pulmonary disease, those with low vitamin D levels were at much higher risk. Individuals with asthma and 25(OH)D levels < 10 were at 5.67 times the risk of URTIs compared to those with levels ≥ 30 ng/mL and the same comparison for those with chronic obstructive pulmonary disease had a 2.26 times enhanced risk.

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RESEARCH REVIEW

BLOOD LIPIDS AND RISK OF DEVELOPING CORONARY ARTERY DISEASE

SOME INCONVENIENT QUESTIONS

William R. Ware, Ph.D.

In so far as a scientific statement speaks about reality, it must be falsifiable, and in so far as it is not falsifiable, it does not speak about reality. Karl Popper.

INTRODUCTION

In the context of coronary artery disease (CAD) and in particular atherosclerosis, blood lipids and total cholesterol and LDL cholesterol in particular, have over the years achieved a near dominant position, and what was merely a hypothesis has progressed to a universally accepted truth on a par with the laws of Newton or thermodynamics. A corollary to this hypothesis is that LDL levels are directly related to the risk of developing atherosclerosis and its progression. But as Karl Popper pointed out, hypotheses are made to be falsified, scientific progress requires efforts in this direction and as well requires the recognition rather than the out-of-hand rejection or disregard of results that provide grounds for falsification. The hypothesis that total or LDL cholesterol is associated in general with the incidence or progression of atherosclerosis has over the years been confronted with a large number of inconvenient questions that relate to results which appear to provide

falsification. What is important is that the failure to recognize these inconvenient questions or reject or ignore them has significantly delayed progress in developing alternative hypotheses, this to the detriment of patients and preventive medicine in this critical area.

In a debate on lipid lowering published in 2008 in the journal C*irculation,*[1] Scott Grundy, a strong advocate of the cholesterol hypothesis and lipid lowering, called LDL the *driving force of atherosclerosis.* He first cites animal studies using as a reference a paper that provided justification for the 2002 National Cholesterol Education Program guidelines. If one looks at that paper for the animal studies, the rabbit is the poster child, but as critics have repeatedly pointed out in the literature and in books dealing with the cholesterol hypothesis, rabbits are rather different than humans in that they evolved to eat quite different diets, and they never ate cholesterol except when forced to in studies trying to tie cholesterol to atherosclerosis. This 2002 paper also points out that animals that do not develop atherosclerosis generally have LDL below 80 mg/dL, but no reference is given. But animals that have recently been held up as examples include elephants and rhinoceroses. Next, Grundy claims that epidemiological studies reveal a strong association between serum cholesterol levels and the prevalence of atherosclerotic cardiovascular disease. The one reference is to a paper published in 1994 by Law *et al* which deals with the relationship between total cholesterol levels, not LDL, and either fatal or non-fatal heart attacks. Some of the studies used by Law *et al* were not in fact epidemiological but clinical trials from the pre-statin era and used fibrates, niacin or both, but this therapy mainly addresses so-called atherogenic dyslipidemia, i.e. low HDL, high triglycerides, and the subclass of small atherogenic LDL particles. It is hard to see that while these drug regimes reduced the rate of events, this demonstrates that LDL cholesterol drives atherosclerosis when fibrates are now looked upon as one of the drugs of choice for raising HDL and lowering triglycerides. Even the broad generalization generated by the meta-analysis of Law *et al* seems inconsistent with a large body of literature concerning individuals who have no symptoms of heart disease. There now appears to be only a weak relationship between cholesterol and the risk of adverse coronary events in this category, and only for young men, and even this may be confounded by exaggerated hypertensive response to anger.[2] In addition, epidemiological studies, which in the Law *et al* analysis, represented the vast majority of subjects, do not establish causality, a point made dozens of time each year in the medical literature. Yet the verb “drives” used by Grundy implies causality. The inadequacy of looking at acute events in order to judge the importance of cholesterol in the incidence and progression of atherosclerosis will be discussed below.

What is more important, Grundy is ignoring a vast body of literature covering several decades up to the present, that looked *directly* at the presence of atherosclerosis and its progression as a function of LDL or total cholesterol levels, i.e. the real question. As will be discussed, this literature contradicts the assertion that LDL is the driving force of atherosclerosis. Grundy also uses the lipid lowering argument. Problems with this argument are also discussed below. Nevertheless, paper after paper takes the same position as does Grundy and treats as an established fact that serum cholesterol drives atherosclerosis. The same message is delivered in TV ads.

Of particular significance has been the huge impact on the cholesterol-atherosclerosis hypothesis of the results of lipid lowering drug therapy on the risk of adverse events in individuals with established CHD. These results have been widely accepted as an absolute proof that there is a causative relationship to serum lipids and that this can be extrapolated to those who have not experienced an adverse CHD event, and to both genders and all ages including children as young as 8 years. This is in spite of the fact that it is acknowledged that the drugs in question exhibit non-lipid lowering (pleiotropic) effects which would be consistent with the treatment results without evoking lipid lowering in the mechanism, and that the pleiotropic mechanisms probably depend on the stage of acute coronary heart disease present.[3] After all, beneficial results are sometimes seen in a few weeks, and even the most ardent believer in the cholesterol-atherosclerosis hypothesis and its “proof” through lipid lowering cannot attribute these rapid results to lipid lowering effects. These pleiotropic effects of statin drugs are currently the subject of a considerable research effort worldwide.

The “lowering’ paradigm appears fundamentally flawed by virtue of the complexity of human biochemistry and microbiology and the inadequate understanding of this chemistry and microbiology when measured against what needs to be understood. To assert unequivocally and with absolute certainty that the introduction of a foreign chemical substance (e.g. a manmade drug) that is known to affect a certain pathway or process, does not also affect numerous other unrecognized processes and pathways requires understanding and knowledge that is not there and may never be there. To assume that one knows all that is necessary to make a causal connection by

using a drug to lower some marker or substance appears to be a manifestation of unjustified arrogance. To quote Karl Popper again, "*Our knowledge can only be finite, while our ignorance must necessarily be infinite."*

This review will examine some important inconvenient questions in order to attempt to put the above-described problem in a more proper perspective. It is offered as an antidote to the constant barrage of statements in the medical literature, popular health magazines and TV ads for statin drugs, all of which assume the cholesterol-atherosclerosis hypothesis constitutes a fundamental truth. Believers in this hypothesis should find these questions inconvenient if not downright disturbing. The focus will be on the hypothesis that serum total cholesterol and LDL cholesterol are associated with the risk of developing coronary atherosclerosis and its progression The relationship to the risk of adverse events such a myocardial infarct or severe angina requiring emergency attention are regarded as a separate issue. That is, incidence and progression are to be considered as the primary issue, not events. The mechanisms, to the extent they are understood, appear different for initiation of atherosclerosis, its progression, and subsequent occurrence or recurrence of acute events. However, some studies of the presence or extent of coronary atherosclerosis, prompted by symptomatic indications of the presence of CAD, also provide insight. Fundamental to this discussion is the assumption that the development of coronary plaque is involved in the progression from being free of the risk of CAD to having risk, with the greater the extent of the plaque burden, the greater the risk of adverse aspects of this disease. There now appears to be general agreement about this.

INCONVENIENT QUESTIONS

The principal questions relate to the correlation of the extent of atherosclerosis and circulating cholesterol, especially total cholesterol (TC) and LDL cholesterol. These questions already surfaced many years ago and prompted a number of autopsy studies, an obvious approach. Questions have multiplied significantly with the advent of electron beam tomography (EBT) used to measure coronary plaque calcification, contrast enhanced CT which allows visualization of all plaque, and the widespread use of various other types of angiography which has also allowed the extent of CAD to be examined in the context of risk factors such as lipid levels. Thus the following inconvenient questions.

- Why do autopsy studies of the correlation between the extent of coronary atherosclerosis and serum cholesterol yield null results? The answer that the blood samples, mostly from accident or suicide victims, were obtained too long after death has been discredited by several studies. There appears to be no reason to suspect that these studies were carried out either incompetently and with selection bias.[4]
- Why did Hecht *et al*[5] find that TC, LDL, and HDL did not correlate with either the extent or prematurely of calcified plaque burden in 1105 consecutive, asymptomatic individuals self-referred for EBT?
- Why did Hecht *et al*[6] fail to find a correlation between LDL and the coronary calcium percentile (correlation coefficient 0.06 with a scatter plot showing no visible correlation) for 304 asymptomatic women?
- Why when type 2 diabetics without evidence of coronary heart disease were subjected to EBT, did Elkeles *et* al[7] find that the progression of coronary calcium was not related to lipid risk factors in the PREDICT study?
- Why when 1653 men and women without a history of CHD were subjected to coronary CT angiography using contrast media did Johnson *et al*[8] fail to find a correlation between total plaque burden (calcified and non-calcified) and total serum cholesterol, a result the authors indicate agreed with other studies? This result was apparently adjusted for statin use. This study, since it looked at total plaque, in fact removes a potential criticism of those studies listed above that the calcified plaque burden is only a fraction of the total burden. Also it was recently shown that 70% of individuals with zero calcium score had no plaque when examined by coronary CT angiography.[9]
- Why in a study by Kim *et al*[10] of 544 Korean men and women considered at low risk for CAD who underwent coronary angiography was the apolipoprotein ratio Apo B/Apo A-1 the only variable that differentiated patients with from those without CAD when the criterion for having CAD was ≥ 50% stenosis in at least one coronary artery?
- Why in a study by Horimoto *et al*[11] involving 437 patients who underwent coronary angiography for suspected CAD, did a multivariate analysis find that only the Apo B/Apo A-1 ratio, among lipid parameters, was an independent predictor of coronary atherosclerosis?

- Given the last two questions, why was "no clinically useful relationship" found between LDL and plasma Apo B, the apparently "bad" apolipoprotein, and that none of the traditional lipids added significant predictive information to the Apo B/Apo A-1 ratio in the context of cardiovascular risk?[12]
- Why in a study of 182 men undergoing diagnostic coronary angiography motivated by chest pain syndromes or abnormal stress test results, was the degree of CAD related only to age, HDL and free testosterone? Why in addition, when the group was divided into two groups, those with and without conventional risk factors which included hypercholesterolemia, was the degree of CAD essentially the same in both groups and the increase of CAD with age not augmented by these risk factors?[13]
- Why in a study of type 2 diabetics using EBT to determine the extent of atherosclerosis, was the risk of a first CVD event strongly dependent on the calcium score, but the calcium score was independent of serum lipids over the full range of calcium scores (Agatston) from 0 to 10,000.[14] A score above 400 reflects a high plaque burden.
- Why is coronary calcium progression "*primarily related to baseline severity of coronary calcification with little relationship to standard cardiovascular factors or to modification of LDL cholesterol levels?*"[15] If one examines a large number of relevant EBT studies, among the standard risk factors, association of progression of atherosclerosis with total cholesterol or LDL is either nonexistent, very weak, or statistically insignificant. The few studies that show a significant association are thus inconsistent with the main body of evidence, suggesting no real association at all. HDL is frequently the only form of cholesterol with a significant association, but the results again are inconsistent.
- How does one explain the apparent paradox that if circulating cholesterol is a significant risk factor for the development and progression of atherosclerosis, even in young adults, cholesterol is also the only raw material for the endogenous synthesis of a variety of essential hormones? It is odd that this could happen during the evolution of our species?
- If circulating cholesterol is so dangerous, why does one find that once individuals with familial hypercholesterolemia (FH) approach middle age, they have life expectancies which converge on that found in the general population in spite of prolonged exposure to highly elevated total and LDL cholesterol?[4] Furthermore, why when comparisons are made between those with FH who have cardiovascular disease (CVD) and those who do not, the most common result after correcting for confounding, is that there are no statistically significant differenced between the levels of total cholesterols and LDL in those with and without CVD, in spite of these individuals all having very high levels of both lipids.[16] Why for individuals with FH, did Jensen *et al*[17] find that age-adjusted coronary calcium scores were not associated with cholesterol as assessed by either plotting or correlation coefficients and that when those with and without coronary heart disease were compared, there was no significant difference in total untreated cholesterol? Finally, as Awan *et al* pointed out in 2008, the lack of correlation between total cholesterol and aortic calcium scores in FH patients raises the concern that the vascular calcification may progress independent of marked decrease in total and LDL cholesterol levels.[18] FH is a complex disorder and its introduction into the cholesterol-atherosclerosis debate in the context of the general population is highly debatable.

DISCUSSION

These questions provide pieces or sets of evidence that, unless discredited or explained away in a satisfactory manner, falsify or seriously undermine the hypothesis that total or LDL cholesterol is associated with the development or progression of atherosclerosis. It does not suffice to present studies that reach a different conclusion—that simply indicates that the hypothesis rests on inconsistent evidence. Nor do studies which find that statins lower the progression of atherosclerosis help resolve the problem being discussed, since these studies suffer from the same potential confounding by pleiotropic effects discussed above. These studies also suffer from being inconsistent. For example, two primary prevention trials showing no effect on progression,[19,20] suggesting the overall benefit is nil. Similar null results were obtained in a randomized placebo controlled clinical trial with intensive statin treatment where reducing systemic inflammation and halving LDL had no major effect of the rate of progression of coronary artery calcification in a group with calcific aortic stenosis and coronary artery calcification.[21]

Since it appears that there is considerable direct evidence that the total cholesterol or LDL serum levels are not associated with the development or progression of atherosclerosis, drugs that lower the levels and impact some measure of the extent or progression of atherosclerosis presumably are operating by a non-lipid lowering

mechanism, and what ever it might be, it may not be the optimum approach. There is also the question of how progression is measured, since serious questions have been raised regarding the concordance of ultrasonic measurements on the carotid arteries and the extent of atherosclerosis in the coronary arteries.[22] Using measures of atherosclerosis in the carotid arteries as a surrogate for coronary atherosclerosis is and has been popular as an endpoint in lipid lowering studies.

The inconvenient questions must be answered since they concern falsification, which is the tool of scientific progress. To ignore this situation simply delays a potentially more effective approach to the primary prevention of atherosclerosis and thus coronary heart disease, but also results in millions of individuals taking drugs for life on the basis of what may be a false hypothesis. This point is underscored by recent studies which find that significant numbers of patients are taking lipid lowering drugs based on current assessment protocols but have zero or near zero risk based on measured total or calcified plaque burden.[4,8,10,12]

Finally, there is the inconvenient result of a recent study which found that more than 50% of patients admitted to hospital for an adverse coronary event had low to very low levels of LDL, in spite of the central position LDL occupies in the assessment of risk. The mean level of LDL was only 104.9 mg/dL and almost half had admission levels of < 100 mg/dL.[23]

The probability that the cholesterol-atherosclerosis hypothesis is false appears high enough to justify a new approach to risk assessment and a focus on other risk factors which do not appear to have a history of constant challenges. These include smoking, hypertension, the metabolic syndrome and its associated insulin resistance, inflammation and dyslipidemia (high triglycerides and low HDL), a low vitamin D status, a low omega-3 index, and psychological stress.[4] Furthermore, there is a need to clarify the different approaches that are appropriate for the prevention of the incidence and progression of atherosclerosis, the primary prevention of CVD events such as heart attacks or the emergency need for revascularization, and secondary prevention after these adverse events have occurred. Too often these are all bunched together under the heading of preventing heart disease. But the physiological aspects are presumably quite different. In addition, the above discussion calls into question the “truth in advertising” aspect of TV ads that imply elevated serum cholesterol is causing plaque to grow and that the problem is easily solved with a pill. Finally, there is need to give greater recognition to the differences between men and women and the young and the elderly. This is highlighted by the compelling data indicating that in general, women do not benefit at all from lipid lowering for primary prevention and that other approaches need to be emphasized.[24,25] The time has come, it would seem, for those concerned with preventing coronary heart disease to stop barking up the wrong tree.

If one looks at the coronary calcification literature for guidance as to what to do to reduce the progression of atherosclerosis, which amounts to preventing symptomatic coronary heart disease, it is surprising what little guidance is forthcoming. Many studies have looked at TC, LDL, HDL, TGs, hypertension, BMI, smoking, diabetes, family history of CHD, and other less common factors. In general, either no factor turns out to consistently have significance, and if a factor is found to be predictive in one or two studies, other studies do not confirm its significance. Those that turn up most often are HDL, TGs, hypertension, diabetes and smoking, but there are as many or more studies find no association even with these factors than find a statistically significant link. That is, a very inconsistent picture emerges when the endpoint is the incidence or progression of coronary calcification and one tries to find risk factors that are consistently important. This level of inconsistency over a large number of studies suggests that researchers are looking at the wrong set of factors. Even when the factors are assembled, such as done in the Framingham risk score, the results are suggestive but far from definitive and again inconsistent. Even studies of the association between coronary calcification and C-reactive protein are inconsistent.

CONCLUSIONS

Thus there is considerable evidence available that appears to falsify the cholesterol-atherosclerosis hypothesis. Furthermore, measurement of the extent of atherosclerosis can lead to a better assessment of risk and prompt preventive action, research so far has failed to produce evidence-based guidance regarding the prevention of this disease, and especially prevention prompted by traditional CHD risk factors. One it seems is forced to go back to the broader generalizations regarding the prevention of heart disease. These involve lifestyle, weight control, the type of diet consumed, psychological stress, systemic inflammation, etc. While these more general

actions impact the risk factors that are discussed above, it may well be that a more global view is necessary which does not isolate one or two risk factors, but instead attempts to optimize all of them through a broad approach to coronary artery health. This conclusion suggests the folly of the focus on LDL. Lifestyle and dietary interventions generally do not work when LDL target levels are used to judge success, and the net result is pharmaceutical intervention. In addition, there are other risk factors that are not generally included in the above-discussed studies which may be important. This leads one back to observational studies which have consistently indicated that the risk of heart disease and diabetes can be dramatically reduced by diet and lifestyle changes. But one must be careful to whom one listens in regard to diet. This will be the subject of future research reviews. In this global approach, one is concerned with eating a prudent diet, exercising regularly, bringing weight to a value corresponding to young adulthood (before the childhood obesity epidemic), making sure that the problem of belly fat is solved if it exists, and avoiding smoking or second-hand smoke. The reader is referred to the Research Review in the July/August 2008 newsletter for a more detailed discussion of global approaches to prevention of heart disease and diabetes. The big mistake is to think that if this does not work after a few months, a cholesterol-lowering pill will. One should keep in mind the results of lipid lowering trials where for women with no evidence of heart disease, there is no statistically significant effect on the probability of adverse events, and for men with no evidence of heart disease, the benefit is small, the absolute risk reductions border on negligible, and the number needed to treat to prevent on adverse event is large. Furthermore, as has been discussed above, there is a large body of evidence to justify the view that LDL cholesterol does *not* drive atherosclerosis.

The decision to agree to take statin drugs for primary prevention should depend on weighing risks and benefits. The benefits judged by *absolute* risk reductions range from small to insignificant, especially in the primary prevention setting. This has been repeatedly pointed out in the literature but ignored in favour of the larger relative risk reductions. The central and very serious problem is that the risks can be viewed as unknown since the acknowledged numbers depend on official reporting which is widely described as picking up only a few percent of cases. It in fact appears that the side effect frequency and severity are substantially underappreciated. This is a serious problem when one considers that the guidelines based on the new JUPITER study discussed in the last Newsletter could lead to 80% of all U.S. men > 50 and women > 60 years of age being considered appropriate candidates for statin therapy (the heart.org, March 9, 2009).

The reader is referred to http://www.spacedoc.net which seems like one of the best sites for keeping up with the rapidly growing list of serious if not devastating statin side effects. This is the website of Dr. Duane Graveline, a retired NASA physician and astronaut with a masters in public health along with his MD. He has a free newsletter and has written two books on statin side effects and is about to come out with a third. He has personal experience with severe and progressing problems he attributes to statins and operates a clearinghouse for anecdotal reports. Dr. Graveline would appear to agree with the thesis of this review since in the newsletter describing his new book *The Statin Damage Crisis*" he states "Cholesterol level appears irrelevant to the process of atherosclerosis"

NOTE: The quotes attributed to the Austrian-British philosopher Karl Popper (1902-1994) were obtained from Internet sources.

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