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William R. Ware, PhD - Editor

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One of the most common notions in medicine and medical and pharmacological research is that when some marker, frequently easily measured from a blood sample, is low or high, and this correlates with some disorder, then the first-choice therapy or intervention is to manipulate this marker, almost always with a drug. The drug generally accomplishes its task by interfering with one or more biochemical paths or processes and those successfully brought to market do indeed reduce or elevate the marker. In some cases this is taken as evidence that the circulating marker is directly related to the etiology of the disorder. Modify the concentration of this marker in the circulation and the risk will decrease or disappear. The problem, of course, is that this whole approach is simplistic in the extreme. The marker may only be a surrogate. The drug may have a number of effects and while one is the reduction or elevation of the marker, this may not get to the central problem associated with the disorder while the drug intervention may cause great problems because of multiple disruptions in various pathways and processes. Thus we have the active and important fields of drug pleiotropic effects and adverse side effects. Statin drugs are a good example where the benefits may derive almost entirely from pleiotropic effects and the simplistic "post hoc, ergo propter hoc" argument is easily shown to be false. The independence of cholesterol levels and the extent and progression of atherosclerosis presents a good example.

Drugs that raise or lower markers have not turned out to be magic bullets, whereas insulin and antibiotics come close to meeting the definition with numbers needed to treat (NNT) to produce one beneficial result approaching one. But when the NNT becomes large, e.g. 75 or 150 or 300, such low absolute benefit becomes of much less interest to the individual patient and merely provides input data for public health calculations and screening justifications where a very small absolute benefit is applied to huge populations with the result that thousands or even millions of individuals are viewed as benefiting. To make matters worse, the small benefits may be close to statistically insignificant as well as clinically insignificant. Such public health calculations rarely take into account side effects or the impact on quality of life. Furthermore, finding that for some serum markers the risk of an adverse event increases by some amount per increase in one unit of concentration does not imply an equivalent risk reduction if the concentration is decreased by one unit. But this argument is constantly used. Among other things, it disregards the fact that the risk being measured may be partly associated with permanent damage which is poorly reversible. It also ignores the potential for the pharmaceutical intervention to cause more harm than good by messing up a variety of important biochemical processes unrelated to the proposed disorder risk reduction. This phenomenon is seen repeatedly on pharmaceutical ads on TV where one cannot help be amazed at the wide variety of human systems that can be adversely influenced while merely attempting to improve, for example, platelet function, erectile function or decrease heartburn. Examining the package inserts would yield even more amazing insight. As discussed in this issue, lowering glucose levels with pharmaceuticals in type 2 diabetics provides another example.

Other research reviewed includes issues with coffee and cancer, chronic fatigue syndrome, the amazing infant mortality rate in the U.S., zinc as a preventive and therapy for the common cold, heavy use of acetaminophen and blood related cancers, gastric bleeding from aspirin plus pain killers or anti-platelet agents, and finally, some new results on the long-chain omega-3 fatty acids found in fish and the treatment of depression.

In addition, a short list of suggested summer reading is included.

Have a safe and healthy summer. The next issue will appear in September.

William R. Ware, PhD, Editor

Highlights

DOES INTENSIVE GLUCOSE CONTROL IN TYPE 2 DIABETICS MAKE SENSE?

The most entrenched conflict of interest in medicine is a disinclination to reverse a previous opinion. John S. Yudkin, Bernd Richter and Edwin Gale.[1]

Both type 2 diabetes patients and those who provide treatment have been under pressure for some time to attempt to achieve low target HbA1c levels (glycated hemoglobin, a long-term measure of glucose control) through medication plus other interventions. Typical target HbA1c values are < 6.0% to < 6.5% which is termed intensive or tight glucose control. Guidelines suggest as goals levels between 6.5% and 7%. The key intervention generally involves more than one glucose lowering drug and, if indicated, insulin.

There is considerable evidence that values over 8% to 9% correspond to a threshold for the risk of microvascular complications common in patients with long-term diabetes. Also, mortality increases substantially in those with HbA1Cc levels over 8-9%. However, added benefits of an HbA1c of 7% against 8%-9% diminish with age and shorter life expectancy and suggest the merits of focusing on those with higher levels which are common among type 2 diabetics. The morbidity and mortality from cardiovascular disease associated with diabetes greatly outweighs the risk of microvascular complication (kidney disease, vision problems, etc.) The issue here relates to the benefits, costs and risk of lowering HbA1c levels from about 8%, a relatively realistic target, to 7% or below in individuals with type 2 diabetes, mainly trough the use of drugs.

Since 1998, there have been five clinical trials involving a total of almost 29,000 patients. As the results of these trials are reviewed, there has recently been a flurry of editorials, commentaries and letters to the editor which have taken the position that the benefits of intensive glucose control through drug intervention are very small, the numbers needed to treat (NNT) to prevent one event very large, and thus the evidence of benefit very weak. For example, based on a meta-analysis the NNT for 5 years to prevent coronary heart disease with intensive glucose lowering is about 140, stroke 768 and cardiovascular disease in general 119. The NNT for microvascular complications such as blindness in one eye, kidney problems, all cause mortality, and cardiovascular mortality range from 272 to 627.[2] These are very large numbers. Some conservative clinicians are uncomfortable with NNTs of 25 or 50!

Risk vs. benefit is of course a major component of the bottom line. For intensified glucose control, the drug therapies are associated with weight gain, heart failure, osteopenic fractures, and hypoglycaemia and increased risk of future dementia.[2] Results from studies of the impact of the treatment on the quality of life range from small[3] to a decrease by one-third.[2] Drug costs are far from insignificant. It is also important to focus on absolute risk reductions rather than relative risk reductions. The NNT neatly expresses the absolute risk reduction benefit.

Finally, to muddy the waters a bit, a recent study looked at the impact of intensified glucose control on the progression of cognitive impairment in type 2 diabetics. The study found that subjects with type 2 diabetes had a type of cognitive impairment typical of subjects with type 1 diabetes. Intensive therapy

resulted in cognitive improvement not shown by regular treatment, suggesting that the negative impact of type 2 diabetes on cognition may be to some extent reversible by means of glycemic control.[4]

An interesting aspect of this whole controversy is the focus on a drug-based approach. Are drug side effects, known or unknown, interfering with the presumed benefits of lower circulating glucose levels? As has been discussed repeatedly in this Newsletter, there are dietary alternatives that have been shown to reduce HbA1c levels to 6% or lower. These involve very restricted carbohydrate diets with the carbohydrates selected on the basis of personal glycemic reactions. While it is easy design and finance large drug intervention trials, the issues addressed in these trials will probably never be addressed in trials of carbohydrate restriction, especially given the large number of subjects needed for statistically significant results for the endpoints in question and the quite considerable compliance issues always present in studies involving long-term dietary interventions that depart drastically from the diets most individuals prefer. The overwhelming emphasis on drug interventions is in fact probably the only realistic approach in the context of public health, but for any given individual, the non-drug alternative appears to be an option well worth considering.[5]

COFFEE AND CANCER

The results of a study conducted by Harvard School of Public Health scientists concerning coffee consumption and prostate cancer has just appeared.[6] The study was part of the long and ongoing Health Professionals Follow-up Study and involved almost 48,000 men with baseline data collected in 1986 and updated every 4 years thereafter. From 1986 to 2006, 5035 prostate cancer cases were identified, including 642 patients with lethal prostate cancer, defined as metastatic or fatal. The results from this study are particularly interesting since prostate cancer is not one of the malignancies generally associated with risk reduction or enhancement from coffee consumption. Furthermore it calls attention to the more general issue of coffee and cancer. Is there risk, benefit, or no effect at all?

In this large, prospective study, coffee consumption was only weakly associated with overall risk of developing prostate cancer. Men consuming six or more cups of coffee per day had a lower adjusted relative risk of prostate cancer compared to non-drinkers of 0.82 but the association was much stronger for the subset with lethal cancer where consumption of six or more cups a day resulted in a 60% risk reduction. Both results were statistically significant. However, coffee consumption was not associated with the risk of non-advanced cancer or low-grade cancers and was only weakly associated with the risk of high-grade cancers. When significant risk reduction was observed, it was independent of the caffeine content of the coffee and thus appears to be related to non-caffeine components such as antioxidants, and compounds which inhibit glucose absorption in the intestine, slow tumor progression or influence sex hormone levels.

Concerning the general question of coffee and cancer, there is a substantial body of epidemiologic literature consisting of over 500 papers including numerous meta-analyses. The following picture emerges. For liver and endometrial cancers, there is strong and consistent evidence of a protective association. For colorectal cancer, coffee is only borderline protective. There appears to be no association with pancreatic, breast, kidney, ovarian or gastric cancer. Heavy coffee consumption appears to increase the risk of bladder cancer among some populations and in particular among men. Also, there is some suggestion of a connection between high levels of coffee consumption during pregnancy and childhood leukemia.[7]

One of the issues with studies on coffee is that there are different methods of brewing and in particular, the two common ones are filtering and boiling. For some cancer sites boiled coffee is protective, in others it is the filtered type. However, in almost all studies stratified by brewing technique, the results are not statistically significant and inconsistencies appear when one compares the results for total coffee consumption with the results stratified by the two distinct brewing methods.[8]

IS CHRONIC FATIGUE SYNDROME CAUSED BY A VIRUS?

Chronic fatigue syndrome (CFS) is a disorder characterized by severe, persistent and unexplained debilitating fatigue. Commonly used definitions require at least 6 months of persistent or relapsing fatigue that substantially reduces social, occupational, education or personal activities and is not significantly alleviated by ordinary rest. In addition, some definitions require 4 or more of the following symptoms to also be present over this period: impaired memory or concentration, sore throat, tender lymph nodes, muscle pain, pain in several joints, new onset headache, unrefreshing sleep or malaise after exertion. However, there is disagreement concerning definitions and whether in fact the illness really exists.[9] It is estimated that, depending on the definition, between 0.01% and 3% of the US population suffers from this disorder. While the cause remains unknown, infectious agents and environmental toxins have been suggested. Other proposed causes include genetic factors, brain anomalies, hyper-reactive immune system, and psychological or emotional conditions. But there appears to be no strong evidence pointing in any direction, and there is no proven cure for CFS nor have any drugs been specifically developed to treat this disorder. Thus patients with CFS have a serious problem concerning effective treatment. The current approach involves some combination of diet, antidepressant drugs, cognitive-behavioral therapy, graded exercise programs and sleep management therapy.

In 2009 two studies appeared that linked a mouse retrovirus XMRV or other mouse leukemia virus-related viruses with chronic fatigue syndrome (CFS). The XMRV retrovirus had been originally found in prostate tumors but in one study turned up in blood samples of 67% of CFS patients vs. 4% of controls. While another group also detected this virus in CFS patient's blood, other teams have failed to confirm the connection. This is important, because the finding has prompted the off-label use of antiviral drugs on CFS patients. If this is not a viral disease, patients are being unnecessarily exposed to the risk of side effects associated with these drugs. In addition, the FDA, on the basis of sparse and conflicting evidence, has recommended that CFS patients be barred from donating blood. That there is a problem can also be seen in anecdotal evidence reflected in scores of blog posts from disappointed, unhappy patients who have received antiviral therapy.[10]

Three studies have just appeared which also fail to confirm the XMRV-CFS connection.[11-13] These new studies strongly suggest that the original findings were due to sample contamination. This was also the conclusion reached in four earlier studies and resulted in a news release early this year flatly stating that CFS was not caused by XMRV.[10] Those who thought this news release was a bit premature now have to consider the three additional studies which fail to find any viral connection. If a new multicenter study in the US goes ahead, it may provide definitive results. Some question whether it is worth the $1.3 million.[10] The corresponding author of the 2009 paper in *Science* which found XMRV in CSF patients has refused a request from the journal editors to retract the paper and the journal has issued an "Expression of Concern."[14]

Several of the authors of these negative studies call for the termination of the off-label use of antivirals for CFS patients since there is no evidence of benefit and the risk of serious harm. It needs to be emphasized that this particular field of research is difficult, highly complicated and easily confounded. In this case we see science working properly with a hypothesis advanced, tested and apparently falsified with little interference from vested interests. But as the authors of the latest study point out, there is considerable prior data to encourage further research into the involvement of other infectious agents in CFS and these efforts should continue.[13] But it is clear that there are probably a number of causes and that intensive research is called for regarding many potential mechanisms including a better understanding of the effects of overwork and/or stress on the human alarm signal to rest and the associated fatigue sensation.[15]

INFANT MORTALITY AND NUMBER OF VACCINE DOSES ROUTINELY GIVEN

Your editor has in general avoided the so-called vaccine controversy, its many aspects and its highly charged emotional content, but a paper by Miller and Goldman recently published in *Human and Experimental Toxicology* presents an amazing correlation between infant mortality rates (IMR) and the number of vaccine doses routinely given to children under the age of one in 34 nations.[16]

Infant (age < 1 year) mortality is generally expressed as the number of infant deaths per 1000 live births. A curious but well known fact is that among 34 developed nations, the US has the highest IMR (6.22) while at the low end Singapore, Sweden and Japan all have rates of less than 3 with the lowest being Singapore at 2.31. This is a huge range (a factor of almost 3); especially when one considers that the list includes countries such as France, Norway, Germany South Korea, Australia, Canada and Italy where most citizens enjoy adequate if not good housing, more or less clean water, and a good if not high standard of medical care and nutrition. It is interesting that developing nations also require vaccinations and have a high percentage of coverage and yet have IMRs that are very high. Gambia requires 22 doses during infancy, has a 91-97% coverage, and an IMR of 69. Mongolia requires the same number of doses, has a coverage rate of 95-98% and an IMR of 40. These examples, according to the authors appear to confirm that IMRs will remain high in nations that cannot provide clean water, proper nutrition, improved sanitation and better access to health care. But these are not issues in the countries involved in the following study.

The authors of this study obtained the IMR figures from the database of the US Central Intelligence Agency and compiled a list of 33 nations with better IMRs than the US. They then conducted a literature review to ascertain the standard of practice concerning immunization schedules in all 34 countries and identified the number of vaccines and the number of doses given to children under one year of age. Doses were determined by individual vaccines not the number of injections. All countries gave DTaP (diphtheria, tetanus and whooping cough) and polio vaccinations and all but 3 gave HIB (haemophilus influenza type B) vaccinations. In countries that used a larger number of vaccines, the most common additions were for pneumonia, hepatitis B, meningitis, flu and rotavirus. The range of doses (e.g. DTaP involves 3 doses per injection) was from 12 to 26. The researchers then formed 5 groups of nations according to the range of doses during the first year of life (12-14, 15-17, 18-20, 21-23, and 24-26. They then used the mean dose in each range and presented a plot of the mean IMR vs. mean vaccine doses. An almost perfect liner relationship was obtained with a correlation coefficient of 0.992, a correlation almost never seen outside the physical sciences. When the nations were not grouped, a linear correlation between IMR and dose was also observed with a correlation coefficient of 0.7. Such strong correlations are not easily dismissed.

The researchers then ask the obvious questions: is it possible that some nations are requiring too many vaccines over too short a period for infants and the additional vaccines are a toxic burden on their health? Are some deaths that are listed within the 130 infant mortality death categories commonly used really deaths associated with over-vaccination? Are some vaccine related deaths hidden in the death tables? These questions are of course at the heart of the vaccine controversy which is highly polarized with strong political overtones, intense conflicts of interest involving the vaccine producers, researchers and government agencies, and a highly organized and well-established conventional wisdom.

However, there is another issue. As the number of doses increases, so do the number of different vaccines. Thus, there are two potential avenues of inquiry. First, the high-dose children receive a much larger and ongoing challenge to their immune systems. But they also are challenged by a wider variety of vaccines, many of which carry distinct preservatives and contaminants. The data presented by Goldman and Miller is at the very least hypothesis-generating and needs to be

confirmed by an independent examination of the data and its sources. But the study will probably go unnoticed and ignored by vaccine researchers.

These results are thus presented for the reader to consider, but the pros and cons of the issues raised by the above questions will be not be discussed, partly because space limitations preclude an adequate analysis of what are in fact very complex issues. The paper by Miller and Goldman is available free online at the journal website (May 4, ahead of print). Interested readers will find a lengthy discussion of the possible connection between sudden infant death syndrome and vaccination.

Experts who believe the current guidelines are in the best interest of their young patients need to explain not only the amazing correlation observed in this research but also address the very high IMR in the US, a country which takes pride in its public health system and the acknowledged sophistication and quality of its medical care.

ZINC AND THE COMMON COLD

It has been recognized for over 4 decades that Zinc is an essential mineral and that deficiency results in growth retardation, hypogonadism, immune dysfunction and cognitive impairment. Zinc is an intracellular signalling atom in monocytes, dendritic cells and macrophages and plays an important role in cell-mediated immune functions and oxidative stress. It also is an anti-inflammatory agent.[17,18] Thus there has been considerable interest in the use of zinc to treat or prevent the common cold.[19] It is well known that zinc inhibits rhinoviral replication. Between 1984 and 2009 there have been 15 placebo-controlled, double-blind, randomized clinical trials of this use of zinc supplementation. The results were inconsistent and resulted in controversy.

Very recently, the Cochran Collaboration has conducted and published a review of studies concerning Zinc and the common cold.[20] They attempted to draw conclusion and pool results only for studies selected according to certain standards of design and quality. Briefly, their conclusions were as follows:

- The intake of zinc within 24 hours of the onset of symptoms is associated with a significant reduction in the severity and duration of common cold symptoms.
- There was a significant difference between control and zinc therapy groups when the endpoint was the proportion of participants symptomatic after seven days of treatment. In the treatment group there was a 55% reduction in this endpoint.
- The risk of developing a cold, school absence and prescriptions for antibiotics were lower in the zinc group as compared to controls.

The discussion in the Cochran Collaboration report and in other recent literature[19] indicates that the story is actually considerably more complex. The two common methods of zinc supplementation or therapy are lozenges and syrups. Zinc in its ionized form in aqueous solution is doubly positively charged and comes associated with negatively charged molecules (anions) to give a neutral compound. Zinc compounds used in studies include zinc gluconate, citrate, tartrate, carbonate, mannitol, sorbitol, glycinate, acetate, stearate, oleate, and palmitate. Only zinc acetate and gluconate appear to be effective with the acetate superior. George Eby has conducted extensive research and provides critical commentary concerning the optimum form of zinc in the context of cold treatment.[19] He found that the active form of zinc in this context is the ionic form, i.e. free doubly charged zinc atoms (zinc ions). But the break up of neutral zinc compounds into the constituent positively and negatively charges species depends on the nature of the anion and the acidity (pH) of the dissolving medium, tissues or tissue surfaces exposed to the lozenges or syrup. Eby presents strong evidence that not only is the free zinc ion the active agent but that zinc acetate should be the compound of choice when formulating either lozenges or syrup. He regards the failure of many zinc compounds to yield significant ionized zinc at physiological pH to seriously impact a number of clinical trials, explain inconsistent results, and as well he

provides evidence of a direct correlation between the concentration of ionized zinc and the reduction of cold duration. Only lozenges yielding high concentrations of ionized zinc are effective in providing dramatic cold duration reduction. He asserts that zinc lozenges slowly dissolving in the mouth over a 20-30 minute period releasing > 18 mg of ionized zinc can, when used every 2 hours, shorten common colds by 6-7 days. This more or less constitutes a cure. Eby cites research suggesting that short-term use of zinc lozenges (not containing magnesium) appears harmless. On the other hand, long-term use can induce copper deficiency with consequent immune suppression and the initiation or aggravation of neurological disorders.

The Cochran review also examined side effects and found that lozenges were more likely to produce them than syrups. Side effects included bad taste, nausea, diarrhoea, and dry mouth. In a commentary on the paper by Eby, Das and Singh, the authors of the Cochrane Collaboration study, note that side effects have an important impact on study outcomes since they influence compliance.[21]

Eby also discusses the use of magnesium throat lozenges, which are used for rescue treatment of adult allergy-induced asthma. He points out that they greatly lengthen and worsen common colds and chronic sinusitis by increasing rhinoviral release. Magnesium can overwhelm the anti-viral effectiveness of ionic zinc. However, these remarks apply only to lozenges, not ingested magnesium since, as he points out, ingestion does not increase the intra-nasal or intra-lung magnesium concentration beyond normal physiological levels.[19]

Popular multivitamins contain up to 7.5 mg of zinc per recommended daily dose. The U.S. RDA is 13-19 mg/day (children 1-3 and 4-8, 3 mg and 4-5 mg/day), but the use of lozenges releasing over 200 mg/day may cause problems for anything other than short-term therapy. A commonly cited threshold for adult zinc toxicity is > 150 mg/day, but this is only over an extended period. High doses of zinc for long periods of time decrease copper absorption which can inhibit iron transport and result in anemia.

ACETAMINOPHEN AND HEMATOLOGIC (BLOOD RELATED) CANCER

Studies have suggested the possibility of a positive association of over-the-counter analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) and hematologic malignancies, but the results have been inconsistent. A recent study just published online in *the Journal of Clinical Oncology* has addressed this issue in a large prospective cohort study with interesting and alarming results.[22] The investigators were from the Fred Hutchinson Cancer Research Center and the University of Washington in Seattle.

The study involved almost 65,000 men and women between the ages of 50 and 76 at baseline. Recruitment occurred from 2000 to 2002. Follow-up continued until December 2008. Participants were classified as non-users, low or high users. The latter two categories were defined as < 4 days/week or < 4 years and ≥ 4 days/week and > 4 years. Participants were asked about the use of low-dose or regular or extra strength aspirin, ibuprofen, naproxen, celecoxib, rofecoxib, piroxicam, indomethacin and acetaminophen. The statistical analysis included correction for confounding. The only drug that yielded a positive association with blood-related cancers was acetaminophen. For this drug, when hematologic malignancies taken together, there was an 85% increase in risk for high use. This positive association was seen for myeloid neoplasms (126% increase in risk), non-Hodgkin's lymphoma (81% increase in risk), and plasma cell disorders (142% increased risk). These results were all statistically significant. The association with total hematologic malignancies was greater among women than men; the reason was not identified. For the high users of acetaminophen, the incidence a hematologic malignancy cases during the study was 16/1000 compared to 8.3/1000 for non-users. There was no significant impact of acetaminophen on chronic lymphocytic leukemia or small cell lymphocytic lymphoma.

The authors comment on potential biologic mechanisms. These include the inhibition by acetaminophen of replicative DNA synthesis and DNA repair synthesis and increases in the frequency of chromosomal damage as seen in cell culture studies and in animal experiments. One of the metabolites of acetaminophen has been shown to cause extensive DNA single-strand breaks and to strongly enhance DNA cleavage in vitro. Another metabolite has been reported to be mutagenic and may not only induce single-strand breaks but also chromosomal aberrations. Animal studies suggest that this drug is genotoxic in vivo in bone marrow cells. It is interesting that this apparently never became a significant issue in the drug approval process. Epidemiologic studies have also reported that acetaminophen is positively associated with several types of kidney or other urinary system cancers.

These results may surprise some readers who regard acetaminophen as a safe, over-the-counter drug for the treatment of chronic pain, although overdoses among children are common and a leading reason for ER visits, and the interaction between acetaminophen and alcohol can be disastrous and even fatal. Unfortunately, as has been discussed several times in this Newsletter, the alternatives for the treatment of chronic pain are not problem free either, with risks associated with adverse cardiovascular events, gastric bleeding and, if one turns to narcotics, constipation and the risk of addiction.

RISK OF UPPER GASTROINTESTINAL BLEEDING BY ADDING ASPIRIN TO OTHER DRUGS

Antiplatelet therapy with low-dose aspirin (ASA) and clopidogrel (Plavix), either in combination or alone, is standard practice for secondary prevention of cardiovascular events. However, there is a serious issue with upper gastrointestinal (esophagus, stomach and duodenum) bleeding (UGIB) with this combination of drugs. A recent study has examined the risk of UGIB among users of low dose ASA and not only this drug but also other medications known to increase the risk of UGIB.[23] This study is of considerable interest because it covers a wide range of drugs that may be used with ASA, including drugs used for pain relief.

The results can be summarized as follows in terms of relative risk (RR) of UGIB. Traditional NSAIDs are for example ibuprofen and naproxen. In all cases, the added ASA was at low dose.

- ASA monotherapy vs. non-use. RR = 1.79
- Clopidogrel without ASA, vs. non-use, RR = 1.48. With ASA, RR = 3.71
- Oral anticoagulants without ASA vs. non-use, RR = 1.77. With ASA, RR = 3.62
- Low to medium dose NSAIDS without ASA vs. non-use, RR =2.03. With ASA, RR = 4.80
- High-dose NSAIDs without ASA vs. non-use, RR = 3.90. With ASA, RR + 4.86
- Traditional NSAIDs without ASA vs. non-use, RR =2.99. With ASA, RR = 4.74
- Coxibs without ASA vs. non-use, RR = 2.38, With ASA, RR = 5.83
- High-dose corticosteroids vs. non-use, RR = 1.89. With ASA, RR = 7.87

These numbers are interesting because the not only indicate the risk associated with a given drug, they also suggest a very large risk increase associated with adding low-dose ASA. With the exception of clopidogrel vs. non-use, all the RRs were statistically significant, and obviously very large.

The absolute risk, however, is not large. A RR of 3.7 translates into an excess risk of 1.4 to 2.7 cases annually among 1000 exposed persons. Nevertheless, these bleeds represent a serious and potentially urgent or even potentially fatal problem when they occur. The increased risk must be compared to the anticipated benefits and this study provides useful numbers for this purpose, both in the context of antiplatelet-anticoagulant therapy but also when ASA is added to analgesics.

OMEGA-3 FATTY ACIDS AND DEPRESSION

The use of omega-3 fatty acids to treat depression has been studied over a number of years with inconsistent results. In a recent review, Lin and Su list 10 double-blind, placebo controlled trials.[24] However, in all but one, patients were already taking mood stabilizers, antidepressants and even antipsychotics. Their meta-analyses failed to obtain statistically significant evidence favoring omega-3 treatment over placebos.

A new study has just reported which examined patients who were not on psychiatric drugs.[25] The subjects were female, between the age of 65 and 95, not obese, and had been in a nursing home for at least 3 months prior to enrolment. All subjects had been diagnosed by a senior psychiatrist as being depressed and met the criteria for major depression as set forth in the DSM-IV, the universal diagnostic manual. Exclusion criteria included the presence of current comorbid psychotic symptoms, current use of psychiatric drugs aside from benzodiazepines (e.g. valium), and the presence of psychotic symptoms. Forty-six patients were randomized to receive 2.5 g/day of long-chain omega-3 fatty acids (1.67g EPA, 0.83g of DHA) or a placebo. The two-month study had as the primary endpoint the improvement of depressive symptoms as evaluated by a standard measures. Secondary endpoints included modification of red blood cell fatty-acid profile (a test of compliance and bioavailability) and quality of life.

After 2 months only the omega-3 group showed significant lower depressive symptoms, significantly improved quality of life, and elevated red blood cell fatty acid levels. The researchers point out that lower concentrations of omega-3 fatty acids have been reported in both plasma and red blood cell membranes of patients with DSM-IV diagnosed major depressive disorders compared to matched non-depressed controls. They also emphasize that depression is not, in their view, a natural part of aging and is often reversible with prompt and appropriate treatment. They also point out that the improvement in quality of life found in the treatment group had never been achieved before and appears to be of great value from a clinical point of view due to the importance of increased satisfaction with a number of key quality of life aspects and a general improvement if the feeling of well-being. Treatment with 2.5 g/day of EPA/DHA was also free of side effects, which is not in general the case with antidepressant drugs. Incidentally, this would not be an unusual long-chain omega-3 fatty acid intake for individuals who take fish oil supplements.

http://www.yourhealthbase.com/vitamins.htm

SUGGESTED SUMMER READING

This year we again recommend some books for the lazy days of summer.

The Big Short. Inside the doomsday machine*,* by Michael Lewis (W. W. Norton & Company, New York, 2010). A spellbinding book concerning the meltdown of the US financial system in the 2008-2009 period. The insight provided by this book regarding the role in this disaster of the big brokerage houses, the bond rating agencies, and the hedge funds would be hard to obtain elsewhere.

13 Things That Don't Make Sense. The most baffling scientific mysteries of our time*,* by Michael Brooks (Anchor Canada—Random House, 2009). This book covers a wide spectrum of subjects including medical topics such as the placebo effect, the giant virus and death. A fascinating discussion of the many aspects of our world and ourselves that are not understood.

Deadly Spin. An insurance company insider speaks out on how corporate PR is killing health care and deceiving Americans, by Wendell Potter (Bloomsbury Press, New York, 2010). A highly acclaimed book by someone called "the ideal whistle-blower." Particularly relevant and timely as the health care debate heats up in the now divided US congress.

Hippocrates' Shadow, Secrets from the House of Medicine. What doctors don't know, don't tell you, and how truth can repair the patient-doctor breach**,** by Dr. David H. Newman, M.D. (Simon and Schuster, New York, 2008). The subtitle adequately introduces this entertaining and fascinating book. See the review in the October, 2008 issue of the Newsletter.

The World According to Monsanto. Pollution, corruption and the control of our food supply, by Marie-Monique Robin (The New Press, New York, 2010). This is a translation of Robin's book published in French in 2008. It documents the results of a remarkable three-year investigation across four continents by an award-winning journalist (Rachel Carson Prise, 2009) and provides insight into the inner workings of the agricultural products division of one of the world's largest and most controversial companies.

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