INTERNATIONAL HEALTH NEWS

Your Gateway to Better Health!

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The big news this month is the grand opening of my new web-based vitamin "store". I am often asked for my recommendations concerning supplements. I have probably tried hundreds of different ones and have now compiled a list of my favorites. I have searched the Internet for the best prices and speediest delivery of these high-quality supplements and have now reached an agreement with ***iHerb.com*** *to provide them to you.*

iHerb *is probably the most reputable supplement supplier on the Internet and has a sterling reputation for prompt delivery. They also provide FREE shipping within the US (except Alaska and Hawaii) on orders over $20.00. I highly recommend them.*

Most importantly, by purchasing your supplements through my web site you will be supporting my research and the upkeep of the site in a very tangible way since ***iHerb*** *has kindly agreed to give me a commission on all orders originating from my "store". They have also agreed to give you, the customer, a 20% discount on all orders. Just enter the word* ***ihn*** *in the coupon section before you finalize your order and you shall receive the 20% discount on already bargain prices. Truly a win/win arrangement!*

Also in my store are some leading edge, very cleverly formulated products from ***Xtend-Life*** *in New Zealand. Their "Total Balance" anti-aging formula contains pretty well all you need in the form of supplements and the enteric-coated capsules ensure the very best absorption. They are well worth a try and their delivery performance is excellent.*

You can find the "store" at www.yourhealthbase.com/vitamins.htm

Other major news in this issue includes the Vioxx fiasco ably covered in detail by William Ware, my comments on the recent article warning about the possible detrimental effects of supplementation with vitamin E, highlights of a new study linking prostate cancer to inflammation, and another item linking coffee drinking to inflammation. We also report on the benefits of plant sterols and folic acid, and on the serious repercussions of the burgeoning medical litigation industry. Lots to read!

Wishing you and your family a Happy Holiday Season and good health in the coming year,
Hans Larsen, Editor

December/January Highlights

Vitamin E studies and mortality

BALTIMORE, MARYLAND. A group of international researchers from Spain, the UK, Norway, and the Johns Hopkins School of Medicine in the US has just released a report claiming that high daily intakes of vitamin E increase all-cause mortality in patients with chronic diseases such as cardiovascular disease, Alzheimer's disease, and Parkinson's disease. The researchers combined the results of 19 vitamin E supplementation trials involving 135,967 mostly chronically ill patients aged 47 to 84 years. The vitamin E dosages ranged from 16.5 IU/day to 2000 IU/day overwhelmingly in the form of synthetic alpha-tocopherol. Over the follow-up period between 1993 and 2004, a total of 12,504 deaths from any cause (including traffic accidents and falls?) occurred among the 135,967 patients.

Although the researchers conclude that, "overall, vitamin E supplementation did not affect all-cause mortality", they do suggest that high doses of vitamin E (greater than 400 IU/day) are associated with an increased all-cause mortality. In the trials using supplement dosages higher than 400 IU/day they observed a 0.34% higher mortality in patients taking vitamin E than in those not doing so. On the other hand, in trials using vitamin E doses of 400 IU/day or less, there was a decrease in all-cause mortality of 0.33%.

The researchers caution that all the trials testing high dosage vitamin E involved patients with chronic diseases and that some trials involved other vitamins (notably beta-carotene) as well. They also point out that their results may not be applicable to healthy individuals. They speculate that their findings could be explained by a pro-oxidant activity of alpha-tocopherol, the displacement of gamma-tocopherol by alpha-tocopherol, or an increased risk of hemorrhagic stroke. The researchers conclude that supplementation with 400 IU/day or more of vitamin E should be discouraged.

Miller, ER, et al. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. **Annals of Internal Medicine** *www.annals.org November 10, 2004 (to be published in January 2005)*

Editor's comment: The primary purpose of this study would seem to be to discourage people from supplementing in order to protect their health and well-being. As I have, on numerous occasions, pointed out the primary benefit of antioxidant supplementation is to PREVENT disease. It seems that whenever the medico-pharmaceutical establishment wishes to discredit an antioxidant they totally ignore this basic fact and gleefully report that it does not stop seriously ill patients from dying.

All chronic diseases have a certain lag time before they become clinically manifest. Cardiovascular disease, breast cancer, prostate cancer, Alzheimer's disease, diabetes, etc. do not happen all of a sudden from one day to the next – they develop slowly over a long period of time (the latency period). What antioxidants do is that they prolong this latency period very significantly, in many cases, providing complete protection from disease during a person's lifetime.

I am much less convinced that the antioxidant property of vitamin C, vitamin E, etc. plays a major role in slowing down or reversing already serious manifest disease, although there is some indication that very large intravenous doses of vitamin C may be helpful in slowing the progression of certain cancers, and that large doses of vitamin E may help slow down Alzheimer's and Parkinson's disease.

So, should you continue to supplement with vitamin E to protect your health? – ABSOLUTELY!! Two very large studies involving over 100,000 female nurses and male health professionals found that supplementation with 100 IU/day or more of vitamin E is associated with a 40% reduction in the risk of developing heart disease. Vitamin E has also been found to protect against heart attacks (400 or 800 IU/day) and has been found helpful in preventing diabetes, cataracts, Alzheimer's disease, and several other conditions (see www.yourhealthbase.com/vitamin_E.htm)

Recent research has shown that it is important to take vitamin E as a combination of gamma- and alpha-tocopherol (about a 3:1 ratio) and with adjuvant amounts of other tocopherols and tocotrienols. In such a complete formulation 100 to 200 IU/day of alpha-tocopherol would likely be quite sufficient. Vitamin E should always be taken in combination with vitamin C, and preferably with alpha-lipoic acid and selenium as well in order to maximize its beneficial effect and prevent any pro-oxidant effect. The optimum daily intake for an individual depends on many factors, including the intake of polyunsaturated fatty acids and the degree of exposure to air pollution and toxic chemicals. Higher dosages may be indicated for women suffering from premenstrual or menopausal

problems, for smokers, for people engaging in heavy, outdoor exercise, and for people having a family history of cancer. A large intake of fish or fish oils has been shown to increase the requirement for vitamin E quite significantly.

There are some cases in which high dosages of vitamin E are contraindicated. Medical advice concerning dosages should be sought by individuals having high blood pressure, those taking anticoagulant drugs (Coumadin, warfarin) or having a tendency to prolonged bleeding, those having a vitamin K deficiency, and those suffering from rheumatic heart disease, an overactive thyroid or diabetes.

Inorganic iron (ferrous sulphate) destroys vitamin E and oral contraceptives deactivate it to some degree. So vitamin E should be taken with the main meal to optimize absorption and at least 6 hours before or after taking an iron supplement or a birth control pill. Vitamin E remains in the body for a long time, so it can be taken once a day or once every second day as convenient.

Plant sterols + exercise improve cholesterol profile

MONTREAL, CANADA. It is well known that regular exercise increases the blood level of beneficial HDL (high-density lipoprotein) cholesterol. There is now also substantial evidence that plant sterols reduce overall cholesterol level and, in particular, the level of LDL (low-density lipoprotein) cholesterol. Margarines incorporating plant sterols are available for use in the prevention of heart disease.

Researchers at McGill University now report that combining an increased intake of plant sterols with regular endurance exercise results in a much improved cholesterol profile with lower triglycerides, total cholesterol and LDL cholesterol, and a significant increase in HDL cholesterol. Their clinical trial involved 74 sedentary, non-smoking individuals between the ages of 40 and 70 years with an average total cholesterol level above 175 (4.5 mmol/L) and no heart disease or diabetes. The participants were randomly assigned into one of four groups:

- Group 1: Control group – remained sedentary and consumed 22 g/day of margarine not fortified with sterols
- Group 2: Exercise group – exercised 3 times a week on stair-stepping machines and stationary bicycles to eventually reach 75% of maximum heart rate (after 6 weeks). They also consumed 22 g/day of non-fortified margarine
- Group 3: Sterol group – remained sedentary, but consumed 22 g/day of a sterol-fortified margarine providing 1.8 g/day of plant sterols of which 46% was beta-sitosterol
- Group 4: Combination group – combined exercise program with the consumption of sterol-fortified margarine.

At the end of the 8-week trial period, the total cholesterol concentration (after correcting for changes in the control group) had decreased by 7.1% in the sterol group, by 5.4% in the combination group, but increased by 2.1% in the exercise only group. LDL cholesterol declined by 11.3% in the sterol group, by 5.9% in the combination group, but increased by 6.9% in the exercise group. HDL cholesterol increased by 5.8% in the sterol group, by 9.2% in the combination group, and by 11.2% in the exercise group. Triglycerides decreased by 1.3% in the sterol group, by 9.7% in the combination group, and by 14.5% in the exercise group. Blood levels of beta-sitosterol increased by 27.0% in the sterol group, by 20.1% in the combination group, and by 3.9% in the exercise group. The researchers conclude that a regimen combining plant sterols with endurance exercise results in the most favourable changes in cholesterol profile.

Varady, KA, et al. Plant sterols and endurance training combine to favorably alter plasma lipid profiles in previously sedentary hypercholesterolemic adults after 8 weeks. **American Journal of Clinical Nutrition**, *Vol. 80, November 2004, pp. 1159-66*

Editor's comment: Beta-sitosterol is also readily available as a supplement.

Prostate cancer linked to inflammation

BALTIMORE, MARYLAND. Several cancers have been linked to inflammation or viral infection. Stomach cancer has been linked to an infection with *Helicobacter pylori*. Liver cancer is associated with hepatitis (inflammation of the liver), and cervical cancer with a human papilloma virus infection. Now researchers at the Johns Hopkins University School of Medicine suggest that prostate cancer may also have its origin in inflammation or viral infection. It is quite clear that prostate cancer risk is related to diet with animal fats promoting it and antioxidant-rich fruits and vegetables preventing it. It is also clear that some anti-inflammatory agents such as aspirin and COX-2 inhibitors help prevent prostate cancer, especially among older men. There is also substantial evidence that antioxidants like vitamin E (especially gamma-tocopherol) and selenium exert a strong protective effect against prostate cancer.

Furthermore, there is clear evidence that the inflammation associated with sexually transmitted infections is associated with increased prostate cancer risk. Close examination of prostate cells obtained from biopsies have shown a strong presence of inflamed cells close to cancer cells, and signs of prostatitis (prostate inflammation) are found in almost all older men in the developed world even though symptoms may be absent. Finally, it has recently been discovered that prostate cancer is associated with silencing of the gene responsible for the production of glutathione S-transferase, one of the body's most important antioxidants.

Putting all this information together, the Johns Hopkins researchers conclude that inflammation of the prostate (prostatitis) may contribute to the development of prostate cancer.

Nelson, WG, et al. The role of inflammation in the pathogenesis of prostate cancer. **Journal of Urology**, *Vol. 172, November 2004, pp. S6-S12*

Editor's comment: These findings clearly underscore the importance of ensuring an adequate intake of antioxidants, especially selenium and gamma-tocopherol, and natural anti-inflammatories such as beta-sitosterol. Sulphoraphanes (found in broccoli and cauliflower) and many other foods, especially green onions (scallions) and garlic, have also been found highly protective.

Is PSA testing obsolete?

STANFORD, CALIFORNIA. An annual test for prostate specific antigen (PSA) has now become a ritual for many men over the age of 50 years. The aim of the test is to obtain an early warning of prostate cancer; however, elevated PSA values are also closely associated with the size (weight) of the prostate itself as well as with the presence of prostatitis (prostate inflammation) and benign prostatic hyperplasia (prostate enlargement).

The PSA test was developed and validated by Dr. Thomas Stamey and colleagues at Stanford University in the early 1980s and was hailed as a great breakthrough in the fight against prostate cancer. In 1989 this group confirmed that PSA level was directly proportional to increasing clinical stages of prostate cancer. In October 2004 Dr. Stamey and his group declared that, "The prostate specific antigen era in the United States is over for prostate cancer." What happened?

The Stanford team examined 1317 prostates removed during radical prostatectomy during four 5-year periods between August 1983 and July 2003. They compared PSA values obtained prior to prostate removal with actual information about the size and aggressiveness (Gleason score) of the largest cancer in the prostate. During the first period (1983-1988) there was excellent correlation between preoperative PSA levels and cancer severity parameters such as the volume of the largest cancer, capsular penetration, positive lymph nodes, percentage seminal vesicle invasion, percentage of largest cancer with a 4/5 Gleason score, and prostate weight. During the period 1999-2003 there was no correlation whatsoever between preoperative PSA values and any of the above parameters, except the weight of the prostate. In other words, during the 20-year period of the study the PSA test has been reduced from being a significant predictor of cancer to being solely a predictor of prostate weight. The researchers conclude that, "PSA today as a basis for diagnosing and treating prostate cancer is related only to the amount of benign prostatic hyperplasia in the prostate."

The problem, of course, is that men are now being so intensely screened that an inordinately large number of prostate cancers are diagnosed and treated even though they were unlikely to ever cause a problem. It is estimated that 8% of men in their 20s and 80% of men in their 70s have invasive prostate cancer and yet only 0.2% over the age of 65 years actually die from it. The researchers also comment on recent suggestions by urologists to lower the cut-off point at which a biopsy is performed from 4.1 to 2.6 ng/mL stating that this would simply "compound the tragedy" by adding millions of men to the biopsy list.

The researchers conclude that the era in which a PSA test was a valid marker for prostate cancer is probably over. However, the test will continue to be useful as a marker for benign prostatic hyperplasia and as a tool for measuring the success, or otherwise, of radical prostatectomy and radiation. They also conclude that a new serum marker, which is truly indicative of serious prostate cancer, is urgently needed.

Stamey, TA, et al. The prostate specific antigen era in the United States is over for prostate cancer: what happened in the last 20 years? **Journal of Urology**, *Vol. 172, October 2004, pp. 1297-1301*

Soy intake and cholesterol levels

OXFORD, UNITED KINGDOM. Several studies have shown that women with a high intake of soy protein have a reduced risk of developing cardiovascular disease. Other studies have shown that a reduction in plasma cholesterol level of 1.0 mmol/L (39 mg/dL) corresponds to a 21% reduction in the risk of coronary artery disease.

Now researchers at the University of Oxford report that women with a moderate intake of soy protein have lower levels of total cholesterol and LDL cholesterol (the bad kind) than do women with a low or zero intake. Their study included 1033 pre- and post-menopausal women, 361 of whom were non-vegetarians, 570 were vegetarians (no meat or fish, but did consume dairy products and eggs), and 102 vegans (no animal products at all). The women enrolled in the study during 1995 and 1996 at which time they provided blood samples and completed a 130-item food frequency questionnaire.

The researchers found that women who consumed enough soy products (soy milk, tofu, soy meat, textured vegetable protein, and veggie burgers) to obtains 6.0 grams/day or more (average of 11.2 grams/day) of soy protein had an average 7.5% lower total cholesterol concentration than did women whose intake of soy protein was less than 0.5 grams/day. The LDL concentration was found to be 12.4% lower and the ratio of total cholesterol to HDL cholesterol (the good kind) was 9.0% lower. The concentration of HDL cholesterol was not affected by soy intake. The researchers conclude that moderate intakes of soy protein are associated with favourable changes to cholesterol concentrations in pre- and post-menopausal women.

Rosell, MS, et al. Soy intake and blood cholesterol concentrations: a cross-sectional study of 1033 pre- and postmenopausal women in the Oxford arm of the European Prospective Investigation into Cancer and Nutrition. **American Journal of Clinical Nutrition**, *Vol. 80, November 2004, pp. 1391-96*

Folic acid protects the heart

KUOPIO, FINLAND. Considerable controversy still surrounds the question as to whether a high homocysteine level is a risk factor for heart disease. Several studies have concluded that it is, while others have found no association. Homocysteine is a sulfur-containing amino acid synthesized from methionine, an essential amino acid found mainly in red meat. Homocysteine requires folic acid, vitamin B6, and vitamin B12 as cofactors during its metabolism and a deficiency of any of these vitamins can lead to high homocysteine levels. Conversely, homocysteine levels can be effectively lowered by supplementing with folic acid, vitamin B6, and vitamin B12.

Finnish researchers have just completed an 8-year study involving 1027 men between the ages of 46 to 64 years and free of cardiovascular disease at enrollment in 1991-1993. The study was designed to determine the effect of homocysteine and folate levels on the incidence of acute cardiac events (heart attack or stroke). During the 7.7-year study period, 61 men experienced an acute cardiac event. Analysis of blood levels of homocysteine and folic acid showed no correlation between the incidence

of acute cardiac events and homocysteine levels, but did reveal a highly significant 61% risk reduction among men with a folate level exceeding 11.3 nmol/L as compared to men with a level below 8.4 nmol/L. The researchers conclude that further trials are needed to determine whether the use of vitamin supplementation to reduce homocysteine concentrations prevents heart disease or whether high homocysteine levels and low folate levels are simply markers of an unhealthy lifestyle that increase the risk of heart disease.

Voutilainen, S, et al. Serum folate and homocysteine and the incidence of acute coronary events: the Kuopio Ischaemic Heart disease Risk Factor Study. **American Journal of Clinical Nutrition**, *Vol. 80, August 2004, pp. 317-23*

Pros and cons of folic acid

TORONTO, CANADA. A folic acid deficiency has been linked to an increased risk of giving birth to a baby with neural tube defects (NTDs), or spina bifida. In 1998 Canada, the US, and Chile passed a law mandating that all flour and uncooked cereal-grain products be fortified with folic acid (140 micrograms/100 grams). Since 1998 the number of babies born with NTDs has decreased by anywhere from 15-50% in the US, Canada, and Chile. Clearly, a superb example of the benefits of active cooperation between science and public health policy – or maybe not?

Dr. Young-In Kim of the University of Toronto now suggests that, while folic acid fortification has been an unqualified success in reducing NTDs, it may have created other problems. In other words, what is good for a relatively small proportion of the overall population (pregnant women) may be detrimental to a much larger part of the population. Dr. Kim points out that, while folic acid is effective in preventing the initiation of many forms of cancer, it may actually accelerate the growth of already existing cancers. Folate plays a very important role in DNA synthesis and replication, which is great when it comes to healthy cells, but not when it comes to cancerous cells. Rapid replication and proliferation is the last thing you want in the case of cancer cells. As a matter of fact, experiments have shown that inducing a folate deficiency inhibits tumour growth and at least two chemotherapy agents (methotrexate and 5-fluorouracil) owe their effect to the fact that they counteract the cell proliferation effect of folic acid.

Dr. Kim concludes that, "The potential cancer-promoting effect of folic acid fortification in the vast majority of the US population, who are not at risk of NTDs, but have unintentionally been exposed to high amounts of folic acid, is a legitimate public health concern and needs careful monitoring".

Kim, YI. Will mandatory folic acid fortification prevent or promote cancer? **American Journal of Clinical Nutrition**, *Vol. 80, November 2004, pp. 1123-28*

Editor's comment: There is substantial evidence that a folic acid deficiency is implicated in Alzheimer's disease, atherosclerosis, heart attack, stroke, osteoporosis, colon cancer, depression, dementia, hearing loss, and of course, NTDs. Thus it is clearly vital to ensure an adequate daily intake of this important nutrient. The generally recommended intake is 400-600 micrograms/day. With the advent of general fortification it has become more difficult to know exactly how much one is consuming and the risk of overdosing is certainly very real. While this is probably not a major problem for healthy people, it could well be for those with established or not yet diagnosed cancer. So the safest approach is to limit one's supplemental folic acid intake to 400 micrograms/day – the amount found in most multivitamins. Folic acid should always be taken together with vitamins B6 and B12.

Determination of omega-3 fatty acids in heart tissue

KANSAS CITY, MISSOURI. There is overwhelming evidence that omega-3 fatty acids or, more specifically, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the main components of fish oils, are highly effective in preventing sudden cardiac death, death from heart disease, and certain arrhythmias. Investigations involving individual heart cells have shown that EPA + DHA prolong the refractory state of the cells by interacting with fast-acting sodium channels and L-type calcium channels. It is thus clear that the cardioprotective effect of EPA + DHA is intimately associated with the degree to which these two fatty acids are actually incorporated into the heart tissue

(myocardium). The ultimate test of the extent of incorporation is, of course, analysis of the heart tissue itself; however this, for obvious reasons, is not terribly practical.

Researchers at the Mid America Heart Institute now report that the EPA + DHA content of red blood cells (RBCs) almost exactly mirrors the concentration in the myocardium. Their study involved 20 heart transplant patients whose EPA + DHA level was measured in heart tissue and red blood cells. The researchers found an almost perfect correlation (r = 0.82) between the content in cardiac tissue and the content of RBCs.

In a subsequent experiment involving 25 heart transplant patients, the researchers measured EPA + DHA in biopsied myocardial tissue, plasma lipids, cells scraped from the cheek (buccal tissue), and red blood cells before and after 6 months of supplementation with 300 mg EPA + 200 mg DHA. The supplementation resulted in a 272% increase in EPA and a 94% increase in DHA in the heart tissue itself. The corresponding increases in plasma lipids, buccal tissue, and RBCs were 365% and 104%, 124% and 95%, and 279% and 84% respectively. The best correlation was between myocardial tissue and RBCs followed by myocardial tissue and buccal tissue. The researchers conclude that EPA and DHA levels in RBCs give an accurate indication of the content in heart cells. Buccal tissue is also a good indicator, but more cumbersome and exacting to obtain than a blood sample. The researchers also point out that RBC content is a good indicator of long-term intake, whereas plasma lipids vary depending on the food consumed on the day immediately preceding the test.

Harris, WS, et al. Omega-3 fatty acids in cardiac biopsies from heart transplantation patients: correlation with erythrocytes and response to supplementation. **Circulation**, *Vol. 110, September 21, 2004, pp. 1645-49*

Fish oils in cancer prevention

STOCKHOLM, SWEDEN. Several test tube (*in vitro*) and animal experiments have clearly shown that the long-chain omega-3 polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the main components of fish oil, help inhibit the promotion and progression of cancer. Their beneficial effect is particularly pronounced in hormone-dependent cancers such as breast and prostate cancer. Some, but not all, epidemiologic studies have also found a beneficial effect.

Researchers at Sweden's famous Karolinska Institutet have just published a comprehensive review of the current knowledge regarding the role of PUFAs in carcinogenesis. They conclude that omega-3 PUFAs are protective against cancer progression, while omega-6 PUFAs, notably arachidonic acid and its derivatives, help promote the growth of cancer. They believe the n-3 PUFAs exert their beneficial effects in several different ways:

- They suppress the synthesis of pro-inflammatory eicosanoids from arachidonic acid and thus produce an overall anti-inflammatory effect.

- They positively affect gene expression or the activities of signal transduction molecules involved in the control of cell growth, differentiation apoptosis, angiogenesis and metastasis.

- They suppress excessive production of nitrogen oxide (NO) during chronic inflammation and thereby help prevent DNA damage and impaired DNA repair.

- They decrease estrogen production and thus reduce the estrogen-stimulated growth of hormone-dependent cancer cells.

- Fish oils improve insulin sensitivity and cell membrane fluidity and may help prevent metastasis through these effects.

Free radicals and reactive oxygen species produced in cells may attack PUFAs resulting in the formation of more free radicals, specifically hydroperoxides. The hydroperoxides, in turn, may damage DNA ultimately leading to cancer. These effects have indeed been observed in some *in vitro* experiments, but not in actual human beings. Many studies have shown that fish oils actually retard aging and suppress so-called free radical diseases such as atherosclerosis and cancer. Other studies have shown that a daily EPA + DHA intake in excess of 2.3 grams decreases the production of superoxide, a potent cancer promoter.

At least one *in vitro* and one animal experiment have observed that EPA + DHA kill human breast cancer cells via the formation of hydroperoxides, but that this effect is strongly inhibited by vitamin E. Thus, at this point, it is not entirely clear whether EPA + DHA exert part of their beneficial effect through an increase or a decrease in the production of free radicals and reactive oxygen species. The researchers recommend more work in this area, but emphasize that the major benefits of fish oils probably are associated with their ability to inhibit the synthesis of arachidonic acid-derived, pro-inflammatory eicosanoids. The Swedish researchers also confirm that fatty, cold-water fish are the best sources of EPA and DHA and that the conversion rate of alpha-linolenic acid (flaxseed oil) to EPA is very low, even in healthy humans – probably in the order of 2-5%.

Larsson, SC, et al. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. **American Journal of Clinical Nutrition**, *Vol. 79, June 2004, pp. 935-45*

Editor's comment: There would appear to be a growing body of evidence to the effect that long-chain omega-3 fatty acids, in particular EPA and DHA, help prevent the promotion and progression of certain cancers, notably hormone-dependent ones. Some of the mechanisms involved in this protective effect are well understood. While others, notably the role of free-radical formation, clearly need more work. Of some concern is the uncertainty surrounding vitamin E. Both vitamin E and fish oils have been found to help prevent hormone-dependent cancers, so taking both for cancer prevention is probably desirable. The situation is much less clear when it comes to slowing down an existing cancer and preventing it from spreading. Should one just rely on vitamin E (particularly the succinate form) or place one's faith in fish oils, or is the combination of the two the best way to go? Clearly more research in this area is urgently required.

Angiotensin II receptor blocker helps prevent stroke

WASHINGTON, DC. An international team of researchers from Germany, Hungary, Italy, the Netherlands, Sweden, and the United States reports that the angiotensin II type 1 receptor blocker candesartan (Atacand) is effective in preventing ischemic stroke in older patients with hypertension. Their study involved 1518 elderly patients (average age of 77 years) with isolated systolic hypertension (systolic blood pressure above 160 mm Hg and diastolic pressure below 90 mm Hg). All patients were taking 12.5 mg/day of the diuretic hydrochlorothiazide (HCTZ) at the beginning of the study and continued to do so during the study period. At the beginning of the study, participants were randomized to placebo or 8 mg of candesartan once daily in the morning; the dose of candesartan could be doubled if necessary, and the daily dose of hydrochlorothiazide could also be adjusted as required for adequate blood pressure control.

During the study period of about 3.6 years (5506 person years) blood pressure was reduced by 22/6 mm Hg in the candesartan group and by 20/5 mm Hg in the placebo group – not a significant difference. The overall incidence of cardiovascular death, heart attack, and stroke during the study period was slightly lower in the candesartan group than in the placebo group; however, the difference was not statistically significant. The incidence of stroke (fatal and non-fatal) was, however, significantly lower in the candesartan group. Here 20 first strokes occurred (7.2/1000 patient-years) as compared to 35 in the placebo group (12.5/1000 patient-years) – a significant risk reduction of 42%. The researchers conclude that candesartan provides significant stroke protection in elderly patients with isolated systolic hypertension. They speculate that this beneficial effect may be due not only to the blood pressure lowering effect of the drug, but perhaps, even more so, to candesartan's ability to block the angiotensin II type 1 receptor. NOTE: This study was funded by AstraZeneca, the manufacturer of Atacand.

Papademetriou, V, et al. Stroke prevention with the angiotensin II type 1-receptor blocker candesartan in elderly patients with isolated systolic hypertension. **Journal of the American College of Cardiology**, *Vol. 44, September 15, 2004, pp. 1175-80*

NEWSBRIEFS

Gulf war syndrome is real. The top-level US Research Advisory Committee on Gulf War Veterans' Illnesses has released a report, which after 10 years of cover-up by both the US and UK governments, admits that the Gulf war syndrome really exists. Thousands of veterans of the 1990 Gulf war have been affected, with the main symptoms being chronic diarrhea, fever, fatigue, pain, and late-night insomnia. The report concludes that the syndrome is caused by exposure to nerve gas and pesticides that caused brain damage in genetically predisposed veterans. A Congressional inquiry report released in June 2004 concluded that most Gulf war troops had been exposed to nerve gas from bombed Iraqi weapons dumps.
New Scientist, October 23, 2004, p. 4

Biased drug results a thing of the past? Suppressing unfavourable results from clinical trials involving new drugs is fairly common and can lead to major disasters as exemplified by the recent Vioxx fiasco. Eleven top medical journals, including *The New England Journal of Medicine, The Lancet,* and *The Journal of the American Medical Association*, are now attempting to put a stop to this reprehensible practice. The journals have instituted a policy whereby they will refuse to publish results of clinical trials unless the size, design and purpose of the trial were publicly recorded prior to the trial beginning. This, hopefully, will prevent drug companies from selectively reporting positive results or putting a positive spin on negative results.
New Scientist, September 18, 2004, p. 4

Coffee drinking linked to inflammation. A systemic inflammation has been linked to heart disease, arthritis, diabetes, prostate cancer, atrial fibrillation, and a host of other common ailments. The extent of inflammation in the body is measured through so-called markers, the most widely used of which are interleukin 6 (IL-6), C-reactive protein (CRP), serum amyloid-A (SAA), and tumor necrosis factor alpha (TNF-alpha). Greek researchers report that drinking more than one cup of coffee a day markedly increases the level of inflammation markers. Their study involved 1514 men and 1528 women without a history of heart disease. Compared with non-coffee drinkers, men who consumed more than one cup of coffee a day had a 50% higher IL-6 level, a 30% higher CRP level, a 12% higher SAA level, and a 28% higher concentration of TNF-alpha. Corresponding numbers for women were 54%, 38%, 28%, and 28%.
American Journal of Clinical Nutrition, Vol. 80, October 2004, pp. 862-67

Even a little exercise helps. There is substantial evidence that regular exercise improves health and increases longevity. What is less clear is whether less frequent, but more vigorous activity is equally beneficial. Researchers at the Harvard School of Public Health recently reported that "weekend warriors", ie. men who only engage in vigorous activity once or twice a week do benefit. Their study included 8421 men (enrolled in 1988 and 1993). The men were classified as sedentary (expending less than 500 kcal/week), insufficiently active (500-999 kcal/week), weekend warriors (more than 1000 kcal from sports/recreation 1-2 times a week), and regularly active (more than 1000 kcal/week). Between 1988 and 1997, 1234 of the study participants died. Men who were physically active on a regular basis had a 36% lower mortality than did sedentary men, while weekend warriors had a 15% lower risk of dying. However, when limiting the analysis to men without major risk factors, then weekend warriors were found to have a 59% lower mortality than sedentary men. The researchers conclude that vigorous exercise once or twice a week can extend life significantly in men with no major risk factors such as smoking, hypertension, high cholesterol, etc.
American Journal of Epidemiology, Vol. 160, October 1, 2004, pp. 636-41

Perils of Caesareans. German researchers are investigating whether birth by Caesarean section increases the risk of asthma and other allergies. Their study of 865 babies found that those (147) delivered by Caesarean had more digestive problems and food intolerances – both signs of inappropriate immune reactions, which ultimately could promote asthma and other allergic reactions. The researchers speculate that babies born by Caesarean do not get a chance to swallow beneficial bacteria during birth and therefore do not develop a proper immune system. Says researcher Sibylle Koletzko of the Ludwig Maximilian University in Munich, "There may be long-term risks of Caesareans that we have not considered before – I would discourage them for all non-medical reasons."
New Scientist, October 30, 2004, p. 19

Doctors concerned about litigation. The cost of medical malpractice awards and associated legal costs reached $24 billion in the US in 2002 – an amount equal to 1.6% of the country's entire spending on healthcare and an increase of more than 100% over the past 10 years. Similar increases have been reported in the UK and Australia. The threat of costly lawsuits has led many doctors to practice "defensive medicine" involving the excessive prescribing of drugs, ordering of inappropriate tests, and even carrying out unnecessary surgery to avoid being sued if the patient does not get better. It seems that the courts look more favourably on a doctor who has caused a lot of medical intervention to be done on a patient than on one who has taken a more reasoned approach to patient care. Doctors are now getting thoroughly fed up with the situation. At the annual meeting of the South Carolina Medical Association, surgeon Chris Hawk proposed a motion that doctors should be able to refuse to treat lawyers and their spouses. The motion was defeated, but some colleagues of Dr. Hawk are putting it into practice anyway. Another fall-out of the litigation epidemic is that some specialists in obstetrics and neurosurgery are refusing to treat patients because of fear of malpractice suits.
New Scientist, October 23, 2004, pp. 38-41

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I just could not resist the temptation to re-publish one of the abstracts from the September 2001 issue of *International Health News*. No comment is really necessary, but I thought it might reassure you that readers of *IHN* would have been warned more than 3 years ago to avoid COX-2 inhibitors such as Vioxx and Celebrex.

COX-2 inhibitors may not be heart healthy

CLEVELAND, OHIO. COX-2 inhibitors have had a rapid rise to fame. They were introduced in 1999 and by October 2000 annual sales exceeded $3 billion in the United States corresponding to about 100 million individual prescriptions. The COX-2 class drugs, celecoxib (Celebrex) and rofecoxib (Vioxx), are mainly used in the treatment of rheumatoid arthritis, but have also been prescribed for general pain relief. They are less likely to promote internal bleeding and stomach ulcers than are aspirin and other NSAIDs (nonsteroidal anti-inflammatory drugs). Researchers at the Cleveland Clinic now warn that the COX-2 inhibitors may not be as benign as originally thought. An extensive literature review turned up the finding that the risk of having a heart attack while on rofecoxib is 42 per cent greater than if taking a placebo (0.74 per cent versus 0.52 per cent annual rate). The same applied to celecoxib where the risk is 54 per cent greater (0.80 per cent versus 0.52 per cent annual rate). The data was extracted from trials involving 23,407 patients. Another trial found that people taking rofecoxib had twice as many cardiovascular events (heart attacks, strokes, angina, etc.) than did patients on the NSAID naproxen. The Cleveland researchers call for large-scale clinical trials to verify or refute their findings, but in the meantime urge caution in prescribing COX-2 inhibitors to people at risk for heart disease. *Mukherjee, Debabrata, et al. Risk of cardiovascular events associated with selective COX-2 inhibitors.* **Journal of the American Medical Association***, Vol. 286, August 22/29, 2001, pp. 954-59*

THE VIOXX SAGA: PERSPECTIVE ON THE RECALL

By William R. Ware

Merck was granted FDA approval to market the painkiller Vioxx (rofecoxib), a so-called COX-2 inhibitor, on May 21, 1999. The same year Pharmacia (now merged with Pfizer) launched Celebrex (celecoxib), a competing drug. "Me Too" drugs followed, some still in the pharmaceutical pipeline. In the five years that elapsed before Merck withdrew Vioxx from the market an estimated 80 million patients took the drug (1). Vioxx was a "blockbuster" with sales over 2 billion US dollars per year. Editorials in both medical journals and the press have suggested that the FDA and Merck knew that Vioxx had serious adverse effects and were both at fault for not acting earlier, implying that

the system protecting the consumer is not working very well. What happened during those five years is thus of considerable interest.

Early warnings of trouble

The first study hinting at trouble (VIGOR) was published in November 2000 (2). Between January and July 1999, over 8000 patients were enrolled in Merck's "Phase 4" post-approval study of upper gastrointestinal (UGI) toxicity of Vioxx. It was a double blind, randomized trial comparing the occurrence of gastrointestinal toxicity of Vioxx and naproxen (Aleve, another non-steroidal anti-inflammatory) in patients with rheumatoid arthritis. The paper indicated that the risk of "important" UGI adverse events was significantly lower in the Vioxx group compared to the naproxen group. As regards the risk of heart attack (MI), the authors claimed that Vioxx significantly increased MI only in people with a previous cardiovascular problem who should have been taking aspirin but did not because of the study design. The hypothesis was also promoted that naproxen was cardio-protective, a hypothesis supported by a Merck review published in 2001 of 16 studies involved in their pre-approval process which found no excess of cardiovascular (CV) adverse events except when Vioxx was compared with naproxen (3).

The November 2000 paper, however, was not based on the complete set of data. Subsequently Mukherjee, Nissen and Topol from the Department of Cardiovascular Medicine of The Cleveland Clinic reexamined the cardiovascular (CV) risk question using all the data submitted to the FDA and the results of the FDA's adjudicated examination of the observed CV events. The results appeared in the *Journal of the American Medical Association* (*JAMA*) in August 2001 (4). Based on adjudicated cases, the risk of developing a CV event was 2.38 higher in the Vioxx group compared to the naproxen controls with a probability that this result occurred by a chance of two in a thousand (p=0.002) i.e. a significant result. For those who should have been taking aspirin, i.e. those with history of stroke, transient ischemic attack, MI, unstable or stable angina, bypass surgery or angioplasty, the Vioxx group had a statistically significant relative risk (RR) of 4.89. There is also the question of corticosteroid use (5). In VIGOR over 50% of the subjects were using oral steroids for osteoarthritis or menstrual or other pain, which is not in keeping with the typical patient profile of many users of Vioxx. The authors of the 2001 *JAMA* article raised serious questions regarding the safety of Vioxx and called for studies to address the question. However, in 2001 the issue was seriously confused by the possibility that naproxen, the control in the VIGOR study, was cardio-protective, an argument Merck also used to explain the enhanced risks seen in their pre-approval clinical trials (3) as well as in the VIGOR study. In April of 2002 the FDA instructed Merck to include precautions about CV risk in the package insert for Vioxx. However, it is well known that many doctors and patients do not study these inserts and that they are a very inefficient method of disseminating a warning (6,7).

In 2002 at least six studies addressed the naproxen hypothesis (the assumption that the adverse CV effects observed with Vioxx when compared to naproxen were due to naproxen being protective rather than to Vioxx being detrimental) (8,9,10,11). No protective effect was seen in two, protection in three, and statistically non-significant protection in one. A clinical study which did not depend on naproxen for a control was published in 2002 in *The Lancet* (8). It was found that Vioxx doses greater than 25 mg/d gave an increased risk (RR 1.7-1.93). This study had a rather short average period of follow-up, and there was still an issue with corticosteroid use. In 2003 a Canadian study found no increase in CV adverse events with Vioxx and no decrease with naproxen, but this was a very short-term study (average follow-up 144 days) (12). Thus at the end of 2003, the situation did not appear to have been significantly clarified. In spite of at least seven studies, the naproxen hypothesis was still alive, and there was only one additional study which indicated potential CV risk for the users of Vioxx and one that was negative.

Confirmation of Vioxx's adverse effects

In 2004 a study in which naproxen was not an issue was published in the journal *Circulation* (13). There was no exclusion for a history of CV disease risk. It was found that for Vioxx doses equal to or greater than 25 mg/d, there was an increased risk for acute heart attacks (AMIs) which disappeared after 90 days of use. Then in August 2004, a paper at an International Pharmacoepidemiology meeting in Bordeaux, France reported the results of an FDA sponsored study involving a huge Kaiser Permanente (US Health Maintenance Organization) database which compared the risk of adverse CV events for users of Vioxx vs. Celebrex. The study, which attempted to project the excess of adverse CV events associated with Vioxx, concluded that more than 27,000 MI and sudden cardiac deaths occurred between 1999 and 2003 which could have been avoided by taking Celebrex rather than Vioxx. Taking 25 mg/d or more of Vioxx resulted in over

three times the risk of AMI or sudden cardiac death as compared to Celebrex use. The relative risk was 1.5 for lower doses of Vioxx. This alarming result, presented at a poster session, is probably not widely known, although on September 27, 2004 the American College of Rheumatology (ACR) issued a hotline prompted by what they called "substantial media coverage" of this study. However, the ACR did not recommend discontinuing Vioxx, but merely suggested that more studies were needed and clinicians needed to be aware of potential adverse events. A fairly complete account of this FDA sponsored study was "published" after the recall in *The Wall Street Journal,* October 6, 2004. The full report has been submitted to *The Lancet* and a version is now available at www.fda.gov (use "graham" as search word). It is important, incidentally, that there is also a supporting biological mechanistic hypothesis that would explain the increase of adverse CV events due to COX-2 inhibition (14). This mechanism applies to all COX-2 inhibitors and has been the basis of calls for more extensive and powerful studies of all drugs in this class.

The recall

On September 30, 2004, in what the press called the largest drug recall in the history of medicine, Merck pulled Vioxx from pharmacy shelves. This recall came after the safety committee concerned with a Merck sponsored clinical study of Vioxx for colon cancer prevention observed what they considered to be excess MIs when Vioxx was compared to a placebo and halted the trial. Media coverage was extensive and doctors reported being swamped with calls from patients wanting another drug. There had not been a drug recall for three years, but it is important to realize that in the US from 1992 to 2001, 10 drugs were recalled because of unacceptable adverse reactions that were discovered after regulatory approval (6), i.e. about 1 drug on average per year. The average time between approval and recall was 5½ years! The system definitely shows signs of "inertia." It will probably never be known how long it would have taken the FDA to act on Vioxx on the basis of the accumulated data as of September 30, 2004 or what action they would have taken, had not their role been preempted by Merck. However, what went on between the FDA and Merck leading up the recall is unknown.

The fall-out

Editorial comments quickly appeared in *The New England Journal of Medicine* (1,15) and *The Lancet* (16) and additional commentary appeared in major newspapers. Eric Topol, one of the authors of the 2001 *JAMA* paper that reevaluated the VIGOR study, contributed an article to *The New York Times* (17) titled "Good Riddance to a Bad Drug." Concern was evident regarding the impact of the recall on the drug safety review process, the time required for drug companies to get regulatory approval, and the confidence of the general public in "the system." Over three years elapsed between the publication in *JAMA* of the full analysis of the VIGOR study and the recall, a recall actually precipitated by a study with an endpoint totally unrelated to the original indications for which Vioxx was marketed.

In the *NEJM* editorial, Eric Topol suggests that Merck should have initiated or been forced by the FDA to initiate an appropriate trial directed at the question of CV risk, given the growing body of evidence (1). In addition he feels that the uncertain CV risk picture should have prompted Merck to stop the intensive direct-to-consumer advertising (e.g. TV ads) until the matter was resolved. However, he does give the FDA credit for sponsoring the Kaiser Permanente study. In a second editorial comment in the same issue, G. A. FitzGerald takes a similar position (15). In his opinion, "the rational basis for addressing the cardiovascular effects of these drugs (COX-2 inhibitors) has been clear for the past five years, yet even the most fundamental questions have not been addressed directly." He concludes "the burden of proof now rests with those who claim that this is a problem for rofecoxib (Vioxx) alone and does not extend to the other coxhibs. We must remember that the absence of evidence is not evidence of absence." John Abramson, who teaches clinical medicine at Harvard, points out in the recent book *Overdo$ed America* (5), that patients taking Vioxx had 21% more "serious adverse events" *of all kinds* (CV, upper GI, etc.) than those on naproxen. He comments "Something is very wrong with a system that leads patients to demand and doctors to prescribe a drug that provides no better pain relief and causes significantly more side effects." This statement was based on data known to the FDA in 2001 and reviewed in the *JAMA* article of August 2001, as well as on his own reevaluation of the data.

The ugly details

In early November 2004 significant new information became available that helps clarify some of the questions raised by the Vioxx saga. On November 5 a new meta-analysis (where a number of studies are lumped together and re-analyzed) of a large number of Vioxx risk studies was published in *The Lancet* (18). The Swiss authors had no connection

with Merck. At the end of 2000, they found on the basis of 13 studies (20,742 patients) that the RR of an MI due to taking Vioxx was 2.30 (p=0.01) and a year later on the basis of 16 studies (21,432 patients) the RR was 2.24 (p=0.007). They also found that the small protection observed for naproxen was insufficient to explain the increased number of MIs. Thus, based on their view of what was known to Merck and the FDA by the end of either 2001 or 2002, the authors concluded that Vioxx should have been withdrawn. One might ask why the FDA failed to do a meta-analysis in 2001 of this same data rather than leave it up to Merck which had an obvious conflict of interest (3).

The Wall Street Journal on November 1, 2004 announced that they had come into possession of both emails and internal documents originating from Merck which suggested that management had been aware from before 2000 that there was a problem but publicly downplayed its importance and taught their sales reps how to field awkward questions from doctors regarding CV risks—the printed policy was characterized by the word "DODGE." In an email on March 9, 2000, Merck's research chief told colleagues that the CV events "are clearly there" and called it a "shame" but the company's public statements continued to reject the link between Vioxx and increased risk. The *WSJ* article also outlines several incidents where Merck attempted to intimidate academic researchers who were making anti-Merck statements. Merck is reported to have taken the position that these emails are being viewed out of context. They also claim that the Swiss meta-analysis had design flaws as did the FDA sponsored study (19).

On November 4, 2004 *The New York Times* published an article discussing the attempts of the FDA to delay and downplay the results of their study first reported in Bordeaux, France. Dr. David Graham, the lead investigator in the study, provided the newspaper with emails to back up the claim that his effort to publish the study was delayed and demeaned by to FDA officials. In his editorial in *NEJM*, Eric Topol called for a congressional investigation of the way in which the FDA handled the Vioxx matter (1). Recent reports in the press suggest this may well happen.

Finally, a paper in the December 2004 issue of *Atherosclerosis* provides a new piece to the puzzle regarding what might be a mechanism for enhanced adverse CV events (20). This paper examined the effect of several COX-2 inhibitors on the susceptibility of human low-density lipoprotein (LDL) cholesterol to oxidative modification. They found that the so-called Sulfone COX-2 inhibitors (Vioxx and etoricoxib) clearly increased the susceptibility of biological lipids to oxidative damage through non-enzyme processes and that this could provide "mechanistic insight" into reported differences in COX-2 inhibitors in connection with adverse CV events since no such increase in susceptibility was found for celecoxib (Celebrex), valdecoxib or meloxicam nor the non-selective inhibitors such as ibuprofen, naproxen and diclofenac. Incidentally, etoricoxib is a Merck drug currently up for approval. The FDA has just announced that it will not approve it before more studies are conducted regarding safety issues. The study in *Atherosclerosis* should reinforce their decision. This new mechanistic hypothesis is distinctly different from that mentioned above (14), which involved adverse effects of COX-2 inhibitors on the blood clotting process with all coxib drugs implicated.

Flaws in the system

The Vioxx fiasco might easily cause the public to lose confidence in both the FDA, the drug companies and clinical and observational studies, especially when it came so soon after the hormone replacement therapy (HRT) flip-flop (21). After all, taking prescription drugs represents an act of faith. i.e. the implicit assumption that the drug company in question is not concealing serious risks for their own financial gain, and that the regulatory agencies are on guard and seeing to the safety issue with all due diligence. In the absence of such faith, taking prescription drugs is like a crap-shoot. But even if this faith is misplaced, without prescription drugs many areas of modern medicine would be essentially paralyzed. Nor would any reasonable person suggest abandoning medical studies with human subjects just because they sometimes yield misleading, inconsistent or even wrong results, or results that may in some cases be influenced by the source of funding. These studies of necessity employ imperfect tools to investigate what are in many cases exceedingly complex questions involving diverse populations, studies that must rely on statistics to a much greater extent than, for example, studies in the physical sciences or even laboratory studies in the biological sciences. The HRT flip-flop has in fact stimulated considerable discussion of the strengths and weaknesses of observational vs. randomized clinical trials (21,22,23) and improvements are being suggested which will probably benefit the science of epidemiology in the future.

One must not lose sight of the fact that until late 2004 the picture was still rather confused, with inconsistent results both of the Vioxx CV risk and the naproxen hypothesis. Contrary to the position of a number of vocal critics, from what has been outlined above, this does not appear to be an open and shut case. One of the authors of the now famous *JAMA* article of 2001, Dr. Steven Nissen, is quoted in an interview with *Business Week*, October 1, 2004, that "Even in August, 2001, when we published our first report on the risks, it was highly speculative. We didn't have hard data. We had some soft data and some suspicions about the mechanism of action. We could just as easily been wrong." When asked if the drug approval process should be changed to avoid such problems in the future, he responded "There's potentially a solution, but it's very costly. We need a more robust post-approval surveillance system to keep track of adverse events with new drugs. The system is voluntary on the part of the drug companies now, but I would have it mandatory. Studies have found that only between 1% and 10% of serious adverse events with drugs on the market are actually reported. So the FDA is making decisions on inadequate data now. This (would be) a very important initiative, in my opinion."

It is probably not generally realized that the number of subjects involved in the trials required for drug approval is small (typically a few thousand, sometimes considerably less), and side effects occurring at a rate of less than 1% are easily attributed to chance since the number of events is very low. Even phase 4 studies generally do not involve really large groups of participants (6,21). Thus the real study of adverse events is highly informal, haphazard and uncontrolled and occurs subsequent to approval, since now the patient base becomes huge as a drug is aggressively promoted both to doctors and directly to the public and free samples flow freely. But, as Nissen points out, the reporting system for adverse drug events is inefficient and only infrequently used, which means that most adverse reactions go unrecorded, a problem which leads to a significant lag time before a serious side effect is recognized, investigated and if necessary, regulatory action taken or "voluntary" recall is seen as the only option by the company involved (6,21,24). Also adverse side reactions may simply go undetected since in many cases the association is difficult or even impossible to make in the normal clinical setting. If an adverse event occurs, let's assume, at a rate of even one per hundred users, how is a physician to make the association with a specific drug if his patient load is say 600 individuals, only a fraction take the drug and similar symptoms are seen in patients not on the drug in question? The only hope would be if the side effect was very unusual. In his editorial Eric Topol estimates that on the basis of total patients exposed, the risk observed in the Merck colon cancer prevention study and VIGOR can be extrapolated to the prediction that there could have been as many as 160,000 MI or stroke incidents related to the total Vioxx exposure (1). Yet post-approval surveillance results appear never to have been cited publicly as a significant source of concern in connection with Vioxx.

Thus the consumer of pharmaceuticals needs to be keenly aware that regulatory approval is not a blanket guarantee of safety for the simple reason that such a guarantee appears in general impossible, and the history of recalls shows that the drug companies understandably are generally in a denial mode until the evidence is overwhelming. The case of Vioxx illustrates the complexity of the problem. Consumers of prescription drugs would be well advised to educate themselves as to the side effects, something that can be done, albeit very imperfectly, by combining information from the pharmacy, the package insert, and the internet or *The Physicians Desk Reference* if available. However, most drugs have long lists of side effects and it is sometimes difficult to identify which are of critical importance and then ascertain the related symptoms, and some warning signs can only be identified with lab tests. Early action is frequently important for the avoidance of permanent damage, disability or even death. The statin class of cholesterol lowering drugs is a good example where early detection of muscle problems is important if very serious consequences are to be avoided (6). But in the case of Vioxx, it may in many cases have been impossible to detect early warning signs of CV problems related to the drug, especially in the case of individuals with pre-existing CV conditions, and sudden cardiac death, by definition, provides no early warning. Also, it appears unrealistic to expect the regulatory agencies to be in there at the first sign of trouble and take rapid, definitive action the public will hear about on the evening news or read in the newspaper (21). The bottom line is always the matter of risk vs. benefit. But as we have seen in the Vioxx fiasco, this relationship is frequently difficult or even impossible to evaluate.

REFERENCES

(1) Topol, E. J., "Failing the public health--rofecoxib, Merck, and the FDA," *N Engl J Med*, vol. 351, no. 17, pp. 1707-1709, Oct.2004.

(2) Bombardier, C., Laine, L., Reicin, A., Shapiro, D., Burgos-Vargas, R., Davis, B., Day, R., Ferraz, M. B., Hawkey, C. J., Hochberg, M. C., Kvien, T. K., and Schnitzer, T. J., "Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group," *N Engl J Med*, vol. 343, no. 21, pp. 1520-8, 2, Nov.2000.

(3) Kronstam, M. A., Weir, M. R., Reicin, A., Shapiro, D., Sperling, R. S., Barr, E., and Gertz, B. J., "Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib," *Circulation*, vol. 104, no. 19, pp. 2280-2288, Nov.2001.

(4) Mukherjee, D., Nissen, S. E., and Topol, E. J., "Risk of cardiovascular events associated with selective COX-2 inhibitors," *JAMA: The Journal of the American Medical Association*, vol. 286, no. 8, pp. 954-959, Aug.2001.

(5) Abramson, J., *Overdo$ed America* New York: Harper Collins Publishers, 2004.

(6) Strand, R. E., *Death by Prescription* Nashville: Thomas Nelson Publishers, 2003.

(7) Woosley, R. L., "Drug Labeling Revisions--Guaranteed to Fail?," *JAMA: The Journal of the American Medical Association*, vol. 284, no. 23, pp. 3047-3049, Dec.2000.

(8) Ray, W. A., Stein, C. M., Daugherty, J. R., Hall, K., Arbogast, P. G., and Griffin, M. R., "COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease," *Lancet*, vol. 360, no. 9339, pp. 1071-1073, Oct.2002.

(9) Ray, W. A., Stein, C. M., Hall, K., Daugherty, J. R., and Griffin, M. R., "Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational cohort study," *Lancet*, vol. 359, no. 9301, pp. 118-123, Jan.2002.

(10) Dalen, J. E., "Selective COX-2 Inhibitors, NSAIDs, aspirin, and myocardial infarction," *Arch Intern Med*, vol. 162, no. 10, pp. 1091-1092, May2002.

(11) Schlienger, R. G., Jick, H., and Meier, C. R., "Use of nonsteroidal anti-inflammatory drugs and the risk of first-time acute myocardial infarction," *Br.J Clin Pharmacol.*, vol. 54, no. 3, pp. 327-332, Sept.2002.

(12) Mamdani, M., Rochon, P., Juurlink, D. N., Anderson, G. M., Kopp, A., Naglie, G., Austin, P. C., and Laupacis, A., "Effect of selective cyclooxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly," *Arch Intern Med*, vol. 163, no. 4, pp. 481-486, Feb.2003.

(13) Solomon, D. H., Schneeweiss, S., Glynn, R. J., Kiyota, Y., Levin, R., Mogun, H., and Avorn, J., "Relationship Between Selective Cyclooxygenase-2 Inhibitors and Acute Myocardial Infarction in Older Adults," *Circulation*, vol. 109, no. 17, pp. 2068-2073, May2004.

(14) Fitzgerald, G. A., "COX-2 and beyond: Approaches to prostaglandin inhibition in human disease," *Nat.Rev.Drug Discov.*, vol. 2, no. 11, pp. 879-890, Nov.2003.

(15) Fitzgerald, G. A., "Coxibs and cardiovascular disease," *N Engl J Med*, vol. 351, no. 17, pp. 1709-1711, Oct.2004.

(16) "Vioxx: an unequal partnership between safety and efficacy," *Lancet*, vol. 364, no. 9442, pp. 1287-1288, Oct.2004.

(17) Topol, E. J. Good Riddance to a Bad Drug. New York Times Oct 2, 2004.

(18) Juni, P., Nartey, L., and et al, "Risk of cardiovascular events and rofecoxib: cumulative meta-analysis," *Lancet*, On-Line November 5, 2004.

(19) Anna Gosline, "Vioxx heart risk apparent for years," *New Scientist*. Published on NewScientist.com, November 4, 2004.

(20) Walter, M., Jacob R.F, and et al, "Sulfone COX-2 inhibitors increase susceptibility of human LDL and plasma to oxidative modification," *Atherosclerosis*, vol. 177, no. December, pp. 235-243, 2004.

(21) Avron, J., *Powerful Medicines. The Benefits, Risks and Costs of Prescription Drugs* New York: Alfred A. Knopf, 2004.

(22) Vandenbroucke, J. P., "When are observational studies as credible as randomised trials?," *Lancet*, vol. 363, no. 9422, pp. 1728-1731, May2004.

(23) Lawlor, D. A., Davey, S. G., and Ebrahim, S., "Commentary: the hormone replacement-coronary heart disease conundrum: is this the death of observational epidemiology?," *Int J Epidemiol*, vol. 33, no. 3, pp. 464-467, June2004.

(24) Topol, E. J. and Falk, G. W., "A coxib a day won't keep the doctor away," *Lancet*, vol. 364, no. 9435, pp. 639-640, Aug.2004.

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