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Drug Safety: Complex and Critical Issues Surround Mechanisms of Evaluation

On September 30, 2004**,** rofecoxib (Vioxx) was withdrawn from the market after 5 years of use in more than 20 million patients following an announcement by Merck that the drug doubled the risk of myocardial infarction and stroke. On September 30, 2006, the *New York Times* ran a front-page article reporting that the Food and Drug Administration (FDA) had issued a warning that the antifibrinolytic drug aprotinin (Trasylol), widely used to reduce perioperative bleeding in patients undergoing cardiac surgery, could cause renal failure, congestive heart failure, stroke, and death. In 2006, Mangano et al. published results from a study involving 4374 patients. Among those patients undergoing uncomplicated coronary-artery surgery, those given aprotinin had a 55% increase in the incidence of myocardial infarction or heart failure and a 181% increase in the incidence of stroke or encephalopathy. In an editorial published in the *New England Journal of Medicine*, William R. Hiatt, MD, Chairman of the Cardiovascular and Renal Drugs Advisory Committee of the FDA writes about the importance of full disclosure and a transparent process in evaluating the findings of all studies germane to drug safety and the public health. REF #1-3

The question of the relative cardiovascular and gastrointestinal safety of long-term treatment with COX-2 selective and traditional NSAIDs is important to patients, doctors, public-health officials, and regulatory agencies. The Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme was a pooling from three randomized double-blind clinical trials, the primary aim of which was to compare thrombotic cardiovascular events with long-term use of etoricoxib, a selective inhibitor of cyclooxygenase 2, and diclofenac, a traditional nonsteroidal anti-inflammatory drug. Etoricixib and diclofenac had similar rates, constant over time, of thrombotic cardiovascular events, complicated ulcers, and events in the lower gastrointestinal tract. Although the quantity and quality of information in MEDAL is significant, safety questions remain about the cardiovascular risk of NSAIDs. Until large-scale randomized trials to address safety concerns can be conducted, some researchers maintain that incidence of pharmaceutical-induced cardiovascular events can be reduced by implementation of pharmaceutical and lifestyle preventative measures. REF #4-6

A recent side note to this question of drug safety is a sharp and unexpected fall in the number of new breast cancer cases diagnosed in the United States. In 2003, after steadily rising for 20 years, new cases of breast cancer diagnosed in the US fell by 7%. Attitudes toward hormone replacement therapy changed abruptly in 2002 when a study that was part of the Women's Health Initiative was terminated early when evidence of health damage emerged. In the scare that followed the release of this information, the number of women aged over 50 taking HRT in the US fell from 30% to about half that. Because some breast cancers need hormones to grow, some researchers attribute the drop in the number of new cases to less frequent use of HRT among women. REF #7

Torcetrapib: A Drug Case Study

Research has shown that raising HDL cholesterol levels may provide benefit in the management of cardiovascular disease, which may have the potential to reduce cardiovascular risk for patients. Torcetrapib is a molecule that was developed by Pfizer to raise HDL levels. Just over a year ago, a clinical trial of a combination of torcetrapib and atorvastatin was underway. Pfizer had invested $800 million dollars in torcetrapib; the successful development of a drug that could raise HDL cholesterol while simultaneously lowering LDL cholesterol had the potential to change the entire approach to heart disease treatment. In late 2006, the clinical Torcetrapib/Atorvastatin Clinical Trial was abruptly halted by the ethics committee overseeing the trial. In reviewing trial data, this committee determined that people taking the new drug had died at a disproportionate rate compared to people taking Lipitor alone. It is unknown at this time if this outcome was caused by the drug itself or by the mechanism by which the drug operates. Although a number of variables may be contributing factors (including patent expirations), Pfizer is reportedly now considering cost-cutting options. REF #8-10

Blood Glucose Levels are a Global Crisis

Although diabetes has been called an epidemic of the 21st century, the effect of this condition on mortality worldwide has been underestimated. Higher-than-optimum blood glucose is a leading cause of cardiovascular mortality in most world regions. In recent analysis that was published in The Lancet, a group of investigators collated exposure data in 52 countries from individual-level records in population health surveys, systematic reviews, and data provided by investigators. In addition to 959,000 deaths directly assigned to diabetes, 1,490,000 deaths from ischaemic heart disease and 709,000 from stroke were attributable to high blood glucose, accounting for 21% and 13% of all deaths from these conditions. The continuous association between glucose and cardiovascular risk places particular focus on population-based prevention approaches. The study investigators concluded that programs for cardiovascular risk and diabetes management and control at the population level need to be more closely integrated. REF #11-12

The focus of the Finnish Diabetes Prevention Study was to examine whether a sustained reduction in the incidence of type 2 diabetes could be achieved by lifestyle intervention. Risk reduction was related to the success in achieving the intervention goals of weight loss, reduced intake of total and saturated fat, increased intake of dietary fiber, and increased physical activity. In an extended follow-up to the original study, researchers assessed the extent to which the originally-achieved lifestyle changes and risk reduction remained after discontinuation of active counseling. With a median total follow-up of 7 years, the findings were that lifestyle intervention in people at high risk for type 2 diabetes resulted in sustained lifestyle changes and a reduction in diabetes incidence, which remained after individual lifestyle counseling was stopped. REF #13

Patients with type 2 diabetes mellitus have a marked increase in the risk of myocardial infarction. Optimal control of blood pressure and low-density lipoprotein cholesterol can substantially reduce excess cardiovascular risk in patients with diabetes. Emerging evidence suggests that thiazolidinediones could be useful for reducing cardiovascular

risk. Carotid artery intima-media thickness (CIMT) is a marker of coronary atherosclerosis and independently predicts cardiovascular effects. A study recently published in the *Journal of the American Medical Association* evaluated the effect of pioglitazone versus glimepiride on changes in CIMT of the common carotid artery in patients with type 2 diabetes mellitus. Over an 18-month treatment period, it was demonstrated that pioglitazone slowed progression of CIMT compared with glimepiride. REF #14

Despite advances in treatment options, lifestyle intervention and reduction in the incidence of type 2 diabetes cases remains the goal of many researchers and appears to be achievable. In a study published in the *New England Journal of Medicine* in 2002, the Diabetes Prevention Program Research Group examined both a lifestyle intervention program and the administration of metformin in preventing or delaying the development of diabetes. While both approaches reduced the incidence of diabetes in persons at high risk, lifestyle intervention was shown to be significantly more effective. REF #15

For patients newly diagnosed with diabetes, lifestyle intervention and administration of metformin traditionally comprise the initial treatment approach. Thiazolidinediones, sulfonylureas, and insulin are generally included as possible second-step medications. Consensus recommendations for the treatment of type 2 diabetes have recently been published that support this approach. The side effects of the thiazolidinediones (which include weight gain, fluid retention, and the risk of congestive heart failure) contributed to the decision not to include them in the first-line treatment of diabetes. In addition, the cost of brand-name thiazolidinediones is higher than that of generic metformin. REF #16

Use of Thiazolidinediones in the Treatment of Nonalcoholic Steatohepatitis

Nonalcoholic fatty liver disease now affects all fields of clinical medicine and is the most common form of chronic liver disease in the United States. Nonalcoholic steatohepatitis represents the extreme end of a large clinical spectrum of nonalcoholic fatty liver disease. Insulin resistance has been closely linked to nonalcoholic fatty liver disease in both clinical trials and laboratory-based studies. This close association between insulin resistance and nonalcoholic liver disease has led to the concept that this disease is the hepatic component of the metabolic or insulin resistance syndrome. No Pharmacologic therapy has conclusively proved to be effective for the treatment of nonalcoholic steatohepatitis. In a recent proof-of-concept study, a group of investigators examined the effectiveness of pioglitazone, a thiazolidinedione that ameliorates insulin resistance and improves glucose and lipid metabolism in type 2 diabetes mellitus. In this study, administration of pioglitazone led to metabolic and histologic improvement in subjects with nonalcoholic steatohepatitis. REF #17-18

Anti-TNF Monoclonal Antibody Therapy in Rheumatoid Arthritis and Risk of Malignancy and Serious Infection

A recent meta-analysis of randomized clinical trials raised concerns about an increased rate of malignancy and serious infection in rheumatoid arthritis patients treated with anti-tumor necrosis factor monoclonal antibodies. Dr. Bland discusses an article that

comments on some of the methodological issues in this meta-analysis and urges caution in interpreting the results. REF #19

What are the New Drug Targets?

The recent approval of drugs that target protein kinases highlights two trends: an emerging realization of the importance of polypharmacology, and also the power of a gene-family-led approach in generating novel and important therapies. Although it is tempting to see advances in technology as transforming the rate of innovation and discovery, there has been little evidence to date improving the ability to tackle new drug target classes with increasing speed and success. As an example, the prevalence and incidence of asthma are very high in the Western world. Because current therapy with inhaled corticosteroids and a long-acting inhaled β2-agonist is highly effective, safe, and inexpensive, there is a hurdle to the development of new therapies that aim to improve on current treatments. Several new treatments are now under development, but many of them are too specific—targeting a single receptor, enzyme, or mediator—and are unlikely to have a major clinical impact. In the case of Parkinson's disease (PD), study of the principal genes that have been shown to cause PD has not led to elucidation of the genes' functions, but recent work implicates abnormal protein accumulation, protein phosphorylation, mitochondrial dysfunction, and oxidative stress as common pathways to PD pathogenesis. In terms of women's health, despite this being the best-educated generation of women in human history, menopause remains something of a mystery. Scientists now understand that menopause is a critical juncture, and what a woman does during menopause (including diet choices) can shape her physical and emotional life for years to come. REF #20-25

Clinician/Researcher of the Month

Jorn Dyerberg, MD
Medical and Scientific Advisor
Marine Nutriceutical Corp/Napro-Pharma AS
Norway

Dr Jorn Dyerberg is a Medical Doctor who was born and educated in Denmark. With his colleague, Dr. Hans Olaf Bang, Dr. Dyerberg is considered a pioneer in the area of omega-3 fatty acid research. In the 1970s, Dr. Band and Dr. Dyerberg visited and studied remote Eskimo settlements in Greenland. Their research uncovered that the low occurrence of ischemic heart disease in these esoteric populations was tied to an intake of long-chained omega-3 polyunsaturated fatty acids from a diet of seal and fish. This finding and further research in the field led to widespread acknowledgement of the beneficial effects of omega-3 and fish oil.

During a recent visit to Seattle, Washington, Dr. Dyerberg and Dr. Bland sat down for a rare live interview. They discuss Dr. Dyerberg's early research, and the far-reaching implications this research has led to in the field of nutritional medicine.

Dietary Lipids and Gene Expression
A high intake of the omega-3 fatty acid docosahexaenoic acid (DHA) has been associated with systemic anti-inflammatory effects and cardiovascular protection. In a recent study, Western blots showed that DHA blocked nuclear p65 NFκB subunit translocation by decreasing cytokine-stimulated reactive oxygen species and ERK1/2 activation by effects on both NAD(P)H oxidase and PKCε activities. This study provides a mechanistic basis for the anti-inflammatory and possibly plaque-stabilizing effects of DHA. REF #26

It is becoming increasingly acknowledged that an individual's genetics can determine responsiveness to nutritional therapy and/or diet-related disease progression. Dietary fatty acids interact with multiple nutrient-sensitive transcription factors. This explains the molecular basis of some of the health effects associated with altered dietary fatty acid composition. REF #26-27

Vitamin D as an Environmental Factor: Autoimmune Disease, Cancer, and Multiple Sclerosis
Experimentally, vitamin D deficiency results in the increased incidence of autoimmune disease. Mechanistically, the data point to a role for vitamin D in the development of self-tolerance. The hormonal form of vitamin D regulates T helper cell (Th1) and dendritic cell function while inducing regulatory T-cell function. There is accumulating evidence pointing to a link between vitamin D and autoimmunity. REF #28

Epidemiologic studies suggest that nutritional phytoestrogens contained in soy are causally related to protection against hormone-dependent cancers. Prevention of colorectal, mammary, and prostate cancer may depend on optimal synthesis of the antimitotic prodifferentiating vitamin D hormonal metabolite (1,25-D3). Nutritional soy or genistein can optimize extrarenal 1,25-D3 synthesis, which could result in growth control and (possibly) in inhibition of tumor progression. REF #29-32

A striking feature of the global distribution of Multiple Sclerosis (MS) is a multifold increase in incidence with increasing latitude, both north and south of the equator. As a potent immunomodulator, a protective effect of vitamin D on MS may be supported by the reduced MS risk associated with sun exposure and use of vitamin D supplements. A recent study published in the Journal of the American Medical Association sought to address the hypothesis that high levels of vitamin D may decrease the risk of multiple sclerosis. This was a prospective, nested case-controlled study among more than 7 million US military personnel who have serum samples stored in the Department of Defense Serum Repository. Multiple sclerosis cases were identified through Army and Navy physical disability databases for 1992 through 2004, and diagnoses were confirmed by medical record review. The conclusions of this study suggested that high circulating levels of vitamin D are associated with a lower risk of multiple sclerosis. REF #33

PI3Kγ Inhibitors are Promising Targets for Management of Inflammatory Disorders

PI3Ks are dual-specificity kinases that have pivotal roles as lipid and protein kinases in numerous intracellular signaling events. The signaling pathways that underlie disease processes are being gradually unraveled, and an emerging understanding encourages the development of effective and safe drugs that target intracellular proteins. REF #34

Multifocal Signal Modulation Therapy

Indole-3-carbinol (I3C) and its congener diindolylmethane (DIM) are derived from cruciferous vegetables such as broccoli and cabbage. Glucosinolates from cruciferous vegetables break down into I3C, which is further converted, primarily into DIM. These and other promising food components have anticancer properties. In animal studies, I3C/DIM not only prevents breast, endometrial, and cervical cancers, but also helps prevent or ameliorate certain diseases such as recurrent respiratory papillomatosis and systemic lupus erythematosus. A case exists for the benefits of I3C/DIM for the treatment of cervical intraepithelial neoplasia (CIN) and thus potential inhibition of cervical cancer. The aberrant behavior of cancer reflects upregulation of certain oncogenic signaling pathways that promote proliferation, inhibit apoptosis, and enable the cancer to spread and evoke angiogenesis. Since multiple pathways are dysfunctional in most cancers, and cancers accumulate new oncogenic mutations as they progress, the greatest and most durable therapeutic benefit will likely be achieved with combination regimes that address several targets. REF #35-36

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