HEALTH AND STRESS

The Newsletter of
The American Institute of Stress

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MORE ON INFLAMMATION, AGING, JOB STRESS & DRUG KICKBACKS

KEYWORDS: CRP, nonsteroidal anti-inflammatory drugs, beer bellies, "inflammaging", bad bosses, bullying, caregiver stress, survivor guilt, drug substitution.

Our last Newsletter provided updates on a few topics we had previously focused on so that readers could "stay tuned" to the latest developments in these areas. Since there was not enough space to include additional important material, this issue will report on other 2003 research findings that are of particular interest. The important contribution of "inflammology" to obesity and a variety of age related diseases continues to be an intense area of investigation despite lack of agreement on the best way to demonstrate or measure inflammation. This is particularly true for Alzheimer's disease.

The role of diet and alcohol in obesity and coronary heart disease continues to be a controversial and confusing topic. Although alcohol related problems are said to be the third leading cause of death, California wineries received approval for making health claims for heart disease on their labels. Drinking red wine is now recommended for diabetics and one study suggests **there is no such thing as a "beer belly"**.

The adverse cardiovascular consequences of job stress were confirmed in several reports using the high demand/low control model. While elevated blood pressure at work during stressful situations has been well documented, one study now shows that this can lead to sustained hypertension. Another found that increased job stress is associated with greater risk for colds and other viral infections as well as gastroenteritis. Job stress due to bad bosses and **bullying may be a greater problem than sexual harassment or racial discrimination** and legislation has been proposed to provide relief similar to that afforded to victims of child abuse and domestic violence. "Caretaker stress" is no longer limited to those caring for chronically ill spouses or relatives. **Women who had to baby-sit or care for their grandchildren for more than nine hours a week had 55% more heart attacks** after four years compared to non-caretaker controls.

Finally, our last Newsletter only scratched the surface of drug company deceit and fraud as well as conflict of interest abuses that abound in government agencies.

ALSO INCLUDED IN THIS ISSUE

Such problems also involve practicing physicians, pharmacists, hospitals and nursing homes. Although the cost to taxpayers may be a billion dollars annually and continues to rise, it seems unlikely that this trend will change in the near future. The NIH director has promised a thorough investigation, but based on past experience, pharmaceutical companies and other powerful vested interests will prevail.

Can Aging And Alzheimer's Be Delayed?

Actuaries predict that rates of Alzheimer's, cancer, cardiovascular disease, and diabetes will double or triple in a few decades as the number of senior and super senior citizens steadily swells. The important role of inflammation has increasingly been demonstrated in these and other age related diseases and supportive evidence continues to accumulate.

Deep abdominal fat is a major source of inflammation because it produces chemicals that stimulate the liver to pour glucose into the circulation. This results in increased insulin secretion that eventually leads to diabetes, insulin resistance and hypertension, all of which are associated with increased risk for heart attack and stroke. There is a close correlation between abdominal obesity and a high CRP, a measure of inflammation that may be a more significant predictor of coronary events than LDL or cholesterol. However, abdominal fat is not the only culprit. The elevated CRP frequently found in non-obese heart attack patients seems to be due to chlamydial and other infections. CRP is also high in hypertension of recent onset regardless of weight, suggesting that inflammation can contribute to cardiovascular disease via multiple mechanisms.

There are strong links with Alzheimer's since patients often show elevated levels of CRP and other inflammation indicators prior to as well as after the onset of symptoms. Many also have high antibody levels to chlamydia and certain viruses and giving broad spectrum antibiotics for three months improved memory and cognitive function compared to untreated controls in one report. A Dutch study showed that **patients who regularly took nonsteroidal anti-inflammatory drugs had 80% less risk for developing Alzheimer's**. Similar findings have been noted in Parkinson's and other neurodegenerative diseases and there is evidence they can reduce risk for certain cancers.

All of this is consistent with research showing that key immune system components become increasingly inflammation-prone as people age. Investigators have identified genetic variants in centenarians that appear to mitigate what they refer to as "inflammaging". They have also shown that elderly people who are frail and sickly are more likely to carry pro-inflammatory gene variants than healthy controls. Elevated blood levels of these inflammatory proteins in senior citizens are also associated with increased osteoporosis, loss of muscle mass, anemia, cognitive decline and other age related problems.

Heredity is very important and scientists are investigating whether aspirin and other non steroidal anti-inflammatory drugs may partially mimic the genetic resistance to inflammation seen in centenarians. Reducing stress could provide benefits for numerous reasons. Stress is a major contributor to the deposition of deep abdominal fat, lowers resistance to infections, and increases homocysteine levels, all of which cause inflammation.

As *The Yellow Emperor's Canon of Internal Medicine* written over 50 centuries ago stated, "I have heard that in early times, people lived to be over 100. But these days people reach only half that age, and must curtail their activities. **Today, people do not know how to find contentment within. They are not skilled in the control of their spirits. For these reasons, they reach only half of their 100 years, and then they disintegrate**."

Big Bellies, Sex, Genes, Booze And Diets

Being overweight can increase risk for diabetes, heart attack, stroke and other cardiovascular complications. This is especially true if those extra pounds come from excess abdominal fat that produces a

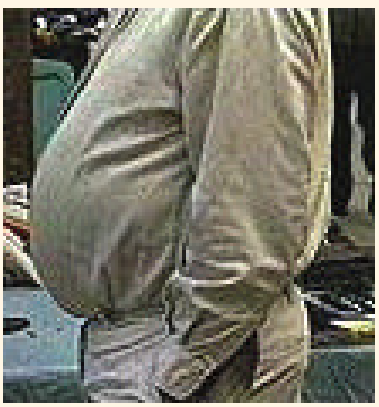
big belly. Obesity rates are escalating and almost one in four American adults now have difficulty seeing their toes when they stand up straight because their bellies get in the way. Scientists at the Centers for Disease Control and Prevention are concerned because most people are not aware of how dangerous this can be. Men are affected more than women, who tend to accumulate fat in their thighs and buttocks that does not appear to be as harmful and may even help prevent coronary disease.

Although a potbelly might be considered to detract from an attractive appearance, this does not seem to be a deterrent for most men with middle-aged spread. It has not interfered with the appeal of golfer John Daly and melon-shaped Garth Brooks seems to be a magnet for pretty young chicks. People tend to like fat men because they are associated with being jolly and good-natured, like Santa Claus. Even Shakespeare had Julius Caesar say, "Let me have men about me that are fat . . . Yon Cassius has a lean and hungry look."

Why some people develop large deposits of deep visceral fat is not clear. A clear link with stress has been demonstrated and there are inherited influences. Researchers recently discovered a gene that stimulates appetite but although overeating is a factor, some people can consume just as many or more calories and stay slender. Obesity does seem to run in some families and a gene has been identified in this population that is transmitted from father to son. However, others with the same gene are not overweight and it is likely that many more "obesity genes" will be found.

Could fats or certain foods be the culprit? Increased alcohol intake has been incriminated but does not seem likely. While obesity is rampant in the U.S., we are far down the list at 32nd in per capita consumption of alcohol compared to other countries and the top six average almost 50 percent more per person.

Beer has gotten an especially bad rap and "beer belly" is apparently a myth according to a recent study of lager lovers. The Czech Republic has the highest per capita consumption of beer of any nation and almost 2000 Czech men and women aged 24 to 65 who drank only beer or no alcohol at all were surveyed. Beer consumption averaged 3.4 quarts/week for men and less than a pint for women. Only 3% of men drank over 3.5 gallons of beer weekly and women rarely consumed half this amount. There was no correlation between weight, waist to hip ratio or body mass index measurements and beer intake. In Munich and other German cities, beer is regarded as more of a food than alcohol and is delivered to homes weekly, much like milk used to be here.



Stout and beer were formerly routinely prescribed during pregnancy to improve health and diabetics are now urged to drink red wine to reduce coronary disease. High fat intake doesn't seem to increase risk for this or obesity but carbohydrates like high fructose corn syrup can. How diet contributes to obesity and heart attacks is a complex and confusing conundrum, as illustrated by a popular posting on several web sites that goes like this:

> The French consume much more fat than the British or Americans but their heart attack rates are much lower. The French and Italians also drink excessive amounts of red wine and Germans consume large quantities of beer and all suffer fewer heart attacks than the British or Americans. The Japanese drink very little red wine and eat very little fat but they also have much fewer heart attacks than the British or Americans. **Conclusion: Eat and drink what you like. It's speaking English that kills you.**

Could Job Stress Be Making You Sick?

Spending years working at a stressful job may lead to high blood pressure, according to researchers at the Mount Sinai School of Medicine. While most authorities would agree that stress itself is not the sole cause of coronary heart disease or hypertension there is good reason to believe it can play a significant role in the progression of these disorders and severity of their symptoms. French researchers found that high-stress jobs can result in elevated blood pressure readings while at work. Doctors from Mount Sinai Medical Center in New York had also previously shown that men who were working in high-stress jobs had systolic blood pressures 6 to 8 points higher than controls in less stressful job situations. In a recent report, they suggest that long-term job stress can also lead to sustained elevations of blood pressure.

The study examined 213 men between the ages of 30 and 60 who were enrolled in the Work Site Blood Pressure Study in New York City. Participants were asked about factors such as freedom to control their own work and freedom to make decisions and other measures were used to assess job demands and pressures. Men who reported spending over 25 years in a high-stress, low-control job had higher systolic blood pressure values both at work (average 4.8 mm Hg higher) and at home (average 7.9 mm Hg higher) when compared with men who held less stressful jobs.

In another long-term study, Finnish researchers recently reported that job stress doubled the risk of death from heart disease. They followed 812 healthy male and female employees of a company for an average of 25.6 years. Information was obtained through periodic interviews, questionnaires, physical examination and laboratory studies to evaluate stress, blood pressure and cholesterol levels, and body mass index. They found that job strain (high work demands and low job control) and effort-reward imbalance (high demands, low security, few career opportunities) were each associated with a doubling of the risk of cardiovascular death among initially healthy employees.

High job stress was also associated with increased cholesterol concentrations and body mass index. Other studies using the high demand/low control model have shown a link between increased job stress and increased rates of hypertension and coronary events. However, this is the first to quantify the association between job stress and cardiovascular mortality and the results are impressive. Having low job control and a high effort-reward imbalance seemed to put workers at greatest risk for cardiac death.

Bad bosses can also drive up your blood pressure and put you at risk for a heart attack or stroke according to a small U.S. study. 28 female healthcare assistants aged 18 to 45 were asked to score the interpersonal style of their supervisors using a validated five-point scale, where 1 equals "strongly disagree," to 5 "strongly agree." The items included statements, such as: "My supervisor encourages discussion before making a decision," and "I am treated fairly by my supervisor." Healthcare assistants are supervised by nurses and take on some of their work with varying levels of responsibility but they are lower down the job status hierarchy.

The researchers analyzed the readings from blood pressure monitors worn by healthcare assistants every 30 minutes for 12 hours over three working days. Thirteen of the assistants were supervised by two people, but on different days, both of whom were perceived to have negative interactions with their staff. A comparison group of 15 worked under just one supervisor or with two whose working manner was more congenial. The comparison group registered a rise of 3 mm Hg in systolic and no difference or a lower diastolic blood pressure when working with their two different supervisors. The other group showed a 15 mm rise in systolic and a 7 mm rise in diastolic blood pressure when working for a supervisor they considered to be unfair. An increase of 10 mm in systolic and 5 mm in diastolic blood pressure is associated with a 16% increased risk of coronary heart disease and a 38% increased risk of stroke.

Harassment and bullying are workplace problems that may be even

more prevalent than sexual harassment or racial discrimination according to an *U.S. News & World Report* study. Ninety percent of workers felt that incivility on the job was a serious problem and almost as many believed it was getting worse. In another "desk rage" survey, 23% of workers admitted they had been driven to tears by this kind of mistreatment during the previous 12 months and 42% said that yelling and verbal abuse at work were commonplace. About 1 in 6 complained of having been subjected to destructive bullying tactics during the past year.

Bullying has been defined as "offensive, intimidating, malicious or insulting behavior, an abuse or misuse of power through means intended to undermine, humiliate, denigrate or injure the recipient." Some common tactics include spreading false rumors, interrupting a person while he or she is speaking, acting in a condescending manner, ridiculing a person's opinions in front of others, failing to return calls or respond to memos, giving the "silent treatment", engaging in verbal sexual harassment, staring, dirty looks, damning with faint praise and showing up late for meetings run by the target. More than four out of five bullies are bosses and half of all bullies are women. Women bullies target females 84% of the time and men bullies target them 69% of the time so that women are the most likely to suffer.

Unlike cases involving violations of federally protected Civil Rights, bullied individuals have few avenues for successful legal recourse. The Office of Occupational Safety and Health (OSHA) deals only with safety issues that pose physical harm, not emotional distress. However that may be changing. The Workplace Bullying & Trauma Institute is working to pass an anti-bullying law similar to child abuse and domestic violence legislation. They were successful last year in introducing California Assembly bill AB 1582 to provide protection against health-impairing bullying and are spearheading similar bills in other states. Such legislation already exists in the U.K. and other countries where these problems may be even greater.

Job stress can take its toll even if you work at home according to a report from the ongoing Nurses' Health Study that followed over 54,000 women for four years. It found that those who took care of grandchildren for more than nine hours a week were 1.55 times more likely to develop heart disease than controls without this responsibility. Other studies had previously found that grandparents who were responsible for raising grandchildren faced the same kind of health problems as people caring for chronically ill spouses or children. Numerous studies show that caregivers for a spouse or relative suffering from Alzheimer's have impaired immune system responses that makes them more susceptible to respiratory and other infections and are also at greatly increased risk for depressive and anxiety disorders.

In addition to cardiovascular disease, job stress can also increase the likelihood of acute infections like the common cold, flu-like illnesses and even gastroenteritis. Dutch researchers followed more than 8,000 employees over a three-year period. They recently reported that workers in highly stressful jobs suffered from colds 20% more often than controls in less demanding positions. The greater the stress the more severe and more frequent the infection. Employees with burnout complaints suffered from gastroenteritis almost twice as often as others without such symptoms. Job insecurity due to downsizing was particularly associated with an increased incidence of flu and gastroenteritis. Shift workers were at greater risk for developing infections than daytime employees, especially if they had to rotate through three shifts.

Downsizing often means that retained workers are subjected to increased stress because (1) they suffer from survivor guilt when they come in contact with friends and former employees who were fired and (2) must work longer hours to maintain productivity. Other researchers report that working longer hours is not a significant problem and it's not how many hours you work but under what conditions that is critical. Situations that diminish self-esteem are the most damaging, which highlights the harmful effects of bullying.

Physician, Pharmacy & Hospital Abuses

Two or three decades ago drug company-sponsored dinners and meetings for doctors and financial reimbursement for attending was quite common. It was not unusual for high volume prescribers and their spouses to be invited to spend a weekend at some elegant resort to attend an "educational" presentation that promoted the company's drugs. Others were given lavish gifts like choice tickets to top theater and sporting events to reward them for using certain products based on pharmacy records. Such practices are now prohibited in guidelines that resulted from proof that this influenced prescribing habits, especially for expensive and very profitable drugs. Much of the impetus for reform has actually come from physicians. The "No Free Lunch" group even objects to coffee mugs, letter openers and other inexpensive items that advertise drugs.

Manufacturers now use other subterfuges to pay physicians, pharmacists, as well as institutions to use their drugs, some of which are illegal. New York's Attorney General recently announced he planned to sue two major pharmaceutical companies for paying doctors and pharmacists to push their products. Six other states are involved in similar litigation they claim has cost consumers, state and federal programs hundreds of millions of dollars over the past few years.

Here's how it works. Pharmacies are rewarded for recommending particular drugs to physicians who use them in their practice. The drug companies establish a price for the drug that the government and insurance companies use to determine how much to pay doctors and pharmacies for their purchases. The same drug is then sold at a much lower price to certain pharmacies and physicians who pocket the difference when they are reimbursed at the government rate. According to the Attorney General's staff, **a doctor might pay as little as $7.40 for 10 milligrams of a chemotherapy drug but would be reimbursed $34.42** based on the average wholesale price. A New York Medicare patient would also make a co-payment of $8.60 so that the doctor would pocket $35.62 in addition to any charges for administering the medication and an office visit.

The New York suit charges Pharmacia and GlaxoSmithKline with consumer fraud and making false statements to government health plans when they established their drug prices, as well as with commercial bribery for trying to wield inappropriate influence on doctors' decisions. It claims that Medicare could have saved $21.2 million for Pharmacia's Adriamycin if wholesale catalogue prices had been used as the basis for reimbursement instead of the published average wholesale prices.

Merck was sued in Louisiana last year for defrauding the federal Medicare and Medicaid programs in marketing Pepcid to hospitals and nursing homes. A physician protested that when he prescribed Zantac, another heartburn drug, for his patients in hospitals and nursing homes, he later found that they were given Pepcid without his permission. He claimed that his patients suffered because Pepcid can be more toxic than Zantac if a lower dose is not used. Although many hospitals have drug substitution policies for equivalent products, the Louisiana Board of Medical Examiners and the Board of Pharmacy both ruled that it is illegal to automatically substitute Pepcid when a prescription calls for Zantac. The suit contends that Merck sold Pepcid to hospitals for about 10 cents a tablet, but charged the government as much as $1.65. Under Federal law, drug companies must give the Medicaid program the lowest price.

California is investigating whether Watson Pharmaceuticals paid kickbacks to doctors to prescribe Ferrlecit, its injectable drug used to treat anemia in dialysis patients. Doctors who attended dinner meetings signed a "consultant agreement" form and were later paid $500 for participating. This procedure was also practiced in several large cities in other states.

In another suit filed in Massachusetts last September, Warner Lambert was accused of illegally promoting the sale of Neurontin. Drug companies are prohibited from promoting or marketing a medicine in anyway for uses that have not received FDA approval for efficacy and safety. However, once a drug becomes available, doctors can prescribe it for anything they believe might benefit their patients.

Neurontin & Other Spurious Promotions

For example, Neurontin had been approved only as an additional drug for epileptics who continued to experience frequent seizures on their regular medication. Obviously, it had very limited applications and sales. Warner Lambert, which has since been acquired by Pfizer, got around this by having physicians promote it for everything from restless leg syndrome, and bipolar disorder to ulcers, osteoarthritis, backache and other painful conditions. Their top speaker, a former professor of neurology at the University of Florida, received more than $300,000 for speeches given over a three year period and six other doctors from top medical schools, received more than $100,000 each. A professor at Harvard Medical School who told physicians that "pain specialists are finding that low dosages of Neurontin are effective" was paid $71,477. A University of Minnesota professor received over $49,000 to speak about Neurontin's benefits in addition to $304,000 to publish his textbook on epilepsy that highlighted ways the drug could be used. Some doctors received reimbursement to write reports on how Neurontin had worked for a handful of their patients. Others were paid to prescribe it in doses far exceeding the approved levels as part of a clinical trial that Warner-Lambert had created solely for the purpose of promoting their marketing efforts.

Warner-Lambert consistently tracked doctors' prescriptions to see if the numbers increased after the doctors attended Neurontin meetings or after they had been hired to speak about the drug. **A Connecticut physician wrote 58 prescriptions for unapproved uses of the drug after he attended a meeting where other doctors spoke about Neurontin's numerous benefits. He had never written a Neurontin prescription prior to the meeting** and was later paid over $1000 for speaking to doctors about the drug. In one survey, half of 503 physicians said they had also been asked by sales reps to give the drug for unapproved uses. Although this is prohibited, almost half of them admitted that they had or intended to increase their Neurontin prescribing.

According to court papers, Medicare and Medicaid paid hundreds of millions of dollars for unapproved uses of Neurontin, which helped make it a **top seller with more than $2 billion in revenue, 90 percent of which was for non approved uses**.

However, that's just the tip of the conflict of interest iceberg. Powerful companies are able to promote their products by providing financial incentives at every stage of the approval process. A survey by Yale University Medical School investigators, published last year in the *Journal of the American Medical Association*, revealed that four out of five academic researchers received discretionary funds and gifts from drug manufacturers and biomedical companies. More than a third were paid consulting fees or had equity positions and other financial arrangements with companies whose drugs or devices they were investigating. Almost 70 percent of U.S. institutions also held equity in companies whose research was being conducted at their facility. This has become an increasingly important source of revenue and some fear that this may have influenced research results and conclusions at some medical schools and universities.

For example, in 61 industry sponsored studies of non-steroidal anti-inflammatory drugs, not a single trial found the comparison drug superior to the sponsor's drug. The lead author of the article, an Assistant Professor of Medicine, explained that this can easily be accomplished in several ways, including: comparing the sponsor's drug with no treatment or placebo; by using a higher dosage of the sponsor's drug than the comparison drug; or by comparing the sponsor's well absorbed medication to one that is poorly absorbed. Negative results are often not reported and the majority of industry sponsored researchers were also required to keep results confidential for more than six months (often while the sponsor filed for patent). In addition, authors may be asked to delay publication until the company has a chance to market their results and some have even been denied access to all study data until statisticians have had a chance to review and possibly manipulate the results.

Federal Employee Conflicts Of Interest With Drug Companies And Grant Recipients

In previous Newsletters, we have detailed how pharmaceutical companies have infiltrated the FDA and influenced their decisions in other ways. In the last issue, numerous similar conflicts of interest involving top NIH officials were detailed, including Stephen I. Katz, director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases who collected between $476,369 and $616,365 during the past decade in fees from Schering AG and six other drugmakers. During this period, his Institute conducted clinical trials involving one of the company's drugs and pledged $1.7 million in small business research grants to another. **Five other present and former senior NIH officials reportedly received up to $2.2 million in company fees and stock options.**

In addition, it now appears that Richard D. Klausner, former director of the National Cancer Institute (NCI), also accepted lecture fees and other cash gifts from universities and research institutions that receive NCI and NIH research grants. A Congressional committee is particularly interested in a $3000 cash award plus transportation and lodging expenses from the Arizona Cancer Center. This NCI-designated comprehensive cancer facility at the University of Arizona Health Sciences Center received more than $25 million in NCI grants and was awarded $486,000 in federal contracts. (The NCI director and other high-ranking NCI officials are prohibited under federal regulations from receiving an honorarium from a private source for a lecture on cancer research that was funded by NCI.) Congress is also investigating whether Klausner steered a $40 million contract to Harvard University while he was a candidate to become the school's president. He currently heads the Global Health Program at the Bill and Melinda Gates Foundation in Seattle.

Stung by these allegations and other accusations contained in a scathing *Los Angeles Times* investigative report, NIH Director Elias A. Zerhouni announced that he would create a blue ribbon panel that would include outside experts to conduct an ethics review of how the agency handles conflict-of-interest matters when top employees receive lucrative consulting contracts from private companies. Every outside consulting relationship that NIH employees have established during the past 5 years will also be scrutinized to determine whether all rules and regulations have been adhered to and that their activities are "in the best interest of the public." That may not cut the mustard. The Chairman of the Congressional Subcommittee on Oversight and Investigations as well as the Chairman of the House Energy and Commerce Committee have already asked Zerhouni to supply by January 8, 2004, all documents relating to the more than $2.5 million in fees and stock options drug companies paid to high-level NIH scientists and officials over the past 10 years. This may be just the tip of the iceberg. The December 7 *Los Angeles Times* report also found that not all of the income received was required to be listed in public reports because of prior agreements and it is likely that some funds were funneled to family members. Stay tuned for more!

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