HEALTH AND STRESS

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The American Institute of Stress

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IMPORTANT RECENT RESEARCH ADVANCES IN STRESS & HEALTH

KEYWORDS: Anxiety, depression, social support, CoQ10, inflammation, NIH duplicity and deficiencies, high fructose corn syrup, leptin, ghrelin, Federal subsidies

We have addressed a variety of controversial topics in our monthly Newsletter that have often concluded with a request to "stay tuned" for more information. Several studies over the past year dealing with these and related issues have now provided strong support for positions and predictions previously expressed.

There is increasing evidence to back up the contention that a high fat diet is not the cause of either elevated cholesterol or coronary heart disease. There is also growing evidence that the cardioprotective benefits of statins are due to their anti-inflammatory effects rather than any LDL lowering activities and that their serious adverse side effects are even more widespread than previously suspected.

ALSO INCLUDED IN THIS ISSUE

A significant link between obesity and cancer has been confirmed and several mechanisms of action have been suggested. Additional links between anxiety and depression and increased susceptibility to certain malignancies have also been uncovered.

The crucial role of stress in promoting deposition of deep abdominal fat and the production of damaging inflammatory cytokines has become quite clear. Abdominal obesity is associated not only with increased risk of cancer but also diabetes and cardiovascular disease. Obesity rates began to progressively escalate around 1975, which correlates with the introduction and increased consumption of high fructose corn syrup as a sweetener in soft drinks and greater use of processed corn in other fast foods. This resulted from a change in Federal reimbursement to farmers that made corn unbelievably cheap. This trend will likely have disastrous consequences but is not likely to change because **government policies subsidize the production of foods we are told to avoid and are dictated by politics rather than public health concerns**.

Several previous Newsletters have exposed serious deficiencies in the ability of the FDA to protect the public from unsafe

medications. This is largely due to pharmaceutical and other powerful vested interests with considerable clout on Congress and regulatory agencies. New evidence indicates similar serious conflicts of interest involving **top NIH officials who are permitted to receive compensation from the very same companies whose drugs they are evaluating**.

This Newsletter will explore all the above topics. A subsequent issue will be devoted to other 2003 advances in stress and health research so that you can continue to "stay tuned".

Can Being Overweight Cause Cancer?

A very large and long-term study published in the *New England Journal of Medicine* concluded that "**current patterns of overweight and obesity in the United States could account for 14 percent of all deaths from cancer in men and 20 percent of those in women**." Researchers under the auspices of the American Cancer Society evaluated almost one million U.S. adults in 1982 and classified them as being normal, overweight, or obese based on their BMI (body mass index). A BMI of between 18.5 and 24.9 is considered normal, between 25.0 and 29.9 overweight, and 30.0 or more is obese. Health status and weight were followed over the next 16 years, during which those who were overweight had higher death rates from a host of different malignancies.

Among both sexes, excess body weight increased the risk of death from cancer of the liver, gallbladder, pancreas, esophagus, colon, rectum and kidney, as well as non-Hodgkin's lymphoma and multiple myeloma. The heaviest men were more likely to die from cancer of the stomach and prostate. In women, deaths associated with being significantly overweight were most often due to cancer of the breast, uterus, cervix and ovary.

The higher the BMI (which takes into account height as well as weight), the more likely a person was to die from cancer. The heaviest people (BMI of 40 and over) had death rates from cancer of any type that was 52% higher in men and 62% higher in women compared to controls with normal values. While this report only dealt with deaths due to cancer, other studies have shown that being overweight also increases the likelihood of developing other diseases of the breast, uterus, colon, rectum, kidney, esophagus, and gall bladder. It's easy to understand why carrying around lots of excess pounds every day could put a strain on the heart that increases cardiovascular death rates, but why obesity should increase risk of death from cancer is not clear.

People who are overweight are more likely to develop gallstones or acid reflux disease, both of which can produce chronic inflammation, an established risk factor for cancer. Individuals with excess abdominal fat also tend to have higher levels of estrogen, insulin and insulin-like growth factor-1 that could play a role. High levels of insulin and growth factor-1 cause cells to grow more rapidly and marked elevations could cause some cells to reproduce so fast that they become malignant.

Being fat and unsightly can also be very stressful, especially in adolescent females and children, where obesity is rapidly reaching epidemic proportions. A study of obese kids aged 5 to 18 reported that they had missed an average of four days of school in the month before their evaluation compared to less than a day for those with normal weight. One reason may be that two out of three had weight-related problems like diabetes and high cholesterol and 13% percent suffered from anxiety, depression or other emotional complaints.

But even obese children without physical or psychiatric problems had a poor quality of life comparable to that seen in classmates with cancer. Kids with cancer often suffer from stressful medical and surgical interventions as well as unpleasant disabilities. However, they may not be subjected to as much teasing as others who are fat, which again illustrates the importance of emotional stress.

More Links Between Stress And Cancer

For example, Norwegian psychiatrists followed over 60,000 people who had participated in a study from 1995 to 1997 to determine risk factors for cancer. The thorough medical evaluation included an anxiety rating test; researchers reported at the May meeting of the American Psychiatric

Association that those with high anxiety scores had 25% more malignant and premalignant conditions than controls with low ratings. A review of the literature at the same meeting also revealed an association between psychological stress and an increased incidence of lymphomas and malignant melanomas, both of which have been linked to impaired immune system function.

Increased stress and particularly depression has been associated with malignancies of the female reproductive organs since Galen first attributed such cancers to an excess of black bile 2000 years ago. Several studies over the past 150 years tend to confirm this relationship and further support comes from a recent report showing diminished immune responses in such patients off of antidepressants compared to treated controls. In one survey of low income women receiving family planning services, all subjects completed a stressful life events questionnaire that included such things as divorce, infidelity, psychological and physical violence in the preceding five years. After adjusting for age, HIV infection and number of sexual partners, increased psychosocial stress was found to be significantly higher in the 122 women with precancerous lesions compared to 160 controls with normal cytology.

Increased stress was also associated with poorer outcomes in a study that tracked women for seven years following the initial diagnosis of stage 2 breast cancer that had not spread beyond regional lymph nodes. All participants filled out detailed questionnaires about various stressors in their lives and when they were experienced. It was found that severe stress after the malignancy had been diagnosed had no relation to recurrence or death. In contrast, major troubles like divorce or death of a loved one in the year prior to diagnosis nearly tripled the likelihood of having a recurrence or dying from breast cancer.

Similar conclusions were reached in a study of over 10,000 female twins born in Finland who were followed from 1982-1996. Participants completed a baseline health questionnaire in 1975 designed to assess known breast cancer risk factors along with individual life events and stressors and this was repeated in 1981 and 1990. Analysis of the 180 cases of breast cancer revealed that increased life event changes and psychological stressors in the five years before the baseline assessment were associated with a significantly increased risk of developing breast cancer compared to cancer-free controls. Another report on 116 newly diagnosed women with breast cancer also found that those with the highest stress levels had a much greater decrease in three measures of immune system resistance than those with low stress. In addition to direct hormonal effects, stress can increase smoking, use of alcohol and drugs or cause sleep problems, all of which can impair immune function.

Stress and lack of social support can also increase risk for developing prostate cancer. Researchers found that men with high levels of stress and lack of satisfying relationships with friends and family had higher blood levels of prostate-specific antigen (PSA), a marker for increased risk of developing prostate cancer. After controlling for age, which increases PSA, the likelihood of having an abnormal PSA test was over three times greater for men with high levels of stress than for controls with low levels (16 percent of high stress men compared with 4.8 percent for low stress men). Similarly, men who were rated low with respect to social support resources were twice as likely to have abnormal PSA tests compared to those deemed to have high levels of support (12.9 percent of low-support men versus 6.8 percent for high-support men).

An Australian judge has just ruled that job stress contributed to the colorectal cancer that killed an officer who had worked at a maximum security prison for over 21 years. His widow claimed that he had been distressed by riots, hostage situations and deaths in custody, was upset about his loss of status in a restructure of positions and had "gone on stress leave" two months before he died.

Statins, Cancer, Depression & Alzheimer's

Statins have been touted to prevent or improve everything from cancer, Alzheimer's disease and depression to atrial fibrillation, multiple sclerosis and osteoporosis. Such alleged benefits could hardly be attributed to

any lowering of LDL or cholesterol. If confirmed, reduction of inflammation would be a more plausible explanation, as has been shown for the cardioprotective effects of statins. Aspirin and NSAID's are also believed to protect against colorectal and other cancers because of their anti-inflammatory effects.

On the other hand, there are increasing concerns that statins could actually cause cancer. All statins have been proven carcinogenic in experimental animals at blood levels equivalent to those seen in patients on commonly prescribed dosages. In humans, the time lag between exposure to a carcinogen like smoking and the diagnosis of lung cancer can take several decades. Therefore, not enough time may have elapsed to determine whether statins can cause cancer in people. In addition, a malignant growth may be present for a considerable time before it is detected. This is less apt to happen with skin and breast tumors and statins have now been linked with an increased incidence of both of these malignancies.

In one large clinical trial, breast cancer was found in 12 women in the statin group but in only one of the controls, a highly significant difference after only a few years of treatment. This is supported by a recent analysis of the records of more than 65,000 women over age 35 enrolled in a health plan and followed for five years, during which the 1512 cases of breast cancer were diagnosed. Statin use was identified from pharmacy records and an analysis of the data led to the conclusion that "young women who are treated with statins may be at increased risk for the development of breast cancer." In another trial, those receiving statins -had a 25% increase in overall cancer compared to controls. Skin cancers are the most likely to be readily detected and non melanoma malignancies (basal and squamous cell) were significantly increased in the statin group in two of the largest and longest statin studies.

This may be very significant and will require careful follow-up since **non-fatal skin cancers have been reported to be associated with increased risk for a future unrelated malignancy**. This was confirmed in a recent study of over 90,000 post-menopausal women. Of the 7,665 with a past history of skin cancer, nearly 25% reported subsequent malignancy of the brain, breast, lung, liver, ovary or uterus. This was over twice the rate of such tumors in women with no evidence of skin cancer.

Statins block the synthesis of Coenzyme Q10 and low Q10 levels have been reported in breast, lung, prostate, pancreas, colon, kidney, head and neck, lymphoma and myeloma malignancies. A statistically significant relationship between Q10 blood levels and breast cancer prognosis has been demonstrated and regression of breast cancer has been reported in patients receiving Coenzyme Q10. Statins similarly block the synthesis of squalene, which has been used to prevent and treat breast, prostate and colon malignancies; statins could contribute to cancer in other ways, such as by interfering with bile acid synthesis.

Studies show that low serum cholesterol is associated with an increased incidence of cancer and various adverse health effects ranging from depression, suicide and other violent behaviors. Similar problems have also been reported in cholesterol lowering drug trials that showed a reduction in coronary mortality but no change in total mortality rates. Just as many patients died from cancer, suicide and other complications as from heart disease. It is important to keep this in mind when evaluating claims that statins prevent cancer and depression since these are based on relatively short-term observations in selected populations where other relevant factors are often not taken into consideration.

With respect to Alzheimer's disease and memory loss there have been numerous reports of transient amnesia in patients that improve after statins are stopped, especially when Q10 is given. In many cases, cognitive problems returned only after statin therapy was resumed, strongly suggesting that there was a causal relationship.

Sweeping Statin Safety Under The Rug

These and other adverse statin effects have been skillfully suppressed by powerful pharmaceutical companies. For example, a recent editorial by Anthony Gotto in the *Archives of Internal Medicine* entitled "Safety

and Statin Therapy: Reconsidering the Risks" purported to be a state of the art review of these issues. The only complications mentioned were myopathy and liver disease. Its real purpose was to support a paper by Smith et al. in the same issue claiming that statins are so safe that it is no longer necessary to monitor CPK or liver functions in most patients, even though severe muscle disease with normal blood tests has been reported in at least two articles.

There was no reference to possible memory impairment and malignancy or that all statins have been shown to cause peripheral neuropathy. This results in numbness, pain, burning or tingling sensations in the feet or hands that makes it difficult to climb or walk. While seen most frequently in diabetics, in one report of new cases the incidence was 16 times higher in patients taking statins. **Here again, symptoms often disappeared or improved when statins were stopped.** Gotto listed a half dozen or more statin manufacturers from whom he has received funds, which may have something to do with these omissions.

Current guidelines mandate increasing the dose of statins until LDL is lowered to a level that the vast majority of patients never achieve. The official recommendation is a goal of 100 or less in all patients with a history of a heart attack or evidence of coronary artery disease. For those having no signs or symptoms of heart disease but two or more risk factors, a LDL under 130 is the target. The drug companies are well aware that these are unrealistic objectives. Studies show that 63 percent of patients with two or more risk factors but no heart disease fail to lower their LDL to the recommended level. The situation is even worse for those at greatest risk because of a previous heart attack or evidence of coronary disease. **Less than one in five are able to get their LDL down to 100 despite diet, exercise and increasing their dosage of statins.**

This is great for statin manufacturers since it essentially guarantees that millions of people will be taking higher and higher doses of statins for the rest of their lives. That is why an 80-mg. Lipitor tablet was recently approved. The tragedy is that statin side effects skyrocket at higher doses. If you increase the dosage of Lipitor from 10 or 20 mg to 40 mg daily, they triple. **At the new 80 mg/day dose of Lipitor, side effects are 12 times more frequent!**

Current recommendations are so inane because the benefits of statins have little to do with lowering LDL or cholesterol for the following reasons:

- Cardioprotection occurs regardless of baseline LDL levels and shows no relationship to the amount of reduction in LDL.
- If statins did work by lowering LDL one would expect to see evidence of a linear dose-response relationship. This has never been demonstrated in any statin study.
- Cardioprotective effects are seen in the elderly, where neither LDL nor cholesterol is a risk factor for heart attack.
- In the HPS (Heart Protection Study) statins were found to prevent ischemic stroke, a disorder in which LDL is not a risk factor.
- Benefits are achieved far too rapidly to be due to lowering LDL. When statins are given after acute coronary events or prior to stenting and clearing of artery blockage, they show benefits within weeks, which suggests that they start working immediately by reducing inflammation.

Most heart attacks are due to an atherosclerotic deposit with an unstable fibrous cap covering a lipid core. This usually does not interfere with blood flow so that there are no symptoms until it ruptures or swells due to thrombus formation. Statins appear to work by rapidly reducing inflammation so that this part of the plaque is less likely to break off into the circulation. Like aspirin, it is also possible that they have anticoagulant activities that reduce clot and thrombus formation.

Although the new Crestor and other statin ads now emphasize that benefits are not related to LDL lowering, there has been no change in therapy guidelines nor are any likely.

How The Public Continues To Be Deceived

One of the most impressive developments during the past year has been fairly conclusive proof not only that elevated cholesterol does not cause heart attacks but that high saturated fat diets do not raise blood cholesterol or LDL. This evidence comes from Atkin's diet and other studies showing that a high fat diet can actually reduce weight and lipid levels. Despite these final nails in the cholesterol coffin the diet-cholesterol-coronary dogma persists.

Scott Grundy, who is largely responsible for dietary fat and lowering LDL guidelines wrote, "Even moderate reductions in LDL levels, such as those obtained by reducing dietary saturated fatty acids, are projected to substantially reduce risk of CHD in populations .... Evidence is abundant that elevated LDL is a major cause of CHD and that lowering LDL levels reduces CHD risk." The references cited did not confirm these claims and some showed just the opposite. Like other cholesterol cartel hired hands, Grundy frequently distorts the facts by incorrectly quoting controversial papers and inflating favorable but insignificant findings. At the same time, solid studies that are not supportive are routinely ignored.

There is just too much money at stake and it seems doubtful that anything will slow much less stop the statin steamroller. In our last Newsletter, a number of attempts by manufacturers to obtain a bigger piece of this lucrative pie with add on products were outlined. Astra Zeneca's recently approved Crestor may replace Lipitor as the leading statin since a six week study in patients with primary hypercholesterolemia showed that 10 mg. lowered LDL more than Lipitor, Zocor and Pravachol at the same and even some higher doses. What was not mentioned was that an 80 mg. dose of Crestor was not approved because of safety issues. There is also evidence that even 40 mg/day can cause kidney damage.

Pfizer countered with a study showing that patients taking Lipitor "experienced a significant reduction in the progression of atherosclerosis, or hardening of the arteries, compared to patients who received Pravachol". They failed to mention that they compared 80 mg. of Lipitor daily with 40 mg. of Pravachol.

Also omitted, in addition to the absence of a level playing field, was that this conclusion was reached because Lipitor allegedly reduced plaque by 0.4 percent after 18 months. This was based on intravascular ultrasound technology that may not be able to accurately measure such small changes. Even if true, this infinitesimal decrease may have no significance in regard to preventing coronary deaths since proof would require long-term mortality studies. The lead author, who developed the technique and was paid by Pfizer, is a member of the FDA Cardiorenal Advisory Panel that reviews applications for new drug approval and changes in the labels of existing agents.

In an interview with the Associated Press he said the data seem to show that "There is no such thing as too low an LDL." MSNBC picked up on this and ran the following headline on their web site: "New research indicates the lower the level of LDL the better." Not only is there no support for this but the Framingham study showed that when cholesterol dropped below 160 coronary heart disease increased and that "**There is a direct association between falling cholesterol levels over the first 14 years and mortality over the following 18 years.**" The National Heart, Lung and Blood Institute's Honolulu Heart Study reported in *Lancet*: "Our data accord with previous findings of increased mortality in elderly people with low serum cholesterol, and show that long-term persistence of low cholesterol concentration actually increases the risk of death."

As previously emphasized, there is no evidence that lowering cholesterol provides any cardiovascular or other benefits in senior citizens. A prior *Lancet* article reported that a study of elderly French women living in a nursing home found that **those with the highest cholesterol levels lived the longest. The death rate was more than five times higher for women with very low cholesterol**. Several studies show that patients with low cholesterol levels have higher rates of infectious disease, AIDS, and cancer and are at increased risk of death from respiratory and GI diseases. Ravnskov recently presented a paper entitled "**High Cholesterol Protects Against Disease**".

Are Conflicts Of Interest The Problem?

There seems to be little doubt that this is a major factor based on a scathing report by a *Los Angeles Times* investigative reporter. He was awarded a second Pulitzer Prize for his exposé of the FDA in a 2000 article showing how conflicts of interest were responsible for the approval of 12 lethal drugs that had to be recalled. He has now turned the spotlight on similar financial shenanigans involving top NIH officials. Here are a few examples:

A patient died as a result of a drug being tested as a treatment for kidney inflammation at a NIH research clinic. Among the first to be notified was Dr. Stephen I. Katz, Director of the Institute conducting the study. Katz could and should have stopped the study and immediately warned doctors elsewhere who were also prescribing it. This would have obviously threatened the future of the drug, which was made by Schering AG, a German company, and nothing was done. What was not known was that **Schering AG paid Katz at least $170,000 and that he had received up to $616,365 from other companies during the past decade. One that paid him over $140,000 for consulting fees was awarded $1.7 million in grants from his Institute before going bankrupt last year.** Katz claimed that his consulting fees did not influence his decisions and that **NIH leaders had approved his arrangement with Schering**. His story is hardly unique.

Dr. John I. Gallin, director of the NIH's Clinical Center, the nation's largest site of medical experiments on humans, received between $145,000 and $322,000 in fees and stock proceeds for his consulting from 1997 through last year. In one case, Gallin co-wrote an article highlighting a company's gene-transfer technology while being paid as a consultant to a subsidiary of that company.

Jeffrey Schlom, director of the National Cancer Institute's Laboratory of Tumor Immunology and Biology, received $331,500 in company fees over a 10-year period. Schlom helped lead NIH-funded studies exploring wider use for a cancer drug — at the same time that his highest-paying client was seeking to make the drug through genetic engineering.

Dr. Richard C. Eastman, NIH 's top diabetes researcher, wrote the FDA to defend a drug without disclosing that he was a paid consultant to the manufacturer. His letter said the risk of liver failure was "very minimal" but six months later, a patient who was taking the drug in a NIH study that Eastman oversaw, died from sudden liver failure. Liver experts agreed that the drug was probably the cause.

Dr. Ronald N. Germain, deputy director of a major laboratory at the National Institute of Allergy and Infectious Diseases, **collected more than $1.4 million in company consulting fees in the last 11 years, plus stock options**. One of the companies collaborated with his laboratory on research. The founder of another of the companies worked with Germain on a separate NIH-sponsored project.

Jeffrey M. Trent, scientific director of the National Human Genome Research Institute from 1993 to 1996 reported between $50,608 and $163,000 in industry consulting fees. Trent, who accepted nearly half of this from a company active in genetic research, was not required to file financial-disclosure statements in 1997 and left the government last year.

Thomas J. Kindt, the director of in-house research at the National Institute of Allergy and Infectious Diseases, accepted $63,000 in consulting fees from a New York biotechnology company and wound up as an inventor on one of its patents. Asked why the government received no consideration, Kindt said that he had contributed to the "basic idea" while using vacation time and that "No work was done on it as a government employee." Kindt's salary is $191,200/ year and with an annual budget of $27.9 billion, NIH officials are among the highest paid Federal employees.

Due to a 1998 ruling, 95% don't have to disclose their consulting income to the agency although this was not found in a survey of 34 other Federal agencies. In several, all top-paid employees regularly submit public reports. NIH officials frequently sign confidentiality agreements with other employers and although they are supposed to pledge not to participate in decisions affecting an outside client, this is often not complied with or enforced.

Is Federal Funding Fueling The Current Epidemic Of Obesity And Diabetes In Kids?

About two-thirds of Americans are overweight and almost one in three is obese. Of particular concern is the rise in obesity in children, which has tripled over the past few decades. Along with this is a startling increase in Type 2 diabetes, previously called "adult onset" diabetes and kids as young as 5 are already showing signs of heart disease. Obesity rates were fairly stable until around 1975, when high-fructose corn syrup (HFCS) became plentiful and much cheaper than cane sugar. The reason for this was an overabundance of corn resulting from a change in government policy. Farmers had previously received "loans" to keep their excess grain off the market until demand caught up with supply. Instead, officials now not only encouraged them to produce as much as possible but began writing a check for every bushel of corn they could grow. Something had to be done with this staggering surplus and the easiest solution was to transform it into cheap HFCS. This quickly became popular with processed food manufacturers because it is very sweet and improves texture. **Since the 1970s, annual consumption has increased more than 4,000 percent and now averages around 63 lbs. per person.** HFCS has become the main sweetener in sodas, soft drinks, candies and cakes and is what allowed Coca-Cola to move from the old standard 8-ounce bottle to today's 20-ounce serving. Cheap corn, transformed into cheap beef, is responsible for McDonald's supersized burgers that sell for less than a dollar, inexpensive chicken nuggets and numerous other new highly processed foods. You can now find it in everything from pretzels to hot dogs and **popcorn is so inexpensive that the bag it comes in costs more than the contents**.

Most of these products are aggressively targeted to kids and adolescents to the tune of $13 billion annually. **The average American child sees 10,000 food advertisements a year on television alone, most of which are for fast food, sugarcoated cereal, soft drinks, candy and other high calorie snacks.** Last year there were more than 2,800 new candies, desserts, ice creams and snacks on the market. High fructose corn syrup soda and soft drink consumption has increased several hundred percent since 1970 and **kids now drink twice as much soda as milk**. Fructose is metabolized differently than glucose, which stimulates the pancreas to release insulin that drives sugar into cells. Glucose causes fat cells to release leptin that makes you feel full and prevents the stomach from releasing ghrelin that makes you hungry, so you eat less. Fructose has none of these effects and in animal studies causes insulin resistance, diabetes, obesity, hypertension and premature death. **If the present trend continues, almost all of generation XL, as it is referred to, will be significantly overweight within 20 years and will be the first to show a decline rather than an increase in longevity.** Farmers plant nearly 80 million acres of corn a year and have averaged $5.5 billion in federal subsidies annually for the last five years. The more they produce the more money they receive, so there is no incentive to cut back. Officials admit that agricultural subsidies are based on political decisions that are not likely to change - but stay tuned!

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