



The Vitamin & Herb Stores

#87

Human Technology Research Synopsis

87th Issue Date 19 AUG 10

Compiled By Ralph Turchiano

www.vit.bz

Editors Top Five:

SCIENTISTS TARGET POSSIBLE CAUSE OF ONE FORM OF BOWEL DISEASE

Pancreatic cancers use fructose, common in the Western diet, to fuel their growth

Acetaminophen tied to childhood wheezing and allergies

FDA moves to withdraw unproven blood pressure drug

After Avandia: Does the FDA Have a Drug Problem?

In this issue:

- 1. At Two Years, Low-carb Diet Beats Low-Fat for HDL-Cholesterol Levels**
- 2. Drug Trials Funded by Industry More Likely to Report Positive Outcomes**
- 3. Certain meat components may increase bladder cancer risk**
- 4. Mind over matter? The psychology of healing**
- 5. Exercise and caloric restriction rejuvenate synapses in lab mice**
- 6. SCIENTISTS TARGET POSSIBLE CAUSE OF ONE FORM OF BOWEL DISEASE**
- 7. Research shows what you say about others says a lot about you**
- 8. SCIENTISTS TARGET POSSIBLE CAUSE OF ONE FORM OF BOWEL DISEASE**
- 9. Disrupted circadian rhythm may cause triglycerides to rise**
- 10. Oral contraceptive use associated with increased risk of breast cancer**
- 11. Sperm may be harmed by exposure to BPA, study suggests**
- 12. Homes of the poor and the affluent both have high levels of endocrine disruptors**
- 13. Acetaminophen tied to childhood wheezing and allergies**
- 14. Surgery better than radiation, hormone treatments for some prostate cancer, study shows**
- 15. Free statins with fast food could neutralize heart risk, scientists say**
- 16. FDA moves to withdraw unproven blood pressure drug**
- 17. After Avandia: Does the FDA Have a Drug Problem?**

Public release date: 2-Aug-2010

At Two Years, Low-carb Diet Beats Low-Fat for HDL-Cholesterol Levels

Previous studies comparing low-carbohydrate and low-fat diets have not included comprehensive behavioral treatment. Researchers sought to evaluate the long-term effects of a low-carbohydrate versus a low-fat diet when combined with a comprehensive lifestyle modification program. Three hundred and seven patients were randomly assigned to either a low-carbohydrate (n=153) or low-fat (n=154) diet with behavior treatment. Weight at two years was the primary outcome, but other effects were measured throughout the study period. At three, six, and 12 months, patients were evaluated for weight, serum lipid concentrations, blood pressure, urinary ketones, bone mineral density, and body composition. The researchers found no differences in weight, body composition, or bone mineral density between the two groups at any point during the study. At two years, both groups had lost a clinically significant amount of weight (about 7 percent of body weight), showing that successful weight loss can be achieved with either approach when coupled with a behavioral modification program. **However, the low-carbohydrate diet produced a greater increase in plasma HDL cholesterol concentration than did the low-fat diet at all assessments points during the two-year study.**

Public release date: 2-Aug-2010

Drug Trials Funded by Industry More Likely to Report Positive Outcomes

Clinicaltrials.gov is a publicly available database that provides details of clinical trials. Researchers studied 546 drug trials listed at clinicaltrials.gov to determine if funding source was associated with published outcomes. Of the trials studied, 346 (63 percent) were primarily funded by industry, 74 (14 percent) by government, and 126 (23 percent) by nonprofit or nonfederal organizations. **The researchers found that industry-funded trials reported positive outcomes in 85.4 percent of publications, compared with 50 percent for government-funded trials** and 71.9 percent for organization-funded trials. Trials funded by nonprofit or nonfederal sources with industry contributions were also more likely to report positive outcomes than those without industry funding. In addition, industry-funded trials were less likely to be published within two years of completion than were trials with other funding sources.

Public release date: 2-Aug-2010

Certain meat components may increase bladder cancer risk

A new study suggests that consuming specific compounds in meat related to processing methods may be associated with an increased risk of developing bladder cancer. Published early online in *CANCER*, a peer-reviewed journal of the American Cancer Society, the findings may be relevant for understanding the role of dietary exposures in cancer risk.

Eating red and processed meats has been linked to an increased risk of developing several different types of cancer. Animal studies have identified a number of compounds in meat that might account for this association. These include heterocyclic amines, polycyclic aromatic hydrocarbons, and N-nitroso compounds. Nitrate and nitrite are added to processed meats and are known precursors to N-nitroso compounds.

Amanda J. Cross, PhD, of the National Cancer Institute in Rockville and colleagues conducted one of the first prospective studies – the NIH-AARP Diet and Health Study—to assess the relationship between intake of these meat-related compounds and the risk of developing bladder cancer. They used information gathered through questionnaires to assess the types of meat consumed as well as how meat was prepared and cooked to estimate the intake of these meat-related compounds.

The investigators had information from approximately 300,000 men and women aged 50 to 71 years from eight US states. At the start of the study (1995 to 1996), all participants completed lifestyle and dietary questionnaires about their usual consumption of foods and drinks. The participants were followed for up to eight years, during which time 854 people were diagnosed with bladder cancer.

People whose diets had the highest amount of total dietary nitrite (from all sources and not just from meat), as well as those whose diets had the highest amount of nitrate plus nitrite from processed meats had a 28 percent to 29 percent increased risk of developing bladder cancer compared with those who consumed the lowest amount of these compounds. This association between nitrate/nitrite consumption and bladder cancer risk may explain why other studies have observed an association between processed meats and increased bladder cancer risk.

"Our findings highlight the importance of studying meat-related compounds to better understand the association between meat and cancer risk," said Dr. Cross. "Comprehensive epidemiologic data on meat-related exposures and bladder cancer are lacking; our findings should be followed up in other prospective studies," she added.

Public release date: 2-Aug-2010

Mind over matter? The psychology of healing

People suffering from diabetes-related foot ulcers show different rates of healing according to the way they cope and their psychological state of mind, according to new research by a health psychologist at The University of Nottingham.

The large study published in the journal *Diabetologia* this month has shown that the way patients cope with the condition and their levels of depression, affect how the wound heals or worsens.

The work by Professor Kavita Vedhara from the University's Institute of Work, Health and Organisations, has sparked a follow-on project to develop psychological treatments to reduce depression in sufferers and help them cope more effectively with this debilitating and potentially life-threatening condition.

Foot ulcers are open sores which form when a minor skin injury fails to heal because of microvascular and metabolic dysfunction caused by diabetes. Up to fifteen per cent of people with diabetes, both Type 1 and Type 2, develop foot or leg ulcers with many suffering depression and poorer quality of life as a result.

The increased morbidity and mortality caused by the condition are estimated to cost UK health services £220 million per year. The costs are exacerbated by slow healing rates with two thirds of ulcers remaining unhealed after 20 weeks of treatment. The five year amputation and death rates among patients are 19 per cent and 44 per cent respectively. Ulcers account for around four out of five lower leg amputations and half of diabetes-related hospital admissions.

During the five-year study 93 patients (68 men and 25 women) with diabetic foot ulcers were recruited from specialist podiatry clinics across the UK. Clinical and demographic determinants of healing; psychological distress, coping style and levels of cortisol (a stress hormone) in saliva were assessed and recorded at the start of a 24 week monitoring period. The size of each patient's ulcer was also measured at the start, and then at 6, 12 and 24 weeks to record the extent of healing or otherwise of the ulcer.

The results of the research showed that the likelihood of the ulcer healing over a 24 week period was predicted by how individual's coped. Surprisingly perhaps, patients who showed a 'confrontational' way of coping (a style characterised by a desire to take control) with the ulcer and its treatment were less likely to have a healed ulcer at the end of the 24 week period.

Professor Vedhara said: "My colleagues and I believe that this confrontational approach may, inadvertently, be unhelpful in this context because these ulcers take a long time to heal. As a result, individuals with confrontational coping may experience distress and frustration because their attempts to take control do not result in rapid improvements."

A secondary analysis of each patient examined the relationship of psycho-social factors with the change in the size of the ulcer over the observation period. Whereas the first analysis showed that only confrontation coping, not anxiety or depression, was a significant predictor of healing, the second showed that depression was a significant predictor in how the size of the ulcer changed over time, with patients with clinical depression showing smaller changes in ulcer size over time i.e., they showed less improvement or healing.

Public release date: 2-Aug-2010

Exercise and caloric restriction rejuvenate synapses in lab mice

Finding may illuminate a reason for the beneficial effects of these regimens on aging

CAMBRIDGE, Mass. -- Harvard University researchers have uncovered a mechanism through which caloric restriction and exercise delay some of the debilitating effects of aging by rejuvenating connections between nerves and the muscles that they control.

The research, conducted in the labs of Joshua Sanes and Jeff Lichtman and described this week in the journal Proceedings of the National Academy of Sciences, begins to explain prior findings that exercise and restricted-calorie diets help to stave off the mental and physical degeneration of aging.

"Caloric restriction and exercise have numerous, dramatic effects on our mental acuity and motor ability," says Sanes, a professor of molecular and cellular biology and director of the Center for Brain Science at Harvard. "This research gives us a hint that the way these extremely powerful lifestyle factors act is by attenuating or reversing the decline in our synapses."

Sanes says their research, conducted with mice genetically engineered so their nerve cells glow in fluorescent colors, shows some of the debilitation of aging is caused by deterioration of connections that nerves make with the muscles they control, structures called neuromuscular junctions. These microscopic links are remarkably similar to the synapses that connect neurons to form information-processing circuits in the brain.

In a healthy neuromuscular synapse, nerve endings and their receptors on muscle fibers are almost a perfect match, like two hands placed together, finger to finger, palm to palm. This lineup ensures maximum efficiency in transmitting the nerve's signal from the brain to the muscle, which is what makes it contract during movement.

As people age, however, the neuromuscular synapses can deteriorate in several ways. Nerves can shrink, failing to cover the muscle's receptors completely. The resulting interference with transmission of nerve impulses to the muscles can result in wasting and eventually even death of muscle fibers. This muscle wasting, called sarcopenia, is a common and significant clinical problem in the elderly.

The new work showed that mice on a restricted-calorie diet largely avoid that age-related deterioration of their neuromuscular junctions, while those on a one-month exercise regimen when already elderly partially reverse the damage.

"With calorie restriction, we saw reversal of all aspects of the synapse disassembly. With exercise, we saw a reversal of most, but not all," Sanes says.

Because of the study's structure -- mice were on calorie-restricted diets for their whole lives, while those that exercised did so for just a month late in life -- Sanes cautions against drawing conclusions about the effectiveness of exercise versus calorie restriction. He notes that longer periods of exercise might have more profound effects, a possibility he and Lichtman are now testing.

Though much of Sanes and Lichtman's work focuses on brain synapses, both have investigated neuromuscular synapses for many years. Neuromuscular junctions are large enough to be viewed by light microscopy, and can be a jumping-off point for brain study, highlighting areas of inquiry and potential techniques.

"These findings in neuromuscular synapses make us curious to know whether similar effects might occur in brain synapses," Sanes says.

While the changes to the synapses through caloric restriction and exercise were clear in the images the researchers obtained, Sanes cautioned that their work was structural, not functional, and they have not yet tested how well the synapses worked.

Public release date: 2-Aug-2010

SCIENTISTS TARGET POSSIBLE CAUSE OF ONE FORM OF BOWEL DISEASE

COLUMBUS, Ohio – A possible cause of irritable bowel syndrome has been traced to a small piece of RNA that blocks a substance protecting the colon membrane, leading to hostile conditions that can produce diarrhea, bloating and chronic abdominal pain.

New research shows that this RNA segment sends signals that stop the activity of the gene that produces glutamine, an amino acid. **Previous research has linked a shortage of glutamine in the gut with the seepage of toxins and bacteria through the intestinal wall, irritating nerves and creating disease symptoms.**

Scientists say that trying to generate glutamine in the disordered bowel by silencing this RNA segment could open up a whole new way of thinking about treating the diarrhea-predominant type of irritable bowel syndrome (IBS). In the meantime, they are making plans to conduct a clinical trial to see if glutamine supplements could also reduce common IBS symptoms.

This form of the disorder is characterized by diarrhea and bloating as well as chronic abdominal pain that is difficult to treat. About a third of IBS patients have the diarrhea-predominant type, another third experience consistent constipation, and the rest experience alternating bouts of diarrhea and constipation.

"We treat the disorder, but we still don't understand it completely. We often have to use multiple therapies to attack the symptoms, but the pain is by far the most difficult to treat. For some patients, the pain responds only to escalating doses of narcotics or tricyclic antidepressants."

In the Ohio State University study, researchers observed that in human tissue samples, the presence of this

small piece of RNA was associated with reduced activity by the gene that produces glutamine. Lower levels of glutamine were seen only in tissue samples from patients with the diarrhea-predominant type of IBS.

A group of these patients also had a condition called increased intestinal permeability, which allows toxins and bacteria into the colon that typically can't get in. The resulting irritation to nerves in the colon is believed to contribute to diarrhea and abdominal pain. The finding suggests that the glutamine deficiency is connected to the increased intestinal permeability, which dramatically increases the likelihood that diarrhea-predominant IBS symptoms will follow.

The researchers say that manipulating that tiny piece of RNA, known as microRNA-29a, has potential as a novel treatment for IBS. "We've known about characteristics of this disease, but we didn't know the reasons behind them. This study helps us connect everything together. Maybe if we can modulate the microRNA, we can heal the disease. That is our whole hypothesis," said QiQi Zhou, assistant professor of internal medicine at Ohio State and lead author of the study.

The research is published in a recent issue of the journal *Gut*.

While testing the effectiveness of glutamine supplementation in IBS patients could lead to a viable treatment for symptoms, the researchers say it is important to continue to pursue the underlying cause of IBS.

"We treat the disorder, but we still don't understand it completely," said study senior co-author G. Nicholas Verne, professor of internal medicine and director of the Division of Gastroenterology, Hepatology and Nutrition at Ohio State. "We often have to use multiple therapies to attack the symptoms, but the pain is by far the most difficult to treat. For some patients, the pain responds only to escalating doses of narcotics or tricyclic antidepressants.

"That's why if we had a specific target for an underlying structural defect, we could try to resolve that defect as a much more effective way to reduce the symptoms."

Zhou, Verne and colleagues are the first group of scientists to report on a link between microRNAs, glutamine deficiency and IBS. Most studies of microRNAs have identified their role in the development of cancer.

RNA in cells is responsible for using instructions carried in the DNA to make proteins, but microRNAs are small segments of RNA that, when they become overactive themselves, can block the protein-building process. Each microRNA can target numerous genes, but Zhou concentrated on microRNA-29a and its connection to the production of glutamine in this study because of glutamine's established connection to intestinal permeability.

The researchers collected intestinal tissue and blood samples from three groups: IBS patients with increased intestinal permeability, IBS patients with normal intestinal permeability and control participants with no bowel disease.

The samples showed that microRNA-29a levels were four times higher in the tissues of IBS patients with increased intestinal permeability than were levels seen in IBS patients with normal intestinal permeability conditions and in participants with no bowel disease.

The scientists further tested this relationship by manipulating the microRNA-29a in experiments. When the microRNA-29a levels were driven up, the function of the gene that produces glutamine was prevented and intestinal membrane permeability increased, as well. When the microRNA-29a was artificially silenced, gene function was active, glutamine was produced and the intestinal membrane permeability was closer to normal.

"We've only tested the one target gene, and we've shown that when the gene activity is low, or the gene is

not expressed, that's when disease characteristics come into play," Zhou said. "But there still may be other target genes related to this process."

The study also sought to determine how much related genetic information was contained in blood microvesicles, which are tiny blood vessel membrane fragments. Because the heightened expression of microRNA-29a was also detected in microvesicles from IBS patients with increased permeability in this study, the scientists believe a specially handled blood sample could provide as much disease information as a tissue sample for diagnostic purposes.

This work was supported by the National Institutes of Health and the Medical Research Service of the Department of Veterans Affairs.

Co-authors, both from Ohio State, include Wiley Souba, dean of the College of Medicine; and Carlo Croce, professor and chair of the Department of Molecular Virology, Immunology and Medical Genetics. Verne and Zhou also are affiliated with the Cincinnati VA Medical Center Research Service.

Public release date: 2-Aug-2010

Research shows what you say about others says a lot about you

How positively you see others is linked to how happy, kind-hearted and emotionally stable you are, according to new research by a Wake Forest University psychology professor.

"Your perceptions of others reveal so much about your own personality," says Dustin Wood, assistant professor of psychology at Wake Forest and lead author of the study, about his findings. By asking study participants to each rate positive and negative characteristics of just three people, the researchers were able to find out important information about the rater's well-being, mental health, social attitudes and how they were judged by others.

The study appears in the July issue of the *Journal of Personality and Social Psychology*. Peter Harms at the University of Nebraska and Simine Vazire of Washington University in St. Louis co-authored the study.

The researchers found a person's tendency to describe others in positive terms is an important indicator of the positivity of the person's own personality traits. They discovered particularly strong associations between positively judging others and how enthusiastic, happy, kind-hearted, courteous, emotionally stable and capable the person describes oneself and is described by others.

"Seeing others positively reveals our own positive traits," Wood says.

The study also found that how positively you see other people shows how satisfied you are with your own life, and how much you are liked by others.

In contrast, negative perceptions of others are linked to higher levels of narcissism and antisocial behavior. "A huge suite of negative personality traits are associated with viewing others negatively," Wood says. "The simple tendency to see people negatively indicates a greater likelihood of depression and various personality disorders." Given that negative perceptions of others may underlie several personality disorders, finding techniques to get people to see others more positively could promote the cessation of behavior patterns associated with several different personality disorders simultaneously, Wood says.

This research suggests that when you ask someone to rate the personality of a particular coworker or acquaintance, you may learn as much about the rater providing the personality description as the person they are describing. The level of negativity the rater uses in describing the other person may indeed indicate that the other person has negative characteristics, but may also be a tip off that the rater is unhappy, disagreeable, neurotic—or has other negative personality traits.

Raters in the study consisted of friends rating one another, college freshmen rating others they knew in their dormitories, and fraternity and sorority members rating others in their organization. In all samples, participants rated real people and the positivity of their ratings were found to be associated with the participant's own characteristics.

By evaluating the raters and how they evaluated their peers again one year later, Wood found compelling evidence that how positively we tend to perceive others in our social environment is a highly stable trait that does not change substantially over time.

Public release date: 2-Aug-2010

Pancreatic cancers use fructose, common in the Western diet, to fuel their growth

Pancreatic cancers use the sugar fructose, very common in the Western diet, to activate a key cellular pathway that drives cell division, helping the cancer to grow more quickly, a study by researchers at UCLA's Jonsson Comprehensive Cancer Center has found.

Although it's widely known that cancers use glucose, a simple sugar, to fuel their growth, this is the first time a link has been shown between fructose and cancer proliferation, said Dr. Anthony Heaney, an associate professor of medicine and neurosurgery, a Jonsson Cancer Center researcher and senior author of the study.

"The bottom line is the modern diet contains a lot of refined sugar including fructose and it's a hidden danger implicated in a lot of modern diseases, such as obesity, diabetes and fatty liver," said Heaney, who also serves as director of the Pituitary Tumor and Neuroendocrine Program at UCLA. "In this study, we show that cancers can use fructose just as readily as glucose to fuel their growth."

The study appeared in the Aug. 1 issue of the peer-reviewed journal Cancer Research.

The source of fructose in the Western diet is high fructose corn syrup (HFCS), a corn-based sweetener that has been on the market since about 1970. HFCS accounts for more than 40 percent of the caloric sweeteners added to foods and beverages, and it is the sole sweetener used in American soft drinks.

Between 1970 and 1990, the consumption of HFCS in the U.S. has increased over 1,000 percent, according to an article in the April 2004 issue of the American Journal of Clinical Nutrition. Food companies use HFCS - a mixture of fructose and glucose - because it's inexpensive, easy to transport and keeps foods moist. And because it is so sweet, it's cost effective for companies to use small quantities of HFCS in place of more expensive sweeteners or flavorings.

In his study, Heaney and his team took pancreatic tumors from patients and cultured and grew the malignant cells in Petri dishes. They then added glucose to one set of cells and fructose to another. Using mass spectrometry, they were able to follow the carbon-labeled sugars in the cells to determine what exactly they were being used for and how.

Heaney found that the pancreatic cancer cells could easily distinguish between glucose and fructose even though they are very similar structurally, and contrary to conventional wisdom, the cancer cells metabolized the sugars in very different ways. In the case of fructose, the pancreatic cancer cells used the sugar in the transketolase-driven non-oxidative pentose phosphate pathway to generate nucleic acids, the building blocks of RNA and DNA, which the cancer cells need to divide and

proliferate.

"Traditionally, glucose and fructose have been considered as interchangeable monosaccharide substrates that are similarly metabolized, and little attention has been given to sugars other than glucose," the study states. "However, fructose intake has increased dramatically in recent decades and cellular uptake of glucose and fructose uses distinct transporters ... These findings show that cancer cells can readily metabolize fructose to increase proliferation. **They have major significance for cancer patients, given dietary refined fructose consumption.**"

As in anti-smoking campaigns, a federal effort should be launched to reduce refined fructose intake, Heaney said.

"I think this paper has a lot of public health implications," Heaney said. "Hopefully, at the federal level there will be some effort to step back on the amount of HFCS in our diets."

Heaney said that while this study was done in pancreatic cancer, these finding may not be unique to that cancer type.

Going forward, Heaney and his team are exploring whether it's possible to block the uptake of fructose in the cancer cells with a small molecule, taking away one of the fuels they need to grow. The work is being done in cell lines and in mice, Heaney said.

Public release date: 3-Aug-2010

Disrupted circadian rhythm may cause triglycerides to rise

When the circadian rhythm gets thrown off, it could come with an unexpected side effect: high triglycerides. The discovery, based on studies in mice with a "broken clock," helps to explain the normal rise and fall in triglycerides, which happens at about the same time each day, according to researchers who report their findings in the August issue of Cell Metabolism, a Cell Press publication.

"We show that the normal up and down [of triglycerides] is lost in clock mutants," said M. Mahmood Hussain of SUNY Downstate Medical Center. "They have high triglycerides all the time." An elevated triglyceride level is a risk factor for atherosclerosis and heart disease.

Several biological, physiological, and behavioral activities show a characteristic recurrence with 24-hour intervals attuned to sunrise and sunset, the researchers explained. That circadian rhythm is driven by the interaction of so-called clock genes.

In normal mice, plasma triglycerides double or triple over the course of the day, reaching their lowest point at night when the nocturnal animals eat and are most active, the new report shows. In clock mutants, triglyceride levels don't change; rather, they stay high all the time.

The researchers delved further into the mechanism linking the animal's internal clocks to triglycerides. They found that a core component of the circadian circuitry—a protein known as CLOCK—controls levels of another protein (called microsomal triglyceride transfer protein, or MTP) that helps to ferry triglycerides through the bloodstream. That control takes place via yet another transcription factor.

"Metabolic syndrome and obesity are major metabolic disorders characterized by high plasma lipid concentrations," the researchers conclude. "Plasma lipids are tightly controlled by mechanisms regulating their production and clearance. Here, we show that light-entrained mechanisms involving clock genes also play a role in regulating plasma triglyceride."

If the findings in mice can be extrapolated to humans, it suggests that the effects of drugs designed to lower triglyceride levels by acting on MTP might depend on when they are taken each day, the researchers said.

"The dose needed may vary depending on the time of day," Hussain said. "Now we can start to think about [the role of] drug timing in controlling disease states."

The findings also suggest that activities that disrupt the circadian rhythm—staying up until 2:00 a.m. or traveling overseas—might come with real consequences for lipid metabolism, he added.

Public release date: 3-Aug-2010

Oral contraceptive use associated with increased risk of breast cancer

(Boston) - Investigators from the Slone Epidemiology Center at Boston University School of Medicine (BUSM) have reported that African American women who use oral contraceptives have a greater likelihood of developing breast cancer than nonusers. The study results, recently published on-line in Cancer Epidemiology Biomarkers and Prevention, were based on data from the Black Women's Health Study (BWHS), a large follow-up study of 59,000 African American women from across the U.S. conducted by investigators at the Slone Epidemiology Center since 1995.

The investigators followed 53,848 participants in the BWHS for 12 years, during which time 789 cases of breast cancer developed on which information on receptor status was obtained. **The incidence of estrogen receptor negative cancer was 65 percent greater among women who had ever used oral contraceptives than among nonusers.**

According to the BUSM researchers, the increase in risk was greatest for women who had used oral contraceptives within the previous five years and whose use had lasted 10 or more years, and the increase was greater for estrogen receptor negative than for estrogen receptor positive breast cancer. Estrogen receptor positive tumors have a better prognosis than estrogen receptor negative breast cancers.

Lead investigator Lynn Rosenberg, PhD, an associate director of the Slone Epidemiology Center and professor of epidemiology at BUSM, points out- that oral contraceptive formulations have changed over time, making it relevant to assess the effects of more recent formulations on breast cancer risk. "Some past studies found a stronger association with estrogen receptor negative breast cancer. This was the first assessment of the effect of oral contraceptive use on the incidence of breast cancer classified by receptor status among African American women," said Rosenberg who is also the principal investigator of the BWHS. "A mechanism to explain an adverse influence of oral contraceptives on development of estrogen receptor negative breast cancer is currently unknown," she added.

Public release date: 3-Aug-2010

Sperm may be harmed by exposure to BPA, study suggests

ANN ARBOR, Mich.—In one of the first human studies of its kind, researchers have found that urinary concentrations of the controversial chemical Bisphenol A, or BPA, may be related to decreased sperm quality and sperm concentration.

However, the researchers are quick to point out that these results are preliminary and more study is needed. Several studies have documented adverse effects of BPA on semen in rodents, but none are known to have reported similar relationships in humans.

BPA is a common chemical that's stirred much controversy in the media lately over its safety. Critics say

that BPA mimics the body's own hormones and may lead to negative health effects. BPA is most commonly used to make plastics and epoxy resins used in food and beverage cans, and people are exposed primarily through diet, although other routes are possible. More than 6 billion pounds of BPA are produced annually.

The new study suggests that more research should focus on BPA and health effects in adults, says John Meeker, assistant professor of Environmental Health Sciences at the University of Michigan School of Public Health.

Meeker is the lead author on the study, along with Russ Hauser, the Frederick Lee Hisaw Professor of Reproductive Physiology at Harvard School of Public Health. Colleagues at Massachusetts General Hospital and the U.S. Centers for Disease Control and Prevention also contributed to the research.

"Much of the focus for BPA is on the exposures in utero or in early life, which is of course extremely important, but this suggests exposure may also be a concern for adults," Meeker said. "Research should focus on impacts of exposure throughout multiple life stages." Meeker and Hauser recruited 190 men through a fertility clinic. All gave spot urine samples and sperm samples the same day. Subsequently, 78 of the men gave one or two additional urine samples a month apart. Researchers detected BPA in 89 percent of the urine samples.

Researchers measured sperm concentration, sperm motility, sperm shape and DNA damage in the sperm cell.

"We found that if we compare somebody in the top quartile of exposure with the lowest quartile of exposure, sperm concentration was on average about 23 percent lower in men with the highest BPA," Meeker said.

Results also suggested a 10 percent increase in sperm DNA damage.

The results are consistent with a previous study by Meeker and Hauser suggesting that certain hormones, specifically FSH (follicle-stimulating hormone) and Inhibin B, are elevated or decreased in relation to BPA, respectively, a pattern consistent with low sperm production and development.

Meeker stressed that further study is necessary due to the study's relatively small sample size and design.

"The study from which these data came is currently in progress," Hauser said. "With a larger sample size and enhanced study design, we will be able to more definitively investigate this preliminary association in the near future."

The University of Michigan School of Public Health has been promoting health and preventing disease since 1941, and is ranked among the top five public health schools in the nation. Whether making new discoveries in the lab or researching and educating in the field, SPH faculty, students, and alumni are deployed around the globe to promote and protect our health.

Public release date: 4-Aug-2010

Homes of the poor and the affluent both have high levels of endocrine disruptors

Homes in low-income and affluent communities in California both had similarly high levels of endocrine disruptors, and the levels were higher in indoor air than outdoor air, according to a new study believed to be the first that paired indoor and outdoor air samples for such wide range (104) of these substances. The study appears in ACS' Environmental Science & Technology, a semi-monthly journal.

Ruthann Rudel and colleagues note concern about the reproductive and other health effects of endocrine disrupting compounds (EDCs), which are found in many products used in the home. Examples include phthalates, which are found in vinyl and other plastics, and polychlorinated biphenyls (PCBs), which are found in older paints, electrical equipment, and building materials. EDCs also are among the ingredients in some pesticides, fragrances, and other materials.

The scientists analyzed indoor and outdoor air samples as well as house dust in homes from two different communities in the San Francisco Bay area for the presence of 104 compounds, including 70 suspected EDCs. The sampling, which took place in 2006, included 40 homes in Richmond, Calif., an urban, industrial, low-income area, and 10 homes in Bolinas, Calif., an affluent, coastal community. Levels were generally higher indoors than outdoors — 32 of the compounds occurred in higher concentrations indoors and only 2 were higher outdoors. The scientists expressed surprise at finding higher concentrations of some phthalates outdoors near urban homes contributing to higher indoor levels as well, but concluded that EDCs "are ubiquitously common across socioeconomic groups."

Public Release: 5-Aug-2010

Surgery better than radiation, hormone treatments for some prostate cancer, study shows

Surgery for localized prostate cancer offers a significantly higher survival rate than either external-beam radiation or hormonal therapies, according to a new study led by researchers at UCSF.

The differences among therapies were more prominent at higher levels of cancer risk, and suggest, the researchers say, that in many cases surgery should play a greater role in treatment strategies for patients with prostate cancer that is likely to recur or spread.

The study is available online in the journal "Cancer," the journal of the American Cancer Society,

Most previous reports comparing treatment outcomes among different treatment options have looked only at PSA responses to treatment, rather than at the more important long-term survival outcomes, according to the researchers. Measuring levels of PSA, or prostate-specific antigen, in the blood, is intended to help determine whether prostate cancer has recurred or spread, although in many cases a rising PSA level does not necessarily mean the cancer will progress.

Roughly one man in six will be diagnosed with prostate cancer, which is the second leading cause of cancer death in American men, according to the American Cancer Society.

"Despite the high incidence of prostate cancer, there is relatively little high-quality evidence on which to base current treatments for localized disease," said Matthew R. Cooperberg, MD, MPH, lead investigator of the study and a prostate cancer specialist in the UCSF Department of Urology and the UCSF Helen Diller Family Comprehensive Cancer Center.

"These therapies can all have significant side effects, so it's important to understand which treatment alternatives are most effective. In current practice, likelihood of undergoing surgery falls progressively with increasing levels of risk, which may be exactly contrary to what the treatment pattern should be," he said.

Researchers found that the risk for cancer-specific mortality was more than three times higher in patients who received hormone therapy versus radical prostatectomy (surgical removal of the prostate) and more than twice as high in patients who received external-beam radiation therapy versus prostatectomy.

For men at low levels of risk, prostate cancer mortality was very uncommon, and differences among the treatment options were small. The survival differences increased substantially for men at intermediate and

high risk, according to the analysis, with the greatest relative benefit for surgery seen for men at higher levels of risk.

The American Urological Association's clinical practice guidelines for localized prostate cancer treatments include active surveillance, radical prostatectomy, external-beam radiation therapy, and brachytherapy (radiotherapy delivered via radioactive seeds), but draw no conclusions about the relative efficacy of each.

Androgen-deprivation therapy, which suppresses the production of male sex hormones, is not endorsed by the American Urological Association clinical practice guidelines for localized prostate cancer, due to inadequate evidence regarding outcomes, yet it is commonly used in practice, the researchers state.

"This is a clear signal to the physician community that prostatectomy should be considered for men with higher-risk prostate cancer. In many cases, surgery would be part of a multimodal treatment approach, including adjuvant radiation or systemic treatments based on the pathology and early PSA response," added Peter R. Carroll, MD, MPH, chair of the UCSF Department of Urology and leader of the Prostate Program at the UCSF Helen Diller Family Comprehensive Cancer Center. Carroll is senior author on the paper.

Because no adequate randomized trials have compared active treatments for localized prostate cancer, the authors analyzed risk-adjusted, cancer-specific mortality outcomes among men who underwent radical prostatectomy, external-beam radiation therapy, or primary androgen deprivation.

The research team analyzed data from 7,538 men with localized disease from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry, a national disease registry comprising men from 40 urologic practice sites from across the country. The team then compared outcomes across treatments after adjusting for risk and age. In total, 266 men died of prostate cancer during follow-up.

Co-authors of the paper are Andrew J. Vickers, PhD, of the Memorial Sloan-Kettering Cancer Center; Jeanette M. Broering, RN, MS, MPH, of the UCSF Department of Urology and the UCSF Helen Diller Family Comprehensive Cancer Center; and the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) Investigators.

Public release date: 12-Aug-2010

Free statins with fast food could neutralize heart risk, scientists say

Fast food outlets could provide statin drugs free of charge so that customers can neutralize the heart disease dangers of fatty food, researchers at Imperial College London suggest in a new study published this week. Fast food outlets could provide statin drugs free of charge so that customers can neutralise the heart disease dangers of fatty food, researchers at Imperial College London suggest in a new study published this week.

Statins reduce the amount of unhealthy "LDL" cholesterol in the blood. A wealth of trial data has proven them to be highly effective at lowering a person's heart attack risk.

In a paper published in the Sunday 15 August issue of the American Journal of Cardiology, Dr Darrel Francis and colleagues calculate that the reduction in cardiovascular risk offered by a statin is enough to offset the increase in heart attack risk from eating a cheeseburger and a milkshake.

Dr Francis, from the National Heart and Lung Institute at Imperial College London, who is the senior author of the study, said: "Statins don't cut out all of the unhealthy effects of burgers and fries. It's better to avoid fatty food altogether. But we've worked out that in terms of your likelihood of having a heart attack, taking a statin can reduce your risk to more or less the same degree as a fast food meal increases it."

One statin, simvastatin, is already available in low doses (10mg) over the counter at pharmacies without a prescription. Other statins are so far only prescribed by doctors, and limited by cost to patients at particular

risk of heart attack or stroke. However, the cost of the tablets has fallen sharply in recent years (from ~£40/month to ~£1.50/month), such that the cost to the NHS of seeing a doctor is much greater than the cost of the tablet.

"It's ironic that people are free to take as many unhealthy condiments in fast food outlets as they like, but statins, which are beneficial to heart health, have to be prescribed," Dr Francis said.

Statins have among the best safety profiles of any medication. A very small proportion of regular statin users experience significant side effects, with problems in the liver and kidneys reported in between 1 in 1,000 and 1 in 10,000 people.

"Everybody knows that fast food is bad for you, but people continue to eat it because it tastes good. We're genetically programmed to prefer high-calorie foods, and sadly fast food chains will continue to sell unhealthy foods because it earns them a living.

"It makes sense to make risk-reducing supplements available just as easily as the unhealthy condiments that are provided free of charge. It would cost less than 5p per customer – not much different to a sachet of ketchup.

"When people engage in risky behaviours like driving or smoking, they're encouraged to take measures that minimise their risk, like wearing a seatbelt or choosing cigarettes with filters. Taking a statin is a rational way of lowering some of the risks of eating a fatty meal."

Studies have shown a clear link between total fat intake and blood cholesterol, which is strongly linked to heart disease. Recent evidence suggests that trans fats, which are found in high levels in fast food, are the component of the Western diet that is most dangerous in terms of heart disease risk.

Dr Francis and his colleagues used data from a previous large cohort study to quantify how a person's heart attack risk increases with their daily intake of total fat and trans fat. He compared this with the decrease in risk from various statins, based on a meta-analysis of seven randomised controlled trials.

The results showed that most statin regimes are able to compensate for the relative risk increase from eating a cheeseburger and a small milkshake.

The researchers note that studies should be conducted to assess the potential risks of allowing people to take statins freely, without medical supervision. They suggest that a warning on the packet should emphasise that no tablet can substitute for a healthy diet, and advise people to consult their doctor for more advice.

Ralph's Note - Enough Said

Public release date: 12-Aug-2010

Acetaminophen tied to childhood wheezing and allergies

NEW YORK (Reuters Health) – A pair of studies suggests that the common painkiller acetaminophen -- better known as Tylenol in the U.S. -- may be fueling a worldwide increase in asthma.

According to one study out Thursday, acetaminophen could be responsible for as many as four in 10 cases of wheezing and severe asthma in teens.

While no one knows if the drug causes asthma by itself, another report -- published along with the first study -- shows for the first time that many toddlers took acetaminophen before they developed asthma symptoms such as wheezing.

"We have confirmed that acetaminophen use comes first, so a causal link is increasingly likely," said Dr. Alemayehu Amberbir, of Addis Ababa University in Ethiopia and the University of Nottingham in the UK.

But large-scale clinical tests are necessary before anyone cleans out their medicine cabinet, stressed Amberbir, whose findings are published in the American Journal of Respiratory and Critical Care Medicine.

His team followed more than 1,000 Ethiopian babies over three years. When the toddlers turned one, the researchers asked the mothers if their babies had breathing problems, and how much acetaminophen they had used.

About eight percent of the kids began to wheeze between ages one and three. Those who had been given acetaminophen during their first year -- before they had breathing trouble -- had up to seven times the odds of developing wheezing.

That increase held even after adjusting for fever and coughs, which in principle could have triggered both the wheezing and the use of painkillers.

"What we have is further information and a stronger association between the use of acetaminophen and asthma," said Dr. Dipak Kanabar, who has written guidelines on painkillers, but wasn't involved in the new studies.

But Kanabar, a consultant pediatrician at Evelina Children's Hospital in London, cautioned that parents' recall isn't always accurate, which could have influenced the findings.

"We have to be careful when we give advice to parents to stress that these studies do not mean that giving acetaminophen will necessarily result in their child developing asthma," he said.

But if the link turns out to be real, it could have a major impact on public health, according to another report in the American Journal of Respiratory and Critical Care Medicine.

In that study, based on more than 320,000 teens from 50 countries, 11 percent of the children had breathing trouble -- only slightly more than the percentage of American children who have asthma.

Those teens who took acetaminophen at least once a month -- one third overall, and more than four in 10 Americans -- doubled their odds of wheezing.

They were also more likely to have allergic nasal congestion and the skin condition eczema, Dr. Richard W. Beasley, of the Medical Research Institute of New Zealand, and colleagues report.

The researchers estimate that acetaminophen could potentially be responsible for up to four in 10 of all asthma symptoms, including severe ones such as waking up gasping for air once a week or more.

McNeil Consumer Healthcare, the Johnson & Johnson subsidiary that sells Tylenol, said in a comment their product "has over 50 years of clinical history to support its safety and efficacy."

"The well-documented safety profile for acetaminophen makes it the preferred pain reliever for asthma sufferers," the company told Reuters Health in an e-mail. The company said there are no gold-standard clinical trials showing "a causal link between acetaminophen and asthma."

However, Kanabar found in his review of the medical literature that ibuprofen -- another painkiller, sometimes sold as Advil -- seemed to trigger less wheezing than acetaminophen.

Ibuprofen, however, is not recommended in people with asthma, Kanabar said, and that most doctors favor Tylenol.

Aspirin, another common painkiller, is generally discouraged in children because it can cause short-term breathing problems and other rare side effects.

According to Kanabar, dropping painkillers entirely is probably a bad idea, and might cause a child to feel worse and drink less liquid, which could slow recovery.

So which painkiller should a parent choose if their child has a headache or a fever -- Tylenol or ibuprofen?

At this point, said Kanabar, "you could go for either."

SOURCE: <http://link.reuters.com/sej74n> American Journal of Respiratory and Critical Care Medicine, online

Public release date: 16-Aug-2010

FDA moves to withdraw unproven blood pressure drug

By MATTHEW PERRONE, AP Business Writer Matthew Perrone, Ap Business Writer

WASHINGTON – Federal health regulators are pushing to withdraw a blood pressure drug that has been on the market for 14 years in spite of the manufacturer's failure to submit evidence that it actually helps patients.

The Food and Drug Administration approved Shire Laboratories' drug ProAmatine in 1996 based on promising early results in treating low blood pressure. **But the company has never conducted a mandatory follow-up study to actually prove the long-term benefits of the drug.**

In letter to the company posted online Monday, the FDA proposes withdrawing the drug from the market and gives Shire an opportunity to schedule a hearing to discuss the matter. The letter marks the first time the FDA has threatened to pull a drug off the market due to missing follow-up data, though it has long held that power.

"This proposal is necessitated by Shire's failure to conduct postmarketing clinical trials that verify and describe the clinical benefit" of ProAmatine, the agency states.

Calls placed to Dublin, Ireland-based Shire seeking comment were not returned Monday afternoon.

Copies of the letter were also sent to five generic drugmakers who manufacture the drug, including Mylan Pharmaceuticals and Sandoz Inc. Those generic products would also be subject to a market withdrawal, unless their manufacturers complete the study requested by the FDA.

Roughly 100,000 U.S. patients received prescriptions for ProAmatine or generic versions last year, according to the FDA. The drug is approved to treat orthostatic hypotension, a type of low blood pressure that causes patients to become dizzy or faint when standing upright.

The letter does not cite any safety or effectiveness problems with the drug, and suggests the action is primarily aimed at enforcing drug approval regulations that have not always been enforced.

ProAmatine is part of a family of heart drugs that help stimulate dangerously low blood pressure. Several companies sell generic versions of the drug phenylephrine, which is used off-label to treat the condition.

For nearly 20 years, the FDA has granted accelerated approval to drugs based on so-called surrogate endpoints, or initial measures that suggest the drug will make real improvements in patient health. In cancer

drugs, for example, tumor shrinkage is considered a predictor of increased survival.

Drugmakers favor the program because it helps them get products to market sooner.

But the program has not escaped criticism from government watchdogs.

Last fall the Government Accountability Office issued a report saying the FDA should do more to track whether drugs approved based on preliminary results actually live up to their promise.

The report singled out ProAmatine as a particularly egregious example of missing follow-up data. The government watchdog said that ProAmatine has generated more than \$257 million in sales even though "the clinical benefit of the drug has never been established."

According to the GAO, the FDA has never once pulled a drug off the market due to missing or unimpressive follow-up data.

The GAO's September 2009 report found that the FDA had requested 144 follow-up studies for drugs since 1992. Of those about 64 percent had been completed and more than one-third were still pending

Thursday, Aug. 12, 2010

After Avandia: Does the FDA Have a Drug Problem?

By Massimo Calabresi with Alice Park

Five days before a 2007 article in the New England Journal of Medicine showed that the diabetes drug Avandia was linked to a 43% increase in heart attacks compared with other medications or placebos, a group of scientists and executives from the drug's maker, GlaxoSmithKline (GSK), gathered in a conference room at the offices of the Food and Drug Administration in White Oak, Md. The GSK goal: to convince regulators that the evidence that the company's \$3 billion-a-year blockbuster drug caused heart problems was inconclusive. To do that, the GSK officials focused not on heart-attack data but on a broader, less well defined category of heart problems called myocardial ischemia. The most recent studies of Avandia, the GSK officials told the FDA, had "yielded information that is inconsistent with an increased risk of myocardial ischemic events," according to sealed court proceedings obtained by TIME.

What GSK didn't tell the FDA was that on May 14, 2007, two days before the White Oak meeting, GSK's Global Safety Board had noted that a new assessment of Avandia studies "strengthens the [cardiac-risk] signal observed in the [previous] analysis." Or that eight days earlier, the company's head of research and development, Moncef Slaoui, had sent an e-mail to its chief medical officer saying Avandia patients showed an "increased risk of ischemic event ranging from 30% to 43%!" Or that the day before the meeting, the company had produced a preliminary draft report that showed patients on Avandia had a 46% greater likelihood of heart attack than those in a control group.

But the mixed-evidence argument GSK presented to the FDA worked. After months of deliberation, the agency decided to keep the drug on the market — a move worth billions of dollars to GSK but that also may have put millions of patients at risk.

Such examples of the drug industry's outmaneuvering FDA regulators are disturbingly common, say both scientists and policymakers who follow drug approval and safety monitoring. More than 140 million Americans take at least one prescription drug in any given month, and they rely on the FDA to ensure those drugs are safe. That trust, the story of Avandia illustrates, is a gamble. In July, an FDA advisory group conducted the second hearing on the drug's safety since its 1999 approval and again concluded that the evidence against the drug was insufficient to pull it from the market. The group instead recommended additional warnings and restrictions on Avandia's use. In the coming weeks, the FDA will decide whether

to take that advice or withdraw Avandia from the market

Gaming the System

Over the past two decades, as drug after drug has been recalled after winning FDA approval, it has been hard not to wonder if FDA regulators have been captured by the drug industry. FDA critics and industry monitors charge that the drug-approval process is too easy for pharmaceutical companies to game. It is in some ways an unsurprising development. **The FDA serves a public insatiably hungry for new medicines. Yet the agency does not have responsibility for performing safety testing. It relies on drug companies to perform all premarket testing on drugs for safety and efficacy. And it relies on industry "user fees" for 65% of its budget for postmarket monitoring of the drugs it approves, thanks to a 1992 law designed to speed treatments to patients. "The FDA's relationship with the drug industry [is] too cozy," says Senator Chuck Grassley of Iowa.**

Federal studies reveal that the FDA doesn't have a complete or accurate list of prescription drugs on the market and is missing or has incomplete information on one-third of the drug-safety and efficacy trials under way. **Over the past three years, the inspector general at the Department of Health and Human Services found that the FDA had inspected only 1% of clinical-trial sites from 2000 to 2005 and lacked financial disclosure data for clinical investigators in half of all industry drug reviews.**

The results of this broken system may prove criminal as well as fatal. In June, FDA whistle-blower Dr. David Graham published an article suggesting that Avandia caused 47,000 more diabetics to suffer heart failure, stroke or death than would have been the case if they had taken an alternative. The risk is especially troubling given that diabetics are already more vulnerable to heart disease because of their condition. Congressional reports revealed that GSK sat on early evidence of the heart risks of its drug. Equally alarming is the revelation that the FDA knew of the dangers months before it informed the public. Now the FDA is investigating whether GSK broke the law by failing to fully inform the agency of Avandia's heart risks, deputy FDA commissioner Dr. Joshua Sharfstein tells TIME. At the least, the story of Avandia shows how drug companies use uncertainty to their advantage — at a risk to public health.

Risk and Reward

In November 1998, SmithKline Beecham (SB), which more than a year later would merge with Glaxo Wellcome to become GlaxoSmithKline, presented the FDA with an impressive application to market Avandia: dozens of boxes, each containing eight volumes the size of the New York City phone book, filled with trial data and chemical analyses. Avandia, or rosiglitazone, was only the second in a new class of antidiabetes drugs that was showing promise in helping Type 2 patients keep their blood sugar in check. But the first product, troglitazone, or Rezulin, was also causing a troubling amount of liver damage, so doctors and patients were eager for a safer alternative. Aware of this, FDA officials put Avandia on a six-month fast track to approval. As the FDA's medical, statistical and pharmacological reviewers went through the mountain of documents, they soon found the same thing: Avandia users experienced more cardiovascular issues, including a rise in bad cholesterol (or LDL) and lipids, than those taking other antidiabetes medications or a placebo. But detailed though the pages of data provided by SB were, they didn't show this danger of heart problems with certainty.

In public, SB executives defended the safety of their drug. At an April 1999 FDA public hearing featuring outside experts charged with recommending whether to approve Avandia, SB's head of research and development, Dr. Tadataka Yamada, maintained that Avandia had a "risk-neutral lipid profile" and "cardiovascular safety ... comparable to placebo and active comparators." FDA scientists disagreed. Concerned about the boost in LDL, FDA pharmacologists recommended against approving the drug. Dr.

Robert Misbin, the FDA's medical officer, said he would support approval only if the company committed to a thorough safety trial that would include monitoring for cardiovascular risks.

The hearing committee, three of whose eight voting members had declared financial conflicts of interest in the case, debated the heart issue and eventually recommended that the FDA approve the drug. (TIME requested the forms that waived the conflicts of interest; an FDA official declined to release them and said none of the conflicts involved a relationship with SB.) Then came the horse trading. After outside experts weigh in on a new drug, but before it receives final approval from the agency, the FDA and the drugmaker negotiate which tests the company will perform once large numbers of people are taking it on the open market.

On May 5, 1999, SB sent its proposal for testing Avandia to the FDA. The company didn't want to do a long-term safety test at all. Less than a week later, in a letter to his superior, Misbin threatened to withdraw his approval recommendation, saying the risk of heart disease may be increased by treatment with Avandia and accusing SB of attempting to divert attention from dangers that Avandia might pose to patients, according to parts of the letter read to TIME.

Then, right at the May 25 deadline for FDA approval, SB made an offer to focus its testing on the drug's ability, as compared with competitor drugs, to lower blood sugar. It was a side step from the question the agency wanted to answer about the drug's safety. Instead of focusing on finding out if Avandia posed a heart risk, SmithKline Beecham was going to run a trial its sales representatives could use to promote the drug. "It was really a marketing study," says Misbin now. But later that day, Dr. John Jenkins, the FDA's director for new drugs, accepted SB's proposal for testing the drug on the market and approved Avandia for sale. By agreeing to the company's version of the postmarket trial, scientists say, the FDA abdicated its responsibility to collect reliable data on Avandia's safety.

Even with the FDA's help, the company had its hands full. In 1999, Dr. John Buse of the University of North Carolina at Chapel Hill, a diabetes expert, using slides that SB officials had presented at their approval hearing, did his own calculations based on the data. In speeches, he highlighted the fact that Avandia users experienced a more than fourfold rise in cholesterol compared with those taking a placebo. Because elevated cholesterol levels are a risk factor for heart disease, Buse wrote to the FDA commissioner, warning that Avandia could cause "adverse cardiac outcomes." In March 2000, officials with the newly merged GlaxoSmithKline got a copy of the letter and, Buse tells TIME, contacted his boss, accusing Buse of being a liar and being for sale, and saying he needed to be muzzled. The company's stock had dropped, and "they threatened to sue me for something like \$4 billion, which was the loss of the company's valuation," he says.

In the meantime, the company took measures to promote Avandia. In 2001, GSK worked on an article, later published in the American Heart Association's journal *Circulation* by Dr. Steven Haffner of the University of Texas Health Science Center at San Antonio, arguing that the class of drugs that includes Avandia could significantly reduce cardiovascular risk factors in animals. At meetings with doctors in 2001, GSK sales representatives denied Avandia had cardiac side effects, prompting the FDA to issue a public letter of warning against the company.

Keeping the Public in the Dark

By 2004, Avandia sales were earning GSK more than \$1.5 billion a year in the U.S. alone. But as more people went on the drug, the picture on cardiovascular risk began to get clearer. GSK began a review of the drug's heart risks, and in 2005 and 2006 the company produced internal analyses showing 29% and 31% jumps in negative heart events. On May 9, 2006, the company provided these results to the FDA. The agency didn't immediately release those studies to the public, because its officials "didn't necessarily agree with some of the methodology used," says Dr. Janet Woodcock, head of the FDA Center for Drug Evaluation and Research. Instead, the FDA put its own statistician on the job. Just before Christmas that year, Misbin looked at the statistician's spreadsheet and found that "in virtually every trial, there were more cardiac events with Avandia than with the comparator," Misbin says. He was convinced enough to call his uncle, who was on Avandia, and advise him to ask his doctor to switch him to another drug.

It was seven years after the drug was approved, and the dangers of Avandia had still not been made sufficiently clear to the public. The FDA was sitting on the new analyses, and GSK, the FDA discovered during an investigation by its inspections unit in the fall of 2007, had failed to report clinical data and other material from 15 tests of Avandia by the end of 2006, according to a March 25, 2008, warning letter to the company. With the company and the FDA maintaining tight control over the full database of information on Avandia's effectiveness and safety, there was little independent scientists could do to assuage their growing concerns about the drug.

Then came a bit of legal serendipity. As part of a settlement with the state of New York over GSK's nondisclosure of possible heightened suicide risk among teenagers taking its antidepressant Paxil, the company agreed to put all its recent clinical studies on a website. Aware of the growing concerns among clinicians about the risks posed by Avandia, in April 2007, Cleveland Clinic cardiologist Dr. Steven Nissen Googled the site and downloaded all of the available Avandia trials. After analyzing the 42 trials, he wrote up his findings and in May submitted them to the New England Journal of Medicine. He had found what GSK and the FDA already knew: a 43% higher rate of cardiac events among Avandia patients compared with those taking other drugs or placebos.

By chance, the New England Journal of Medicine chose as a prepublication reviewer of the Nissen article Haffner, the University of Texas doctor who was the lead author on the 2001 paper that had suggested that Avandia's class of drug could decrease cardiovascular risk. He faxed a copy of Nissen's article directly to GSK. Now GSK faced the threat of broad public awareness of the hazards of its drug. So with the clock ticking until Nissen's article was to be published on May 21, 2007, GSK harvested data on cardiac events from the recently completed efficacy trial Jenkins had signed off on back in 1999. Because the trial had been designed to show efficacy, not safety, its cardiac data were inconclusive.

As it prepared for the pivotal May 16, 2007, meeting in White Oak with FDA regulators, GSK came up with an additional counterattack to Nissen's study. Unlike the FDA, European regulators had insisted on a long-term cardiac-safety study, called RECORD, when they approved the drug. So GSK argued that the only prudent approach would be to let the RECORD trial run to completion in 2009 to reach a definitive answer on cardiovascular risk. To top agency officials, it seemed like a reasonable solution at the time. But three years and hundreds of millions of dollars in Avandia sales later, it turns out the RECORD trial may not be as reliable a study of cardiac risk as agency officials had hoped.

Regulator, Regulate Thyself

By 2008, after the painkiller Vioxx and the cholesterol-lowering medication Baycol were pulled from the market because of side effects and complications, House and Senate overseers both began investigations of the drug-approval process and the relationship between the drug industry and its federal minders. The Senate Finance Committee concluded in January 2010, after a two-year review, that GSK failed to promptly alert the FDA about Avandia's drug risks. In response, FDA commissioner Dr. Margaret Hamburg initiated another review of whether to keep Avandia on the market. As part of that review, FDA investigator Dr. Thomas Marciniak presented a devastating report on RECORD's shortcomings, detailing how the RECORD study minimized Avandia's heart risks: one death among the drug takers, for example, was missing from the final tally, and discrepancies in some cardiovascular data favored Avandia by a ratio of 4 to 1. The congressional investigation also uncovered e-mails indicating that GSK executives had managed to persuade the trial's supposedly independent steering committee to publish interim results that demonstrated how inconclusive the heart risk was. The trial's design, Marciniak found, was "completely inappropriate and biased."

For its part, GSK insists the drug is indeed safe and says it has played fair with the data. It lists multiple studies that are inconclusive or show no increase in heart risk for Avandia. It says it has disciplined the sales representatives who triggered the FDA admonition; it updated its report on Avandia tests after the FDA's 2008 warning letter. "GSK continues to stand behind Avandia," says spokesman Kevin Colgan. "The facts will support our position." Using the most powerful argument of all, GSK says diabetics desperately want and need drugs to lower their blood-sugar levels. All of this persuaded the FDA advisory

group this July to narrowly vote not to pull Avandia off the market, citing a lack of strong evidence that it should be withdrawn. Eleven years after the drug was approved, neither GSK nor the FDA could yet prove Avandia was safe.

GSK certainly had reason to dispel the uncertainty if it could. In 2001, it ran a calculation of what the "net sales downside" would be if the cardiovascular "safety issue intensifies" and found that for 2002-04, potential lost revenue amounted to \$600 million, according to the civil-court proceedings obtained by TIME. GSK reported a 10% drop in profits for the fourth quarter of 2007, partly as a consequence of a drop in Avandia sales following the publication of the Nissen article. Now GSK has other financial concerns. In March the company put aside \$3.5 billion for "legal and other disputes." In May it paid \$60 million to settle 700 Avandia civil cases; in July it reportedly offered to pay \$460 million to settle civil cases claiming the drug caused heart attacks. GSK declines to discuss the costs of — or anything else about — the investigation the FDA is undertaking against it.

That investigation may indicate that change is coming to the FDA. Government and independent watchdogs say the agency has made some progress. In 2009, government auditors found that the FDA had begun to bolster the role of drug-safety monitors. The Health and Human Services inspector general said last March that the FDA has boosted its prescription database of postmarket reports.

But none of that addresses the issue at the heart of the Avandia case. Science is often inconclusive, and the FDA rightly argues that surveys like Nissen's are sometimes wrong. Where the FDA fell down on Avandia was in allowing GSK to perpetuate the uncertainty about safety rather than clarify it. In 2007, the FDA gained new powers to require postmarket safety trials, but FDA leaders admit they're still learning how to use them. Grassley wants to give FDA safety monitors even more power, and former FDA chief Mark McClellan says the agency should use newly computerized medical records to track safety data in near real time.

But with the FDA ever more dependent on industry user fees, and with new drug-safety concerns emerging year after year, it will take more than faster data retrieval to restore the reputation of an agency that was once synonymous with trust in the public mind. The FDA will have to start forcing companies to be transparent and call them out on it when they're not. Says the medical reviewer Misbin: "Companies are always going to present their best face. It's our job to say no." In that sense, the FDA just needs to perform the task it was charged with more than 100 years ago: protecting the public interest by keeping industry honest

Ralph's Note - Thank you Time Magazine....

These reports are done with the appreciation of all the Doctors, Scientist, and other Medical Researchers who sacrificed their time and effort. In order to give people the ability to empower themselves. Without the base aspirations for fame, or fortune. Just honorable people, doing honorable things.