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CONVERTING HEALTHY PEOPLE INTO PATIENTS

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In a remarkably candid 1976 *Fortune* article, Merck CEO Henry Gadsen complained that his only customers were people who were sick. He said he wanted his company to make drugs for healthy people so that he could "sell to everyone", much like the manufacturers of Wrigley chewing gum. Three decades later, that dream has become a reality that may have turned into a dangerous as well as expensive nightmare.

Pharmaceutical companies have successfully expanded the definition of sickness and lowered the threshold for prescribing drugs by creating millions of new patients who fear they are or will become sick from some trivial or poorly understood ailment. This has been accomplished by a combination of manipulative marketing and massive corruption of the medical care system that has permitted ordinary and relatively minor complaints to become magnified and progressively "medicalized". This triumph of salesmanship over science has also boosted the bottom line of pharmaceutical manufacturers to firmly establish them as the most profitable industry on earth.

In a strange twist, The Wrigley Science Institute was recently created to cash in on this growing community of the "worried well". Its stated mission is to "Lead the advancement of scientific knowledge and education on the consumer health and wellness benefits of chewing gum and other confections." Some of these rewards include weight reduction, stress relief, cognitive gains (enhanced concentration, learning skills) and increasing salivation to reduce cavities and promote oral health. Since poor dental health has been linked to coronary disease, there could be additional health claims.

ALSO INCLUDED IN THIS ISSUE

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- Dr. Eric Topol, Vioxx, Conflicts Of Interest & Corruption At Cleveland Clinic
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It's difficult to watch television today without being bombarded with advertisements urging you to ask your doctor if a certain prescription drug "is right for you." Many of these are for diagnoses you may have never heard of or are hardly serious health problems. Some illustrations include "social anxiety disorder" (SAD), "premenstrual dysphoric dysfunction", "restless

leg syndrome", (PMDD), "female sexual dysfunction", "cyclothymia" or "bipolar disorder" in children and onychomycosis. ADHD (Attention Deficit Hyperactivity Disorder) and ED (Erectile Dysfunction) have already become part of everyday language.

Lamisil And Digger The Dermatophyte, Plavix And "Aspirin Resistance"

Some of the drugs for these disorders may also be new to you but will not be for long. A good example is Lamisil (terbinafine), manufactured by Novartis for the treatment of onychomycosis. This is a fungus infection that turns toenails yellow and thick but is usually not painful or hazardous to health. Lamisil ads lure TV viewers with Digger the Dermatophyte, an ugly short yellow devil-like cartoon character who lifts up a large toenail as if it were the hood of a car. He creeps under the nail as he announces in a raspy Brooklyn accent, "I'm not leavin", and then invites all his little yellow friends to also make their home there. According to a very recent *Forbes* article, Novartis has spent $236 million on Lamisil ads in the past three years. During this period, sales jumped 20% to $1.2 billion in 2004 and have continued to increase. The initial ad showing Digger and his friends being crushed by a giant Lamisil tablet, had to be modified since it exaggerated the drug's benefit and only cures the condition in 38% of patients. The FDA has linked Lamisil to 16 cases of liver failure and 11 deaths, there can be serious reactions with other medications and it is advised to refrain from alcohol during treatment. Yet, 10 million Americans have taken Lamisil at a cost of $850 for three months. The average time for a complete cure is 10 months so the total cost could be several thousand dollars with no guarantee for most patients. A three-month supply costs $180 in Canada, which will give you some idea of the enormous profit margin.

Lamisil's patent expires later this year, and although a less expensive generic version has already been approved, that does not mean it will be available here. Generic drug manufacturers are frequently paid to keep their products off the market and may also share in the profits. The Federal Trade Commission (FTC) has opposed this restriction of trade and several years ago, successfully sued Bristol-Myers Squibb for obstructing the entry of low-price generic equivalents of three of their popular drugs in order to protect nearly $2 billion in annual sales. In addition to filing baseless patent infringement suits to hold things up, it paid one company $70 million not to bring a competitive product to market costing consumers hundreds of millions of dollars in overpayments for important and often life-saving medications. This practice has now been resumed as a result of Circuit Court of Appeals decision that the FTC has asked the Supreme Court to reverse. A FTC Commissioner reported three such deals in 2005 and six so far this year that will allow brand name drugs to continue to be sold at premium prices. He cited the example of Plavix, a blood-thinner made by Sanofi-Aventis and distributed in the United States by Bristol-Myers Squibb with $3.8 billion in annual sales and almost $6 billion worldwide. The two companies recently paid Apotex Corp. an undisclosed sum to defer marketing a generic version until 2011.

Plavix popularity is similarly the result of a massive media blitz, manipulative marketing as well as corruption due to conflicts of interest. Sales are up 60% from two years ago, making it now second only to Lipitor as the best selling drug in the world. Plavix interferes with blood coagulation by a mechanism that is different from aspirin and both are routinely prescribed for patients with cardiac stents and others who are at increased risk for developing clots. However, a study of 15,000 patients published two months ago found that adding Plavix ($4.00-$4.50/day) to low-dose aspirin (2-3 pennies/day) was no more effective than aspirin alone for preventing heart attacks, strokes and cardiovascular deaths. In fact, Plavix plus aspirin nearly doubled the heart disease death rate. Many patients have also suffered severe bleeding problems with combination Plavix and aspirin therapy and disabling brain hemorrhages have been reported following mild head trauma, especially in elderly patients.

Dr. Eric Topol, Vioxx, Conflicts Of Interest & Corruption at Cleveland Clinic

That was not what the drug companies who sponsored the study wanted to hear but a damage control program to discredit aspirin had already begun. Bayer trademarked aspirin for its brand of acetylsalicylic acid in 1899, so it has been around for well over 100 years. It therefore seems strange that there was essentially nothing in the literature about "aspirin resistance" until four years ago, when Plavix came on the scene. Since then, medical publications and promotional literature have increasingly warned about the dangers of this new discovery and the need to test for this. In 2003, Eric Topol, head of cardiology at the Cleveland Clinic, published a paper in *The Journal of the American College of Cardiology* reporting that **people who were resistant to aspirin are three times more likely to die or suffer a heart attack or stroke** compared to those who responded normally. The paper suggested, "Future treatment of aspirin resistance with additional antiplatelet agents such as clopidogrel [Plavix] may significantly improve the poor prognosis." The study looked at 326 patients, 17 of whom were determined to be aspirin resistant using the Accumetrics test. Four of these either died, had a heart attack or stroke, but had there been one less, the results would not have been statistically significant. Topol's group also used another method for determining aspirin resistance that found no significant difference between the aspirin resistant and normal patients but these results were not published. The following year Topol was quoted in an Accumetrics press release as saying that its aspirin test was "prototypic of the future of individualized medicine" and would allow doctors to "improve outcomes for a large number of patients." The article didn't mention that Topol was a consultant to Accumetrics. He was also a consultant to AspirinWorks, another aspirin resistance testing firm and companies making or developing aspirin alternatives, including Bristol Myers, Sanofi-Aventis, Eli Lilly and Medicines Co.

In addition to consulting for Accumetrics, Dr. Topol helped the company get venture capital funding. In April 2003, Essex Woodlands Health Ventures of Chicago listed Dr. Topol as an "adjunct partner" who provided advice on "all aspects of the venture capital process." Essex Woodlands led a $13.5 million round of investment in Accumetrics in 2004 and has since invested more in the company. When interviewed, the director of Essex Woodlands declined to reveal how much his firm paid Dr. Topol for the part-time position and Topol said he didn't remember his compensation package for this or the various consultancies noted above. He also hit the lecture circuit to build awareness of aspirin resistance. At the annual meeting of the American Heart Association in November 2004, a packed room of doctors attended his symposium, "The Cleveland Clinic Presents the Diagnosis and Management of Antiplatelet Resistance", sponsored by Accumetrics and two drug companies making anticlotting drugs. Topol, who is one of the world's most quoted cardiologists attracted national attention because of his claims starting in 2001 that Vioxx caused heart disease and his criticism of Merck for concealing this information. Two days after a videotaped deposition at a Vioxx trial in which he accused Merck of scientific misconduct, he was told early in the morning not to attend an 8 AM meeting of the Cleveland Clinic's board of governors because the position of chief academic officer, which gave him a seat on the board, had been abolished. His demotion also cost him his seat on the conflict of interest committee, where he had been a vocal critic of Cleveland Clinic CEO, Delos Cosgrove who narrowly beat Topol out for this position in 2004.

Cleveland Clinic had been struggling with conflict of interest issues that came to a head when Merck pulled Vioxx from the market in September 2004 after a study showed that the drug increased the risk of heart attacks and strokes. Shortly thereafter, *Fortune* magazine reported that Topol was a paid consultant to an investment fund that shorted Merck, or bet its stock would fall, just before the company decided to withdraw Vioxx from the market. Vioxx had been one of Merck's blockbuster drugs, with $2.5 billion in sales in 2003. Its stock has fallen over 40% since it was withdrawn, a drop in value over $50 billion to shareholders. Over 12,000 lawsuits have now been filed alleging wrongful death and accusing Merck of

withholding negative information about Vioxx that could cost the company up to $20 billion. As an aside, during this period when the stock was plunging CEO Raymond Gilmartin made around $54 million, including close to $38 million in profits from cashing out stock options during the past two years. Gilmartin stepped down as CEO in May 2005 but agreed to stay on as a consultant for ten months. His severance package included a pension worth $784,0000/year, an office and a secretary for at least seven years. Merck can well afford it since their balance sheet at the end of December was $16.7 billion in cash and investments.

Last February, Dr. Topol resigned or was forced out of his prestigious position at Cleveland Clinic and is now a professor of genetics at nearby Case Western Reserve University. He said he had hired a team of lawyers to negotiate his exit, including one who is handling hundreds of cases against Merck and won a $253.4 million verdict against them last August. The conflict of interest and possible corruption claims involving Cleveland Clinic also involved CEO Cosgrove, a cardiovascular surgeon. A few days after Topol's demotion, the *Wall Street Journal* revealed a web of financial connections between Cosgrove and AtriCure, a company selling a medical device used in a surgical procedure promoted by the clinic. The *New York Times* reported that, "It is well known that device makers give surgeons who are in a position to choose their products (with others paying the cost) lucrative consulting contracts, in some cases running to hundreds of thousands of dollars a year." While a member of the conflicts of interest committee, Topol had inquired about the financial arrangements of Cosgrove and other doctors involving the use of clinic patients in tests of medical devices made by companies in which they and the clinic had financial interests. Cosgrove also participated in a venture-capital fund that had long invested in companies doing research at the hospital without ever disclosing those ties to patients. After an internal review found "institutional and individual inattention" regarding both of these problems, the clinic announced it would toughen its policies. The same review found Cosgrove's disclosure practices "contained some shortcomings" but took no action.

Getting back to the aspirin resistance fiasco, last July, Daniel Simon, a Harvard Medical School associate professor, wrote in *Physician's Weekly* that **"aspirin resistance may afflict as many as 30% of the 25 million Americans taking aspirin to protect their heart and that they may need "other anticlotting drugs."** Although publications routinely ask if there are any conflicts of interest, the article did not disclose that Dr. Simon receives research funding from Accumetrics and is also a consultant and paid speaker for Schering-Plough, which makes a drug being tested as potentially beneficial for patients labeled as aspirin-resistant. *Physician's Weekly* is a trade publication distributed to over 250,000 physicians. The Managing Editor indicated that he knew of these ties but didn't disclose them because he never discloses possible conflicts of interest. This information is used for other purposes such as contacting drug or other companies to see if they want to place an advertisement near the doctor's commentary. It's all about making more money rather than improving medical care. Medicare paid for 43,000 laboratory tests used to measure aspirin resistance in 2004, double the number of tests it paid for just two years earlier. This will undoubtedly continue to escalate since in addition to hospitals, a recent press release stated that Accumetrics plans to put their testing device in 50,000 physicians' offices to monitor the 25 million Americans taking aspirin. Dade Behring in Illinois has its own blood test to measure aspirin resistance based on platelet aggregation. It reported annual double digit increases in income, 2005 revenues of almost $1.7 billion and a 41% growth in earnings for share for the first quarter of 2006. One cardiologist administers the Accumetrics blood test to all his patients that take aspirin. Medicare reimburses $30 for the test that provides results in 10 minutes but he also receives a few dollars for drawing the blood and $22.00 for a "lower level" visit, for a total of $55.00. Other insurers reimburse more. While the device costs around $5,000 a doctor receives it at no charge as long as a box of 25 tests a month is ordered. Since the cost/test is around $22 **this provides a minimum additional income of $10,000/year for a 15-minute procedure involving work done mostly by**

office staff. Accumetrics also offers a similar test to measure resistance to Plavix that costs more but is again fully reimbursable by Medicare and other insurers.

By coincidence, Dr. Simon is leaving Harvard in July and will be joining Dr. Topol at Case Western Reserve as Chief of Cardiology. He has initiated a $2 million, 600-patient study that will use the Accumetrics test to determine if patients about to undergo angioplasty are resistant to aspirin or Plavix. Patients classified as resistant to either will be placed into two groups — one receiving Integrilin, an injectable anticlotting medication sold by Schering-Plough, and one receiving a placebo. The researchers will compare the two groups for differences in heart-attack rates. Accumetrics and Schering-Plough are funding the study. Many physicians believe the problem of aspirin resistance had been blown out of proportion to promote Plavix and testing devices. While they agree that aspirin fails to have a desirable anticlotting effect in a small number of patients and that there are gender differences, simply taking two 81-mg. baby aspirin tablets might solve many problems since this is still half the amount of a regular aspirin tablet. They also emphasize that there are different definitions of aspirin resistance and different ways to measure it so it is not known how many patients have this problem or how high their cardiovascular risk is. For example, a 2002 study by Dr. John Eikelboom and colleagues found that a high level of aspirin resistance as measured by a certain urine test could more than triple the risk of cardiovascular death. However, Dr. Eikelboom now agrees that this test is "the wrong marker" and shouldn't be used. He also cites the lack of evidence that changing treatment for aspirin-resistant patients does any good and the fact that there are no studies showing that a drug or any other treatment can reverse or reduce aspirin resistance. In addition, platelet aggregation or clumping, which is widely used to measure aspirin resistance can be influenced by many factors. It can be increased 20% by smoking or nicotine, is accelerated by insulin, low blood sugar, in patients with mitral valve prolapse and replacement or estrogen therapy in women. Stress related hormones like adrenaline have a particularly powerful effect and their sudden surge shortly after waking up are thought to explain the increased incidence of heart attacks in the morning and on Mondays as anticipating another week of job stress begins.

Not surprisingly, some of the strongest criticisms of aspirin resistance have come from researchers with ties to Bayer. In September 2004, the journal *Circulation* published a "special report" on aspirin resistance warning that the "current usage of the term aspirin resistance implies a linkage between a laboratory test and a clinical outcome that is presently unsubstantiated." The lead author, Charles Hennekens, who conducted a landmark study in the 1980s demonstrating the benefits of taking an aspirin a day, that is still supported by the American Heart Association, disclosed that he was a consultant for Bayer. Two of the other authors also listed various associations with Bayer but these were inadvertently omitted due to a production error according to a spokeswoman for the American Heart Association, which publishes *Circulation.* In a December 2004 commentary in *Physician's Weekly*, Hennekens cautioned that "exaggerated concern about this undocumented phenomenon may have the negative consequence of reduced aspirin use." As usual, his connection to Bayer was not disclosed to promote aspirin advertising. Last December, the *New England Journal of Medicine* published an extensive review, which concluded that **"none of the aspirin tests is currently recommended" and that there was "no scientific basis for changing antiplatelet therapy."** The four authors of the article all disclosed that they had financial ties to Bayer.

How To Sell "Lifestyle" Pills That Are Looking For Ills Or Off Label Uses

A 2003 Reuters report targeted to pharmaceutical industry executives prophesized that, **"The coming years will bear greater witness to the corporate sponsored creation of disease."** This has also proved to be an accurate prediction as drug companies have increasingly created new disease and new indications for off label use of their products. Physicians are free to use any approved drug for other situations where they think it might be

beneficial. While manufacturers are prohibited from promoting products for such off label purposes there are ways to get around this. There is nothing to stop a doctor from reporting that excellent results have now been found in another condition and that "further investigation of these preliminary results is indicated." Such findings or even opinions often appear in pseudoscientific publications like *Physician's Weekly* and other free medical journals supported by the manufacturer's lucrative advertising. They may also be "leaked" to the media as well as organizations and patient groups with a particular interest in this or some similar disorder. Despite disclaimers such as "more research is needed" or "these initial promising results need to be confirmed by others", their significance is frequently exaggerated to attract attention. This is especially true as these findings are trumpeted on myriad Internet sites providing medical information over which there is little if any control.

Inventing new indications that can gain FDA approval is particularly important for top selling products whose patents are about to expire since this can provide an extension that will continue to bring in billions of dollars a year. One example is Social Anxiety Disorder (SAD), which is apparently little more than a tendency to be shy in certain situations. Several years ago, GlaxoSmithKline needed to find a new application for its controlled release anti-depressant Paxil CR in an attempt to extend the patent. The easiest solution was to create a new indication and they found a brief mention of a little-known condition called Social Anxiety Disorder in a psychiatric journal. The symptoms of feeling nervous, sweaty, or shy when attending parties or group functions were not that impressive but a PR firm was able to turn it into a new disease that affected millions. They rounded up patients, experts and celebrity sufferers and marketed it with an advertising blitz that included a catch phrase "Imagine being allergic to people." Two football icons, Terry Bradshaw and Ricky Williams, kicked off National Mental Health Awareness Month in a May 2003 event in New York as part of a five city tour sponsored by GlaxoSmithKline to explain how Paxil CR had transformed their lives by curing their depression and social anxiety. Williams said, "At one point I would have not been able to get on a plane or talk to a group of three people. Now, I look forward to traveling across the country to speak to large groups about taking the first step towards a better life." A new disease with famous names was hard for the media to ignore. The *New York Times* ran a long feature, *Vogue* and other publications quickly followed suit and thousands of people began to believe that they suffered from SAD. The company proudly announced in October 2003 that the FDA had approved Paxil CR as the first and only controlled-release SSRI for Social Anxiety Disorder, which they now described as the most common anxiety disorder. GlaxoSmithKline made millions and the public relations company won an award for their PR program.

Bradshaw and Williams even had a web site to provide tips on how to handle depression and social anxiety but it was discontinued the following year when Williams stopped taking Paxil and was quoted in the *Miami Herald*, *Sports Illustrated* and other publications as saying **"Marijuana is 10x better for me than Paxil."** Bradshaw also terminated his speaking tour after the dangers of Paxil that the company had concealed for 12 years were widely publicized. Social phobia, described as "an intense, irrational and persistent fear of being scrutinized or negatively evaluated by others, that "typically provoke an immediate anxious reaction ranging from diffuse apprehension to situational panic" has been an accepted psychiatric diagnosis since 1994. The onset is typically between the ages of 11 and 19. That's a lot different than the company's advertising, which suggested that almost anyone experiencing anxiety, fear, or self-consciousness in social situations is an appropriate candidate for Paxil CR, especially since this is most likely to occur in children and adolescents. As indicated in prior Newsletters, prescriptions for Paxil and other antidepressants in patients under the age of 19 skyrocketed between 1998 and 2004, doubled in girls aged five and under and increased 64% in preschool boys. Most of these were for minor behavioral problems. In addition, Paxil was no better than placebo in clinical trials and had been shown to increase risk for suicide in anyone under the age of nineteen.

Paxil was the first SSRI to be banned in Britain in this age group and while Glaxo sent a letter warning all physicians there that Paxil should not be given to children, this was never revealed to U.S. doctors. Congressional committees sent the FDA a strong letter asking why they did not take more stringent action and why they prevented their own expert, Dr. Andrew Mosholder, from presenting his review that found Paxil and similar drugs significantly increased risk of suicide in children at a public hearing to approve their use in adolescents. His report had been replaced at the last minute with a more favorable analysis by a FDA official who had originally approved most of these drugs. FDA Commissioner Lester Crawford told Dr. Mosholder that his attendance at the hearing was permissible under the condition that he only answer questions from an approved script. Since then, there have been an alarming number of wrongful death and other suits filed on behalf of children for whom Paxil had been prescribed. SmithKlineGlaxo has also been sued by New York and California's Attorney Generals for concealing safety and efficacy tests in children; is currently facing criminal charges in the UK over its "suicide pills" and is being investigated by Congress. Yet, it was less than three weeks ago that the company finally sent letters to US doctors warning that "Paxil appears to increase the risk of suicide attempts in some young adults" and agreed to include this in its labeling. Dr. Crawford is currently under criminal investigation by a federal grand jury because of accusations of financial improprieties concerning the sale of stock by him and his wife in drug companies that had been regulated by the FDA during his tenure as well as lying to Congress. He resigned unexpectedly last September saying it was time for someone else to lead the FDA but it seems likely that he was made aware of the impending investigation, which was announced a few weeks later. Crawford was quickly hired to be "senior counsel" for Policy Directions Inc., a Washington lobbying firm whose **web site currently boasts about its ability to intercede with the FDA and that they "Successfully achieved FDA advisory committee support for a product that had originally been voted down."**

Like Social Anxiety Disorder, PMDD (premenstrual dysphoric disorder) is another new questionable disease that is difficult to distinguish from normal life. Perhaps 20-40% of US women suffer from premenstrual syndrome (PMS) symptoms such as swelling due to fluid retention, increased irritability and headache that can often be prevented or reduced with diuretics or mild analgesics. PMDD is essentially a more severe form of this that significantly impairs normal activities but the diagnosis requires a review of daily symptom diaries for 2 to 3 consecutive months that are rarely available. Paxil and other serotonin reuptake inhibitor (SSRI) antidepressants have now been approved for treating PMDD although Paxil CR is the only extended release product in this category. Pfizer's Zoloft became the "first and only approved PMDD treatment that is effective if it is taken every day or for the two weeks before a woman's period". The first drug indicated for PMDD was Lilly's Sarafem, which is identical to Prozac (fluoxetine). Lilly justified calling the same drug something else by explaining that it hoped to "reduce confusion about the differences between depression and PMDD" and thus increase sales by avoiding the stigma of mental illness. It is more likely that the reason was that its patent on Prozac was about to expire and that several articles and a very popular book had called attention to the dangerous side effect of Prozac and SSRIs.

The European equivalent of the FDA refused to approve drugs for PMDD because of its poor distinction from PMS and concerns that women with "less severe premenstrual symptoms might erroneously receive a diagnosis of PMDD resulting in widespread inappropriate short- and long-term use of fluoxetine". The Irish regulatory agency prohibited GlaxoSmithKline from making PMDD claims for Paxil and although SSRIs can be prescribed for PMDD in Australia their costs are not covered as in the US. A large survey found no evidence that depression and anxiety, much less PMDD were caused by serotonin deficiency as is widely touted. There are also concerns that patient requests for advertised medicines could lead to off-label antidepressant prescribing for "adjustment disorder", a condition involving temporary distress due to a troubling life situation that rarely requires drug therapy.

Restless legs syndrome is another disorder few people heard of until GlaxoSmithKline launched a 2003 publicity campaign describing the benefits of Requip (ropinirole), a drug that had previously been approved for Parkinson's disease. A subsequent press release entitled "New survey reveals common yet under recognized disorder — restless legs syndrome — is keeping Americans awake at night" suggested that 10-12 million people were affected. Requip was granted approval for restless legs syndrome 12 months ago although many physicians had already been prescribing it for various restless legs symptoms. Since then, the restless leg campaign has developed into an international multimillion dollar media blitz with articles reporting that "This is the most common disorder your doctor has never heard of", that "many people can suffer in silence for years before it is recognized". People were referred to the "nonprofit" Restless Legs Foundation where they were encouraged to ask their doctor whether restless legs might explain problems such as insomnia, feelings of fatigue, depression and attention deficit disorder in children but were not informed that this was subsidized and controlled by GlaxoSmithKline. Actually, the diagnosis of restless legs syndromes requires the presence of all the following four symptoms:

1. An urge to move the legs due to an unpleasant feeling in the legs.
2. Onset or worsening of symptoms when at rest or not moving around frequently.
3. Partial or complete relief by movement (e.g., walking) for as long as the movement continues.
4. Symptoms that occur primarily at night and that can interfere with sleep or rest.

Few patients receiving Requip satisfy all these criteria and in many instances, massage, avoiding alcohol, smoking and caffeine can provide significant relief. Nevertheless, sales of Requip have more than quadrupled since the advertising campaign began.

Irritable Bowel Syndrome (IBS) is another disease blown out of proportion to promote sales of Zelnorm (tegaserod). The diagnosis of IBS requires a year's history of at least 12 weeks of pain or abdominal discomfort that is relieved by defecation or is associated with a change in stool frequency or form. Symptoms are relatively mild, intermittent and not disabling in 90-95% of patients. Patients with gastrointestinal complaints like "spastic colon", chronic constipation, abdominal cramps, and "mucous colitis" are not infrequently diagnosed as IBS even though they do not satisfy the diagnostic criteria.

Novartis received FDA approval of Zelnorm for the treatment of IBS in 2002 and launched a powerful publicity campaign. It featured bulging bellies with Magic Markers displaying what was called the "ABC's" of IBS (Abdominal pain, Bloating, and Constipation). Sales of Zelnorm subsequently skyrocketed to $10 billion in 2004 when the FDA deemed it to be a serious health risk and ordered significant changes to be made in its warning label.

The revised 2004 warning stated, "Serious consequences of diarrhea, including hypovolemia, hypotension and syncope have been reported in the clinical studies and during marketed use of Zelnorm. In some cases, these complications have required hospitalization for rehydration. Zelnorm should be discontinued immediately in patients who develop hypotension or syncope. Zelnorm should not be initiated in patients who are currently experiencing or frequently experience diarrhea." They also warned that it could cause ischemic colitis noting that "Since Zelnorm went on sale in 2002, the FDA has received 20 reports of ischemic colitis, plus three

reports of a similar intestinal problem." Fourteen patients were hospitalized and four died. They also had 21 reports of diarrhea so severe that it caused low blood pressure and fainting and sixteen patients required hospitalization. Since over 90% of adverse reactions to drugs are never reported these figures are undoubtedly low.

It should be emphasized that Zelnorm is approved only for the short-term treatment of IBS in women whose predominant complaint is constipation. It is contraindicated in women with a history of frequent or severe diarrhea, which is what most IBS patients suffer from, although it is not listed in the company's "ABC" of symptoms. It has not been shown to be safe or effective in men and should not be used in children or people with a history of liver or kidney disease or abdominal adhesions. Zelnorm was only 5 to 10 percent better than a placebo in clinical trials and it seemed to work best during the first month of its use after which benefits steadily waned. Taking it for more than 10-12 weeks is not recommended although this is frequently ignored. This is not the first time the FDA had been overly hasty in approving an IBS drug. GlaxoSmithKline's Lotronex (alosetron) was approved in February 2000 but was withdrawn only nine months later because of serious, life-threatening, gastrointestinal side effects. In an amazing reversal, the FDA again approved Lotronex in June 2002 as part of a drug company-sponsored educational program that would restrict its use only in women with IBS who had severe and persistent diarrhea that had failed to respond to any other treatment.

Last year the European Union refused to approve Zelnorm for the treatment of IBS and when the company appealed this decision three months ago it was again rejected. The Public Citizen advocacy group has petitioned the FDA to withdraw it here because it is "a drug that is, at best, minimally effective and that may be causing substantial harm." They contend there is no proof that Zelnorm relieves constipation better than Metamucil and appeared to increase the risk of developing ovarian cysts. The CEO of Novartis denied this and said the company was also doing studies to see whether Zelnorm could be approved to treat general chronic constipation and heartburn, which would bring in additional billions of dollars. However, it is likely that many with these and other gastrointestinal complaints are already receiving the drug since it is estimated that three out of four Zelnorm prescriptions are for patients for whom there is no evidence that the drug would be helpful. As previously noted, once a drug is approved a physician can prescribe it for any complaint it might possibly benefit. A very recent report found that about one out of every five medications prescribed by US physicians are for conditions that are not approved by the FDA. Over three-quarters of these off-label uses were not supported by scientific evidence for safety or efficacy.

Osteoporosis, which is a normal consequence of aging, has now become a disease of low bone density rather than a risk factor for vertebral or hip fractures. Osteoporosis produces few symptoms in most patients but almost all, especially postmenopausal women, are urged to take calcium supplements and drugs in an attempt to slow its progression. Most relied on hormone replacement therapy until 2002, when a large study reported that estrogen increased risk of breast cancer, heart attack and stroke. Prescriptions for bisphosphonates used for other bone diseases like Merck's Fosamax (alendronate) shot up 32 percent. Last year, within a record-breaking six months after its application had been submitted, Fosamax became the first drug approved for the treatment of osteoporosis. Fosamax brought in $3.2 billion in 2005 and was projected to reach $3.6 billion in 2006 although this may change because of safety concerns and lawsuits. The drug has significant side effects, including esophageal ulceration, gastrointestinal bleeding, obstruction or perforation, eye pain and various skin complaints. It must be taken on an empty stomach with a full glass of water, after which patients are advised to remain upright and refrain from eating for 30 to 60 minutes. They must also avoid taking calcium supplements or hormone replacement therapy, which many women need, and there can be interactions with several foods and drugs, including aspirin.

In December 2004, doctors at Long Island Jewish Medical Center reported that they had discovered a link between Fosamax and other biphosphonates with osteonecrosis of the jaw. They described this as "a condition in which the bone tissue in the jaw fails to heal after minor trauma such as a tooth extraction, causing the bone to be exposed." This often leads to infection and fracture and may require long-term antibiotic therapy or surgery to remove the dying bone tissue. While most of the patients had been receiving intravenous biphosphonates for cancer chemotherapy a significant number had been taking Fosamax. Another review released three months ago found that more than 2,400 patients who were taking the injected form of bisphosphonates had suffered bone damage to their jaws since 2001. In addition, 120 patients taking the drug orally "had been stricken with such incapacitating bone, joint, or muscle pain that some became bedridden and others required walkers, crutches or wheelchairs." A Texas researcher told the LA Times "We've uncovered about 1,000 patients (with jaw necrosis) in the past six to nine months alone, so the magnitude of the problem is just starting to be recognized." As previously noted, 90 percent of such drug reactions are never reported.

Merck now faces a growing number of legal challenges for not revealing information they had on the harmful effects of Fosamax. A Florida woman who took Fosamax for six years is now seeking "seven figures" for personal injury because of the necrosis that rotted her mouth and exposed bone in her jaw. Another who experienced significant bone loss as well as some teeth after taking it for nine years has filed another Federal suit. The attorney who represents both expects to present about 300 more Fosamax cases in a class action suit that will also demand that Merck establish a fund to pay for a state education program about the drug's risks and for dental screening of Fosamax patients. There are at least 15 similar suits in other states. Although it may improve bone density, some researchers say that **when taken for more than 10 years, Fosamax will actually make bones more brittle and therefore more susceptible to fracture.** As one researcher wrote, "Many people believe that these drugs are 'bone builders,' but the evidence shows they are actually bone hardeners." What is worse is that **even when patients stop taking Fosamax it can remain in the body for up to ten years.** This problem is reminiscent of the 12,000 lawsuits accusing Merck for concealing evidence from their own studies about the ability of Vioxx to cause cardiovascular damage and deaths. Although the drug was withdrawn, this number will surely increase because of new findings that patients remained at risk for a year after they stopped Vioxx.

Elevated cholesterol and other lipid abnormalities are also now viewed as diseases that require frequent testing and aggressive treatment to prevent heart attacks. As emphasized in prior Newsletters, a high cholesterol is simply one of several hundred other risk markers like a deep earlobe crease, premature vertex baldness or abdominal obesity that show an increased association with heart attacks but do not cause this or other coronary events. Nevertheless, cholesterol lowering products are the best-selling prescription drugs in the world with annual sales of $26 billion, mostly from statins. Originally prescribed for people with high cholesterol or LDL, this was later extended to anyone at high risk for a heart attack, including all diabetics, hypertensives and anyone with a family history regardless of cholesterol levels. Some now suggest that everyone over 45 should take statins to prevent deaths from heart disease. The Boomer Coalition (www.boomercoalition.org) ran a 30 second ad costing around $1.3 million during the 2004 Academy Awards telecast memorializing boomer icons like baseball star Don Drysdale who died prematurely from heart disease. The coalition purports to be a nonprofit grass roots group of health activists who encourage baby boomers and others to register to determine their risk for America's #1 killer. However, few are aware that it was created and funded by Pfizer to promote Lipitor for healthy people. Television ads for Zocor (simvastatin) admonish viewers to "Ask your doctor about the Heart Protection Study from Oxford University." There are no ads urging anyone to ask about large studies like EXCEL, ALLHAT, ASCOT, MIRACL or PROSPER that not only showed no benefits from statins but also the potential for great harm.

Zocor is now available without a prescription in the UK, where some have proposed adding it to the drinking water supply although there is no evidence that it reduces premature heart attacks in healthy people. A 2003 review of all such primary prevention studies found no difference in mortality rates between patients taking a statin or a placebo. Nevertheless, 2004 revised cholesterol treatment guidelines guaranteed millions of new patients by lowering the LDL target goal to an arbitrary level that few can achieve. This despite overwhelming proof that statins do not work by lowering cholesterol or LDL and that these guidelines will only lead to higher statin doses that can cause more complications. As also noted in previous Newsletters, all statins are carcinogenic in laboratory animals and there are numerous other serious side effects in humans that have been suppressed. Baycol was withdrawn, the FDA has been petitioned to ban Crestor and several Lipitor lawsuits have been filed, including one for wrongful death. At least two class action suits on behalf of the elderly and women allege that Pfizer engaged in a massive campaign to convince doctors and patients that Lipitor would benefit everyone by lowering cholesterol. No studies have shown that statins are beneficial for anyone 65 or older, senior citizens with low serum cholesterol have higher mortality rates compared to controls with normal or elevated levels and Lipitor side effects are increased in the elderly. There is no evidence that Lipitor should be prescribed for women of any age, with the possible exception of patients with heart disease or diabetes. The ASCOT study, the largest clinical trial of statin efficacy in females, found that women at increased risk for heart disease who received Lipitor suffered 10 percent more heart attacks than placebo controls. As John Abramson, author of *Overdosed America* noted, **"Millions of women and seniors are spending huge sums to take Lipitor every day despite a lack of proof that it's doing anything beneficial for them, and may actually be harming the elderly."** Several states are suing drug companies for inflating Medicaid and Medicare prices by hiding true drug prices via secret rebates, discounts, free products and other means. **The U.S. Department of Justice found that a company had set its average wholesale price for one drug at $926.00 when the actual cost was $1.71!** Lipitor is the second most Medicare prescribed drug and Plavix and Fosamax are also high on the list.

I have only skimmed the surface of how drug companies have deceived the public by creating fake diseases and exaggerating the dangers of others. Additional information can be found in books like *Disease-mongers: How Doctors, Drug Companies, And Insurers Are Making You Feel Sick* - Lynn Payer; The *Truth About the Drug Companies: How They Deceive Us and What to Do About It* - Marcia Angell; *Selling Sickness: How the World's Biggest Pharmaceutical Companies Are Turning Us All into Patients* - Ray Moynihan. The website http://collections.plos.org/diseasemongering-2006.php has eleven excellent articles covering all the above and other fake diseases and www.thincs.org and www.spacedoc.net list the dangers of Lipitor and statins. Stay tuned for more about such sources of stress and why, when a medical resident was asked to define a well person, the response was "someone who has not been completely worked up."

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