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STRESS FROM DECEPTIVE & DEADLY DRUG PROMOTIONS

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Pharmaceutical companies understandably will try anything to preserve their profits when the patent for one of their blockbuster drugs is due to expire and/or a generic is approved. As noted in previous Newsletters, Bristol Myers stock fell 22% in 2006 when a generic Apotex version threatened its $5.2 billion/year in Plavix sales. They offered to pay Apotex $400 million to delay marketing it until 6 months before the Plavix patent expired in 2011. However, this ruse failed due to a dozen lawsuits alleging the deal violated antitrust laws and the threat of a Federal criminal investigation.

Also Included In This Issue

Schering-Plough **raised the price of its blockbuster Claritin thirteen times during the five years before its patent expired, which resulted in a 50% increase in cost**. To preserve its $2 billion/year cash cow, the company quickly launched an advertising blitz for Clarinex that falsely claimed it was much more effective. Doctors were also offered inducements to switch their patients from Claritin to prescription Clarinex.

The major reason Claritin had been so successful is that it was the first non-sedating antihistamine, at least in the 10-mg. tablets used in the clinical trials that led to FDA approval. However, it was only 10 percent better than a placebo, and many European patients complained that they often had to take 3 or 4 tablets to obtain relief, which usually also made them drowsy. Once Claritin became generic and did not require a prescription, its price

dropped 75 percent and there was a radical change in advertising. The company now admitted that it was actually not very effective for treating allergies. What patients needed was their new superior medication, Clarinex, even though **in clinical trials Clarinex was only 8 percent better than a placebo, and Claritin is actually converted to Clarinex in the body.** But since the Clarinex patent does not expire until 2020, it will have no generic competition for another decade, and Schering-Plough can continue to charge top dollar. The European Agency for the Evaluation of Medicinal Products has reviewed all of the studies conducted here and abroad on both drugs and concluded that Clarinex is "probably not superior" to Claritin. It is also investigating a possible link with birth defects when given during pregnancy. Nevertheless, these and other equally blatant examples of how drug companies deceive and rip-off the public when profits from a blockbuster are threatened pale in comparison to what transpired when AstraZeneca's main patent on Prilosec was due to expire in October 2001.

Prilosec's Perils Prevented By Planning, Promotional Hype And Perjury

Prilosec was often referred to as the little "purple pill" in advertisements, which turned out to be particularly appropriate, since purple is the color of royalty and Prilosec was the undisputed king of the hill of prescription pharmaceuticals. A drug is considered to be a blockbuster if it reaches over $1 billion in yearly sales and Prilosec achieved this in 1995. It was the first drug to bring in $5 billion in 1998 after the FDA also approved it as a component of the triple therapy used to eradicate H. pylori infections that caused ulcers and increased risk for gastric cancer. Annual sales were over $6 billion in 2000, at which time Prilosec had been the best selling prescription drug here and abroad for five years. There was no hint of this stunning success when it was initially approved in 1989 to treat duodenal ulcer symptoms. It was the first proton pump inhibitor (PPI), a class of drugs that prevented stomach enzymes from making acid and was more powerful than Zantac, Tagamet, Pepcid and other H2 acid reducers that blocked the ability of histamine to stimulate acid producing cells and had been popular for many years. Prilosec's price was $4.00/pill compared to less than a dollar for histamine blockers, but it only had to be taken once a day rather than twice for Tagamet, and more frequently for over the counter antacid products. By 2001, when its patent was due to expire, Prilosec accounted for more than a third of all antacid prescriptions despite its hefty price. This included newer PPIs like Prevacid and Protonix that were also less expensive but relatively unknown. Everyone had now heard about the wonderful little "purple pill" due to aggressive TV promotions and ads in medical journals, leading magazines and subway signs. Some patients even referred to it as "purple Jesus" and AstraZeneca was determined to preserve its golden goose whose purple eggs had brought in $26 billion during the previous five years.

As soon as it realized in 1995 that Prilosec would be a blockbuster, the company assembled a team of patent and corporate lawyers, marketing mavens, chemists and other scientists to spearhead what came to be known as The Shark Fin project. Its purpose was to preserve the billions provided by Prilosec that would likely vanish when significantly less expensive generic versions became available. Over the next ten years, a multi-pronged approach was developed and implemented that had the tactical precision of a superbly well-designed military maneuver. A total of 50 options were initially considered that were later winnowed down to a dozen, including a "Prilosec 2.0" pill that worked faster, longer or was possibly more powerful, combining Prilosec with another heartburn medication, changing its delivery system to a liquid gel or some extended-release form that could lead to a new patent, searching for some successor that was superior, or even a drug that was not necessarily much better but would enjoy several more years of patent exclusivity. At the same time, the legal team was meticulously studying ways to defend or extend Prilosec patents and to explore any loophole in the law that would allow them to delay generic competition. The name Shark Fin was chosen to illustrate the sales chart shape if they did nothing: an inverted V with a sharp up, but sharper down.

All of these carefully coordinated efforts to prepare for and hopefully prevent the impending disaster were incredibly successful because of a combination of luck, and what one commentator called "brilliant biochemical chutzpah." What he was referring to was the development and marketing of Nexium, "the new purple pill." Like many other drugs, Prilosec is composed of two "isomers" or mirror images that are a left-hand and a right-hand version of the molecule. Isomers can differ from each other or the parent drug with respect to an increase or decrease in side effects, efficacy, absorption or metabolism. Although such changes are usually not dramatic, the Patent Office has ruled that a compound consisting of one of its isomers is different and a new "invention", as they did with Clarinex, which is simply an isomer of Claritin rather than a new or innovative drug. The Shark Fin team did something similar with Prilosec (omeprazole), and the isomer they used was esomeprazole (within omeprazole). They then had to prove that this isomer was superior to Prilosec in clinical trials and decided to demonstrate this for erosive esophagitis, a disorder in which stomach acid reflux injures the lining of the lower esophagus. It was a huge gamble, since if the isomer had more side effects or was less effective, the project was doomed. In addition, any results would be influenced by the dose of esomeprazole, and it was difficult to determine what the optimal dose would be.

AstraZeneca commissioned four studies that compared 40 mg. of the isomer that would later become Nexium, with 20 mg. of Prilosec, half as much. While that might not appear equitable or fair, the company could justify this

because it was seeking approval of a 40-mg. dose of Nexium for erosive esophagitis, and the recommended dose of Prilosec was 20 mg. Two of the studies found that even this double dose did not provide faster or better healing compared to Prilosec, but two did demonstrate some added benefits. In the only one in which 20 mg. of Prilosec went head to head with 20 mg. of Nexium, no difference was seen after four weeks. However, at the end of two months, the Nexium "Son of Prilosec" had a slight edge, with a 90% percent healing rate compared to 87% for its parent. The two positive studies were published but the company refused to release details of the negative ones. And the 3% difference was considered so minuscule; that the FDA official who reviewed the data concluded that AstraZeneca's claim that the Nexium isomer represented a "significant clinical advance" over Prilosec was "not supported by data." Despite this, the FDA approved Nexium in February 2001 for treating erosive esophagitis, gastroesopahgeal reflux and duodenal ulcers, although after the FDA has approved a drug, physicians could prescribe it for any disease or complaint they believe it might benefit.

AstraZeneca now had eight months before its Prilosec patent was due to expire to convince doctors to switch their patients to Nexium. It immediately quadrupled its sales force by hiring 1,300 additional representatives to call on physicians and explain why Nexium was superior to Prilosec because of faster healing, fewer interactions with other drugs and other safety concerns. Sales reps were instructed to remind doctors that the company had been the manufacturer of the leading proton pump inhibitor and had done the most research on them. Prilosec was not to be mentioned, other than to compare it unfavorably with Nexium. Free samples of Prilosec were no longer available and were sometimes surreptitiously removed from office cabinets that were now being restocked with generous amounts of Nexium samples. It has been well established that when physicians have a choice of prescribing similar drugs, they tend to select whichever one they have free samples of, and that patients usually continue on with paid prescriptions.

AstraZeneca also marketed Nexium directly to consumers by flooding magazines, journals, television and radio with advertisements that exaggerated its superiority over similar products and other multiple benefits. In the 12 months after it was approved, the company spent an estimated half billion dollars on this promotional blitz and Nexium was the most heavily advertised pharmaceutical in the U.S. The fact that it had only been approved for erosive esophagitis was drowned out by claims that it was superior to the top selling Prilosec. The Shark Fin Team had anticipated that most of Nexium's growth would come at the expense of Prilosec and this prediction was correct, since 60% of patients made this switch. By April 2002, Nexium's share of new heartburn prescriptions was already up to 19% after little more than a year, while Prilosec had dropped to 25% from 49%.

The Shark Fin team also pondered over the best way to highlight Nexium but still take advantage of the wide recognition of Prilosec's "purple pill nickname. Ads had also reminded everyone "today's purple pill is Nexium. From the makers of Prilosec." As one team member explained, we decided on a purple pill to leverage the brand and racing stripes to distinguish it." Since it was being promoted as Prilosec's superior successor, calling Nexium the "new" or "healing" purple pill also seemed particularly appropriate.

Prilosec (omeprazolle)

Nexium (esomeprazole)


generic omeprazole

Purple is a color between red and blue, and as can be seen to the left, the shade selected for Prilosec was not very vivid. It was more reddish than Nexium in the center, which had tinges of violet and royal blue. The gold racing stripes enhanced its regal appearance and others later capitalized on this. The generic Prilosec on the right mimicked Prilosec's color and added yellow stripes to resemble Nexium, for which no generic was available.

Legal Lapses, Marketing Machinations And The Purple Pill Predicament

In that regard, the team's patent attorneys had been exploring every possible legal method to prevent or delay any approval for a generic version of Prilosec. Pharmaceutical companies routinely obtain patents for everything they can think of that might possibly apply to a new drug since such "patent estates" can be legal minefields for competitors. Lawyers began applying for such incidental patents in the U.S. in 1985, four years before Prilosec was approved, and they have continued to search for ways to file additional protective patents. When it became apparent that ulcers were due to an infection, a patent was obtained on a drug that combined Prilosec with antibiotics. Lawyers then argued that competitors could not offer a generic Prilosec because doctors might prescribe them with antibiotics, which would represent a violation of this patent. They patented a substance formed for a brief period after Prilosec is swallowed and then claimed that any generic version that also did this would be a patent violation. Such patents would likely not be upheld when challenged but they tied up competitors in lengthy and expensive lawsuits and subsequent appeals, during which AstraZeneca could continue to conduct business as usual.

For example, Prilosec's active ingredient is quickly destroyed by stomach acid and an enteric coating is required to prevent this so it can reach the

small intestine where it is absorbed. However, since this enteric coating is also slightly acidic, chemists added a thin middle coat to protect the active ingredient. AstraZeneca then applied for a patent that would give them exclusive rights for putting two coatings on Prilosec's active ingredient to provide maximum protection. The problem was that this had been such a common problem with other drugs that it was described in textbooks, and chemical companies had long sold such middle coatings for other drugs. As one commentator wrote, "It was like patenting the discovery that hamburgers are best served with the tomato slice sandwiched in between the lettuce and the meat so the bread doesn't get soggy. Yet Astra's lawyers persuaded patent clerks in Europe and the U.S. that its scientists had made a novel discovery when they came up with this triple layer for Prilosec. A British judge later invalidated this patent because of "obviousness", but the U.S. patent validity trial dragged on until April 2007, 6 years after the original Prilosec patent was due to expire. (The company had later obtained a six-month extension to October 2001 by invoking a Federal law that provides such a delay if the manufacturer is conducting trials on the use of a drug in children.) Although AstraZeneca lost this patent fight, it collected on average $10 million for every day the litigation continued. It also gained additional precious time to switch Prilosec patients over to Nexium.

Prilosec's patent expired in 2002, and the following year, it became available without a prescription that was distributed by Procter and Gamble. In most instances, when a drug becomes available over the counter, it can no longer be sold by prescription unless there are differences in the dosage. But in 2003, the FDA allowed prescription Prilosec as well as Prilosec OTC to be sold even though both contained the same 20 milligrams of omeprazole. Lawyers had successfully argued that patients were not supposed to take Prilosec OTC for more than two weeks at a time without a doctor's supervision, so that the two had different indications. **This allowed the sale of Prilosec OTC for three years without any competition**. Schering-Plough had a similar problem when Claritin's patent expired but were unable to persuade the F.D.A. to allow it to continue to sell prescription Claritin when OTC versions became available. The immediate generic competition caused Claritin sales to plunge and many insurers also refused to cover prescription Clarinex because there were much less expensive alternatives that were just as effective.

In sharp contrast, Prilosec OTC was a huge success because there was no other nonprescription equivalent, and it only cost 70 cents/pill, compared to $4.00 or more for prescription Prilosec or Nexium. It was the first non-prescription drug to become a National Football League sponsor in a contract that cost $10 million for the first two years. It was aggressively advertised as the most effective treatment for heartburn and GERD, and although other

products that did not require a prescription would have sufficed, the once daily dosage was a strong selling point. Many with mild and intermittent heartburn a few times a week that responded to antacids, found that when they discontinued Prilosec, there was a rebound phenomenon that resulted in more persistent and severe symptoms that now necessitated taking it daily. The subsequent widespread demand resulted in such an unanticipated nationwide shortage, that in March 2005, a full page article in *The New York Times* was entitled "Where Has All The Prilosec Gone?" Patients who depended on it were forced to buy prescription products, which often entailed the additional expense of an office visit. And since the most popular alternative was Nexium, AstraZeneca's profits skyrocketed and irate consumers accused the company of deliberately creating this crisis.

AstraZeneca's advertising campaign to switch patients from Prilosec to Nexium had also been extremely successful and the marketing team took advantage of this by offering hospitals and third parties financial inducements to insure that Nexium was their exclusive proton pump inhibitor. Nexium 40 mg. was deeply discounted so that it was less expensive than Prilosec 20 mg., and since it was also considered to be more effective, two of the most prestigious hospitals, Massachusetts General and Brigham and Women's Hospitals agreed to make Nexium their primary drug to treat ulcers and GERD. Other hospitals quickly made similar arrangements. Agreements were also reached with numerous insurance companies and other fiscal intermediaries to insure that Nexium would be covered and also receive some sort of reimbursement priority. By October 2002, Nexium was on 77% of managed care formularies and in a high reimbursement position in most. Analysts had predicted that combined sales of Prilosec and Nexium would decline by over $1 billion in 2002 and even more the following year, but they increased in 2002 and continued to climb in 2003 due to the lack of generic competition.

The Nexium price reduction was not passed on to patients who continued to complain about what they considered to be price gouging. In 2004 and 2005, class action suits were filed in California State Court by the American Federation of Labor & Congress of Industrial Organizations (AFL-CIO), Congress of California Seniors, California Alliance for Retired Americans; in Massachusetts State Court by Health Care for All and The Commonwealth Care Alliance and in Delaware Federal Court by members of the Prescription Access Litigation Project and the Pennsylvania Employee Benefit Fund. These claimed that AstraZeneca's deceptive marketing practices violated California's Unfair Competition Law and False Advertising Law, the Massachusetts Consumer Protection Act, and the Delaware Consumer Fraud Act. The suits were similar, and alleged that AstraZeneca undertook a "misleading advertising campaign resulting in billions of dollars of

unnecessary drug expenditures by third party payers and hundreds of thousands of patients have taken Nexium and continue to do so when they should not." Plaintiffs also argued that advertisements emphasized that Nexium was more effective than Prilosec, which was blatantly misleading because the studies measured the efficacy of different doses of the two drugs and various state laws prohibited "unfair methods of competition and unfair or deceptive acts or practices."

All of these and other lawsuits were dismissed since the "safe harbor" provision of state consumer protection laws, which reduces or eliminates liability if actions were performed in good faith, prevents companies from being sued if their statements and activities were approved by a federal or state regulatory agency. All of Nexium's labeling claims had been approved by the FDA, which the courts ruled meant that the agency had determined that the information contained therein is not "false or misleading." In addition, the plaintiffs had not specifically claimed or demonstrated that they relied on AstraZeneca's advertisements when they purchased Nexium. In summary, "little or no proof" had been provided that AstraZeneca had committed an actionable tort. Nexium continued to thrive and sales are now $6 billion/year. Some of its patents will expire in 2014 and the remaining will be not be valid after 2019, so that there is a constant search for new ones. Approval was later obtained for treating children and gastric ulcers associated with prolonged use of cortisone-like steroids. A new delayed release suspension formulation was approved in 2006 that facilitated its administration via a nasogastric tube and to pediatric patients. Since Motrin, Naprosyn and other NSAIDS as well as aspirin can cause ulcers and GERD, it is not surprising that Vimovo, a Nexium-naproxen (Naprosyn) pill was approved earlier this year. Axanum, a similar combination with aspirin, was approved in Europe but was rejected by the FDA last month. Continued efforts will undoubtedly be made to reverse this decision and to find other novel ways to increase income from Nexium and prolong its patent life.

Osteoporotic Fractures, C. difficile And Other Infections, Esophageal Cancer

The reason Axanum was not approved was not revealed, but could be due to safety concerns. Nexium's bright future may be dimmed by mounting reports of sinister and sometimes serious side effects that were never anticipated. Proton pump inhibitors have now been found to increase or decrease the action of numerous common medications, including Valium, coumadin, digoxin, ampicillin, and any containing iron. The FDA advised Plavix patients to avoid PPIs last November, after a study showed a 25% increased risk of dying or being hospitalized for a recurrent heart attack or revascularization procedure. A black box warning was mandated in March. When Prilosec was first approved, it was to be taken when needed to prevent heartburn and peptic ulcer symptoms, but only for a period of two

or three weeks. There were a few occasional minor side effects such as nausea, headache, dry mouth or change in bowel habit, but these disappeared when treatment was discontinued, and rarely required medication. It was never intended to be taken daily for more than three weeks and physicians or pharmacists could readily determine if it was being abused by the number and dates of refills.

When Prilosec OTC became available, the instructions were that it "**should be taken once every 24 hours for 14 days. Do not take more than one tablet per day or repeat treatment more often than every 4 months.**" However, patients seldom read these package inserts, which also apply to nonprescription Prevacid and Zegerid, and may take these drugs more frequently or for much longer periods of time. Nexium was later approved for two months of daily use for certain conditions and when it was suggested that GERD could cause premalignant Barrett's esophagus, PPIs were often prescribed for a year or indefinitely. In one study that showed no preventive protection for Barrett's, some patients had been taking them daily for 13 years. Advertisements reassured patients that these drugs reduced irritating stomach secretions, but still left enough to preserve normal digestive functions. However, this did not apply to prolonged daily use since its consequences had not been adequately evaluated, especially with respect to the lack of acid effects on the absorption of foods and drugs.

Stomach acid kills or inactivates bacteria and is the first line of defense against these and other ingested pathogens. Red flags were raised when it was reported that patients on long term PPI therapy for reflux disease were at increased risk for pneumonia. When you sleep flat on your back, small amounts of stomach contents tend to travel up the esophagus and get into the respiratory tract via the trachea. Bacteria that have not been destroyed because of lack of stomach acid can rapidly proliferate once they enter the lungs. Patients with gastroesophageal reflux are much more likely to aspirate stomach contents, even when they are not lying down. PPI patients have 74% more C. difficile gastrointestinal infections that are no longer prevented by stomach acid. These can be lethal because this organism is frequently resistant to antibiotics. An even more common side effect are hip and spine fractures, especially in older individuals. In one study of subjects aged 50 or older, those on PPIs for more than a year had 44% more hip fractures than controls. Studies show that 15% to 20% of patients die within a year after suffering a hip fracture, and that this increases to 36% in the elderly. As a result, the FDA recently ruled that all prescription and non-prescription drugs containing a PPI must change their labeling to warn consumers of increased risk of hip and other fractures.

Several theories have been proposed to explain this observation, including interference with calcium absorption and osteoblastic activities and increased homocysteine. In that regard, I discussed various aspects of PPI problems in 2002 and 2003 Newsletters, and again in 2007, when I called attention to the hip fracture problem and other side effects. I received several responses from readers, including one from Kilmer McCully, who first called attention to the link between elevated homocysteine and coronary atherosclerosis. Kilmer pointed out that the recent increase in hip fractures correlated with high homocysteine levels and that one of the main causes of this was poor vitamin B12 absorption, especially in the elderly. Proton pump inhibitors decrease the release of vitamin B12 from foods because they inhibit the production of gastric juices that perform this function. The Framingham and other studies had shown that high homocysteine was an accurate predictor of future hip fractures and a risk factor for ischemic strokes as well as heart attacks. Hip fractures occur 2 to 4 times more frequently in hemiplegic stroke victims, presumably because they are more likely to experience falls, but could homocysteine be the culprit? And since administering vitamin B12 and folate can lower elevated homocysteine levels, could giving such supplements reduce the incidence of hip fractures?

This was investigated in a 2005 double blind study of over 600 stroke victims aged 65 years or older with hemiplegia for at least one year. Patients received either 5 mg of folate and 1500 mcg of B12, or a double placebo, and were followed for two years. At baseline, both groups had high levels of plasma homocysteine and low levels of serum B12 and folate. After 2 years, plasma homocysteine levels decreased by 38% in the treatment group but were increased by 31% in placebo controls. **Hip fractures were reduced by 80% in those taking vitamin B supplements despite the fact that there was no difference in bone density or the number of falls between the two groups**. It could be argued that homocysteine is simply a marker for low vitamin B levels and that the reduction in fracture rates were due to these supplements. However, a 2008 analysis of the Framingham Study data similarly concluded "Low B-vitamin concentration may be a risk factor for decreased bone health, but does not fully explain the relationship between elevated homocysteine and hip fracture."

Kilmer also indicated that it had been suggested that proton pump inhibitors might actually be contributing to esophageal cancer, as follows:

> Many of our VA patients have GERD and Barrett's esophagus, and increasing numbers are developing adenocarcinoma of the esophagus. Dr. Grant Rodkey of our Surgical Service has speculated that proton pump inhibitors may decrease inactivation of pancreatic enzymes in the stomach because of decreased acid production. Active pancreatic enzymes are very irritating to normal tissues and may lead to metaplasia and dysplasia of the esophageal mucosa.

A gastroenterologist at the same VA hospital wrote that he and others were "amazed with the prevalence of bile and intestinal enzyme refluxate" associated with premalignant Barrett's esophagus, which supported Dr. Rodkey's suggestion. Kilmer had also noted back in 1994 in an article on "Chemical Pathology of Homocysteine", that B12 deficiency increased homocysteine and interfered with the production of a compound that had anticarcinogenic as well as antiatherogenic properties, and expanded on this in a 2009 update. Since PPIs cause B12 deficiency by blocking gastric acid, this was another possible way they could contribute to cancer. I wondered whether others had considered this connection, but the only information I found after searching medical and other databases was a Google link to a 2008 Boston TV interview, in which a prominent Massachusetts General Hospital endoscopist expressed concerns that Prilosec and Protonix could be contributing to the recent rise in esophageal cancer. I obtained a copy of the transcript confirming this, but the physician who interviewed him did not know what this was based on. When I contacted the endoscopist, he said that he had no recollection of making this claim or evidence to support it.

After another search using different keywords, I retrieved several studies from unrelated approaches that proved surprisingly relevant and suggested other mechanisms of action that supported Dr. Rodkey's speculations. They are too detailed to summarize here, but the May 10 issue of *Archives of Internal Medicine* included two editorials and five articles dealing with fractures, infections and other proton pump inhibitor complications. Since no mention was made in any of these of a possible link to gastroesophageal cancer, I synopsized my findings in the following letter to the editor.

Could Proton Pump Inhibitors Boomerang And Cause Cancer?

In addition to increased risk of osteoporotic fractures, Clostridium difficile and other infections[1], proton pump inhibitors may have also contributed to the sharp rise in gastroesophageal malignancies seen over the past two decades. This is especially true for esophageal adenocarcinoma, which was previously uncommon, and mirrors the increased use of these drugs.[2,3] It has been suggested that the resultant decrease in gastric acid no longer inactivates pancreatic enzymes that are very irritating and can cause dysplasia in esophageal tissue in patients with reflux disease. There is also evidence that GERD may not develop due to direct superficial injury, but rather stimulation of esophageal cytokines that attract inflammatory cells to submucosal tissues. In animal studies where GERD is created by connecting the esophagus to the duodenum, researchers expected there would be injury and death of superficial cells that later spread to deeper layers. It was just the opposite. Although no topical erosive damage was seen three days after surgery, inflammatory cells were found in the deeper layers of the esophagus that did not rise to the surface until three weeks later, which is more consistent with an immune-mediated response.[4]

Further support comes from the observation that GERD patients usually show no evidence of mucosal damage on endoscopy. The earliest changes appear to be dilated intercellular spaces (DIS) in the esophageal epithelium demonstrated with

transmission electron microscopy. In one such animal study to evaluate responses to acute stress, hydrochloric acid, ethanol, aspirin, and prednisolone, no gross or microscopic evidence of inflammation was seen in the esophageal mucosa. However, esophageal epithelial intercellular space diameters in the stress and aspirin groups were three and two-fold greater compared to controls, supporting the sensitivity of DIS measurements. More importantly, pretreatment in both these groups with esomeprazole (Nexium) to reduce gastric acid had no effect on DIS, suggesting that this early abnormality is not due to acid reflux.[5]

Association never proves causation, and more obesity, endoscopic procedures, use of biphosphonates and other factors may be relevant. Nevertheless, although counterintuitive, the possibility that proton pump inhibitors could be contributing to increased rates of gastroesophageal cancer needs to be investigated more thoroughly because of their widespread and often indiscriminate use

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Since such letters are limited to 400 words and five references, I was prohibited from including additional material and citations that could have made my commentary more convincing, like new molecular imaging studies show that basic defect in GERD is a disturbance in esophageal motility rather than acid refux. I was also unable to acknowledge my debt to Kilmer McCully and Grant Rodkey for launching this quest to find meaningful information that might help to answer questions such as: Does protracted use of proton pump inhibitors cause cancer? Which pharmaceutical advertisements are deliberately deceitful? Why are adverse side effects of drugs seldom reported? Why are our current post-marketing surveillance regulations so inadequate? Can anything be done to correct these deficiencies?

Envoi: Putting The Purpose of Pharmaceutical Promotion In Proper Perspective

During the course of these investigations, I was reminded of Thoreau's "men have become the tools of their tools." which Marshall McLuhan paraphrased as "We shape our tools and thereafter our tools shape us." They were not aware of how our growing dependence on Blackberries, iPhones or the Internet would later confirm this, but many pharmaceutical promotions are also good illustrations. Drug advertisements have increasingly been devoted to converting us into a nation of the "worried well" by creating new diseases,

exaggerating the significance of relatively minor symptoms, convincing people that prescription pharmaceuticals are required to prevent or treat the normal consequences of aging, and other scare tactics. Examples include drugs for osteopenia, trivial complaints related to toenail fungus, irritable bowel and restless leg syndrome, or erectile dysfunction. Although some of these may be indicated for certain patients, this represents a small minority of users and several drugs were later recalled or received Black Box warnings because of serious safety concerns. In addition 75% of new drugs advertised as superior to existing products, are "me too" copies that provide no advantages and were approved only because they were better than a placebo. Proton pump inhibitors fall into many of the above categories and may also suffer a similar fate because of unanticipated harmful side effects. There is no evidence that PPIs prevent or improve precancerous esophageal lesions, and they could be contributing to the rise in cancer of the esophagus and other diseases that result from a severe lack of gastric acid.

In my opinion, their unwarranted prolonged use is entirely due to deceptive advertising that has been facilitated by regulatory authorities, legislators, prominent physicians and organizations that receive substantial funding for their support. Contrary views are unlikely to be published because medical journals are reluctant to lose their lucrative advertising income due to swift retaliation. This may explain the surprising lapse of memory experienced by the Mass General endoscopist despite the transcript of his comments. In addition, the physician interviewer and producer of this TV program recalled receiving numerous inquiries from concerned patients and there were several Internet postings. It is difficult to overestimate the clout drug companies have over academia, the media and FDA or the disastrous results of this power. Ivan Illich warned in *Medical Nemesis* that it was the nature of most institutions and organizations to eventually end up by performing in a manner opposite to their original purpose because of corruption and greed, and that medicine was a perfect example. **But this was written almost four decades ago!** The situation has significantly worsened since then and will continue to deteriorate unless corrective measures are implemented to prevent these abuses — so stay tuned for some suggested solutions!

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