

Cascara, energy, cancer and the FDA's laxative abuse

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The medical culture and the general culture share some attitudes about the nature of the most common ailments--colds, cancer, arthritis, constipation, heart problems, etc., and they often agree about which things can be treated at home, and which require special medical care.

These background ideas are important because they influence the actions of insurance companies, legislators, and regulatory agencies. They also influence the judgments people make about their own health, and, too often, the way physicians treat their patients.

The prevalence of chronic constipation in North America has been estimated to be 27%, and in a ten year study, the occurrence of new cases was about 16%--the prevalence increases with aging. In some studies, women are 3 times as likely as men to suffer from constipation. A recent Canadian article commented that "While chronic constipation (CC) has a high prevalence in primary care, there are no existing treatment recommendations to guide health care professionals."

Almost everyone in the US is familiar with the idea of "laxative abuse," of using laxatives when they aren't absolutely necessary, and with the idea that chronic laxative use will create a dependency, the way an addictive drug does. Contemporary doctors are likely to prescribe stool softeners for constipated old people, rather than "stimulant laxatives," probably because "softener" doesn't have the pejorative connotation that "stimulant drug" has--not because there is a scientific basis for the choice.

Many doctors advise constipated patients to drink more water and exercise. While there is some physiological basis for recommending exercise, the advice to drink more water is simply unphysiological. A study in Latin America found no evidence of benefit from either of those recommendations, and recommended the use of fiber in the diet. The right kind of fiber can benefit a variety of bowel problems. However, some types of fiber can exacerbate the problem, and some types (such as oat bran) have been found to increase bowel cancer in animal studies.

Despite the greater prevalence of constipation in women and older people, even specialists in gastroenterology are very unlikely to consider the role of hypothyroidism or other endocrine problems in chronic constipation.

Because of the cultural clichés about constipation--that it's caused by not eating enough fiber or drinking enough water, for example--and the belief that it's not very important, there is seldom an effort made to understand the actual condition of the intestine, and the causes of the problem.

Aging and stress increase some of the inflammatory mediators, tending to reduce the barrier function of the bowel, letting larger amounts of bacterial toxins enter the bloodstream, interfering with energy metabolism, creating inflammatory vicious circles of increasing leakiness and inflammation.

Often people visualize something like a sausage casing when they think of the intestine, but when the intestine is becoming inflamed its wall may swell to become an inch thick. As it thickens, the channel narrows to a few millimeters in diameter, and may even close in some regions. In the swollen, edematous, inflamed condition the contractile mechanism of the smooth muscle is impaired. The failure of contraction is caused by the same structural changes that increase permeability. (Garcia, et al., 1996; Skarsgard, et al., 2000; Plaku and von der Weid, 2006; Uray, et al., 2006; Miller and Sims, 1986; Schouten, et al., 2008; Gosling, et al., 2000.)

Obviously, in the very swollen, structurally deformed intestine, with almost no lumen, neither a stimulant nor a simple fibrous bulk could restore functioning, because even with stimulation the smooth muscle is unable to contract, and the closed channel won't admit bulk. Even gas is sometimes unable to pass through the inflamed intestine. Mechanical thinking about the intestine fails when inflammation is involved; now that inflammation is known to play an important role in Alzheimer's disease and heart disease, it will be more acceptable to consider its role in constipation.

The contractile ability of smooth muscle, that's impaired by swelling and inflammation, can be restored by antiinflammatory agents, for example aspirin (or other inhibitor of prostaglandin synthesis) or antihistamines. This applies to the muscles of lymphatic vessels (Wu, et al., 2005, 2006; Gosling, 2000), that must function to reduce edema, as well as to the bowel muscles that cause peristalsis.

If someone thinks of constipation as the result of a lack of neuromuscular stimulation, then it might seem reasonable to design a drug that intensifies the contractions produced by one of the natural transmitter substances, such as serotonin, histamine, or acetylcholine. That's apparently what Novartis did, with tegaserod, a drug that increases the bowel's sensitivity to serotonin. That drug, called Zelnorm, was approved by the FDA in 2002, after a couple of years of publications praising it. At the time of its approval, there was already evidence that people using it were more likely to have abdominal surgery, especially for gallbladder disease, and there was doubt about its effectiveness.

Strangely, the drug was approved to be used for only 4 to 6 weeks, taking two tablets daily without interruption. When patients benefitted from the first treatment, they might be eligible for an additional 4 to 6 weeks, but then it would be necessary for them to find another way to deal with their constipation.

Zelnorm side effects: abdominal pain, chest pain, flushing, facial edema, hypertension, hypotension, angina pectoris, syncope, arrhythmia, anxiety, vertigo, ovarian cyst, miscarriage, menorrhagia, cholecystitis, appendicitis, bilirubinemia, gastroenteritis, increased creatine phosphokinase. back pain, cramps, **breast cancer, attempted suicide**, impaired concentration,

increased appetite, sleep disorder, depression, anxiety, asthma, increased sweating, renal pain, polyuria. (Later, it was found to cause heart attacks and intestinal ischemia/necrosis.) Why would the FDA approve a drug, without evidence that it was more effective than harmless things that were already widely available?

Zelnorm Prices ~ In the US, Novartis estimates that Zelnorm tablets will sell for somewhere in the range of \$3 to \$4 each. The drug is expected to generate \$1 billion in annual sales for Novartis.

During the years just before the new drug was approved, there were several publications reporting that emodin, the main active factor in cascara, a traditional laxative, had some remarkable antiviral and anticancer activities. Other studies were reporting that it protected against some known mutagens and carcinogens. Less than 3 months before approving Zelnorm, the FDA announced its Final rule [Federal Register: May 9, 2002 (Volume 67, Number 90)] "Certain Additional Over-the-Counter Drug Category II and III Active Ingredients." "the stimulant laxative ingredients aloe (including aloe extract and aloe flower extract) and cascara sagrada (including casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, and cascara sagrada fluidextract)," determining that they "are not generally recognized as safe and effective or are misbranded. This final rule is part of FDA's ongoing OTC drug product review. This rule is effective November 5, 2002."

Historically, the FDA has ruled against traditional generic drug products when the drug industry is ready to market a synthetic substitute product.

In 2007, the FDA withdrew its approval for Zelnorm, but allowed it to be licensed as an "Investigational New Drug." *"On April 2, 2008, after more than eight months of availability, the company has re-assessed the program and has made a decision to close it. Novartis is in the process of communicating this decision to physicians participating in the program. Patients who had access to Zelnorm via this program are instructed to discuss alternative treatment options with their physicians."*

Cascara and aloe are not among the treatment options approved by the FDA, so cascara isn't widely available (though anyone can grow aloe plants easily). However, there is considerable interest in the drug industry in the possibility of developing products based on emodin, or aloe-emodin, as anticancer or antiviral drugs. Even if it were proved to be safe and effective for use as a laxative, its potential use as an alternative to extremely profitable cancer and virus treatments would make it a serious threat to the drug industry.

Although the standard medical journals have only recently begun writing about it as a cancer treatment, emodin and related chemicals have been of interest as a non-toxic way to treat cancer, allergies, and viral and bacterial diseases for a long time.

In 1900, Moses Gomberg demonstrated the synthesis of a stable free radical (triphenylmethyl), but for years many chemists believed free radicals couldn't exist. A student of Gomberg's, William F. Koch, came to believe that cellular respiration involved free radicals, and experimented with the metabolic effects of many organic molecules, quinones of several kinds, that can form free radicals, looking for the most useful ones.

For more than 50 years the U.S. Government and the main medical institutions actively fought the idea that a free radical or quinone could serve as a biological catalyst to correct a wide variety of health problems.

A free radical has an unpaired electron. In 1944 Yevgeniy Zavoisky devised a way to measure the behavior of unpaired electrons in crystals, but it was many years before it was recognized that they are essential to cellular respiration. Alex Comfort demonstrated them in living tissue in 1959.

By the time coenzyme Q₁₀, ubiquinone, was officially discovered, Koch had moved to Brazil to continue his work with the biological effects of the quinones, including the anthraquinone compound of brazilwood, which is used as a dye. He also used a naphthoquinone, lapachon. Although vitamin K was identified as a quinone (naphthoquinone) not long after coQ₁₀ was found to be a ubiquitous component of the mitochondrial respiratory system, it wasn't immediately recognized as another participant in that system, interacting with coQ₁₀.

Although Koch was unable to publish in any English language medical journal after 1914, his work was widely known. In the 1930s, Albert Szent-Gyorgyi, following Koch's ideas about electrons in cells, interacting with free radicals, began working on the links between electronic energy and cellular movement. Since free (or relatively free) electrons absorb light, Szent-Gyorgyi worked with many colorful substances. When he came to the US in 1947, and wanted to expand his research, a team of professors from Harvard investigated, and told the government funding agency that his work didn't deserve support. For the rest of his life, he worked on related ideas, expanding ideas that Koch had first developed.

Emodin and the anthraquinones (and naphthoquinones, such as lapachone) weren't the reagents that Koch considered the most powerful, but emodin can produce to some degree all of the effects that he believed could be achieved by correcting the cellular respiratory apparatus: Antiinflammatory, antifibrotic (Wang, et al., 2007) antiviral, antidepressant, heart protective, antioxidant, memory enhancing, anticancer, anxiolytic and possibly antipsychotic.

Working backward from these effects, we get a better perspective on the "laxative" function of emodin and cascara. Koch and Szent-Gyorgyi believed that cellular movement and secretion were electronically regulated. In one of his demonstrations, Szent-Gyorgyi showed that muscles could be caused to contract when they were exposed to two substances which, when combined, partially exchange an electron, causing an intense color reaction, but without causing an ordinary chemical (oxidation-reduction) reaction. This kind of reaction is called a Donor-Acceptor reaction, and it is closely related to the phenomenon of semiconduction. The reacting molecules have to be exactly "tuned" to each other, allowing an electron to resonate between the molecules.

In a muscle, any D-A matched pair of molecules would cause a contraction, but the same molecules, combined in pairs that weren't exactly tuned to each other, failed to cause contraction. Szent-Gyorgyi believed that biological signal substances operated in a similar way, by adjusting the electronic balance of cellular proteins.

An effective laxative (besides preventing inflammation) causes not only coordinated contraction of the smooth muscles of the intestine, but also adjusts secretions and absorption, so that an appropriate amount of fluid stays in the intestine, and the cells of the intestine don't become water-logged.

In the presence of bacterial endotoxin, respiratory energy production fails in the cells lining the intestine. Nitric oxide is probably the main mediator of this effect.

The shift from respiration to glycolysis, from producing carbon dioxide to producing lactic acid, involves a global change in cell functions, away from specialized differentiated functioning, toward defensive and inflammatory processes.

This global change involves a change in the physical properties of the cytoplasm, causing a tendency to swell, and to admit dissolved substances that normally wouldn't enter the cells.

The interface between the cells lining the intestine and the bacteria-rich environment involves processes similar to those in cells at other interfacial situations throughout the body--kidney, bladder, secretory membranes of glands, capillary cells, etc. The failure of the intestinal barrier is especially dangerous, because of the generalized toxic consequences, but the principles of maintaining and restoring it are general, and they have to do with the nature of life.

Some leakage from the lumen of the intestine or the lumen of a blood vessel can occur between cells, but it is often claimed that the "paracellular" route accounts for all leakage. (Anthraquinones may inhibit paracellular leakage [Karch & Wanitschke, 1984].) When a cell is inflamed or overstimulated or fatigued, its cytoplasmic contents leak out. In that state, its barrier function is weakened, and external material can leak in. This was demonstrated long ago by Nasonov, but the "membrane" doctrine is incompatible with the facts, so the paracellular route is claimed to explain leakage. Since the cells that form the barrier begin to form regulatory substances such as nitric oxide when they are exposed to endotoxin, it is clear that major metabolic and energetic changes coincide in the cell with the observed leakiness. Permeability varies with the nature of the substance, its oil and water solubility, and the direction of its movement, arguing clearly that it isn't a matter of mere holes between cells.

Besides endotoxin, estrogen, vibrational injury, radiation, aging, cold, and hyposmolarity, increase NO synthesis and release, and increase cellular permeabilities throughout the body.

Estrogen excess (relative to progesterone and androgens), as in pregnancy, stress, and aging, reduces intestinal motility, probably by increasing nitric oxide production. The anthraquinones inhibit the formation of nitric oxide, which is constantly being promoted by endotoxin.

Cells regulate their water content holistically, and, to a great extent, autonomously, by adjusting their structural proteins and their metabolism, but in the process they communicate with surrounding cells and with the organism as a whole, and consequently they will receive various materials needed to improve their stability, by adjusting their energy production, sensitivity, and structural composition.

When these intrinsic corrective processes are inadequate, as in hypothyroidism, with increased estrogen and serotonin, extrinsic factors, including special foods and drugs, can reinforce the adaptive mechanisms. These "adaptogens" can sometimes restore the system to perfect functioning, other times they can merely prevent further injury. Sometimes the adaptogens are exactly like those the body normally has, but that are needed in larger amounts during stress. Coenzyme Q₁₀, vitamin K, short-chain fatty acids, ketoacids, niacinamide, and glycine are examples of this sort--they are always present, but increased amounts can improve resistance to stress.

Another kind of adaptogen resembles the body's intrinsic defensive substances, but isn't produced in significant quantities in our bodies. This type includes caffeine and the anthraquinones (such as emodin) and aspirin and other protective substances from plants. These overlap in functions with some of our intrinsic regulatory substances, and can also complement each other's effects.

Emodin inhibits the formation of nitric oxide, increases mitochondrial respiration, inhibits angiogenesis and invasiveness, inhibits fatty acid synthase (Zhang, et al., 2002), inhibits HER-2 neu and tyrosine phosphorylases (Zhang, et al., 1995, 1999), and promotes cellular differentiation in cancer cells (Zhang, et al., 1995). The anthraquinones, like other antiinflammatory substances, reduce leakage from blood vessels, but they also reduce the absorption of water from the intestine. Reduced water absorption can be seen in a slight shrinkage of cells in certain circumstances, and is probably related to their promotion of cellular differentiation.

All of these are basic antistress mechanisms, suggesting that emodin and the antiinflammatory anthraquinones are providing something central to the life process itself.

Zelnorm was said to "act like serotonin." Serotonin slows metabolism, reduces oxygen consumption, and increases free radicals such as superoxide and nitric oxide; the production of reactive oxygen species is probably an essential part of its normal function. Emodin has an opposing effect, increasing the metabolic rate. It increases mitochondrial oxygen consumption and ATP synthesis, while decreasing oxidative damage (Du and Ko, 2005, 2006; Huang, et al., 1995).

The Zelnorm episode was just an isolated case of a drug company's exploiting cultural beliefs, with the FDA providing a defensive framework, but the contrast between tegaserod and emodin hints at a deeper and more deadly problem.

W.F. Koch's approach to immunity emphasized the role of energy in maintaining the coherence of the organism, in which toxins were oxidized and made nontoxic. There was no emphasis on destruction either of bacteria or of cancer cells, but only of the toxic factors that interfered with respiration. He demonstrated that the udders of healthy cows could contain more bacteria than those with mastitis, but the bacterial toxins were absent after the cows were treated with his catalyst. He identified the "activated carbonyl group" as the essential feature of antibiotics, the same group that makes coenzyme Q₁₀ function in the respiratory system.

Koch's understanding of the oxidative apparatus of life, as a matter of electron balances, involved the idea that molecules with a low ionization potential, making them good electron donors, amines specifically, interfered with respiration, while quinones, with a high affinity for electrons, making them electron acceptors, activated respiration. The toxic effects of tryptophan derivatives, indoles, and other amines related to the behavior of their electrons. (Serotonin wasn't known at the time Koch was doing his basic research.) Koch believed that similar electronic functions were responsible for the effects of viruses.

Both chemical and physical interactions of substances cause electrons to shift in each substance, according to its composition. The shift of electrons accounts for the ability of adsorbed molecules or ions to form multiple layers on a surface, and changes in the electrons of a complex biological molecule affect the shape and function not only of that molecule, but of the molecules associated with it. Interactions of the large molecules of cells, and their adsorbed substances, tend toward stable arrangements, or phases. The type of energy production, and the nature of the regulatory molecules that are present, influence the stability of the various states of an organism's cells. (For more information on cooperative adsorption, see www.gilbertling.org.)

Koch and Szent-Gyorgyi were applying to biology and medicine concepts that were simultaneously being developed in metallurgy, electrochemistry, colloid and surface science, and electronics. They were in the scientific mainstream, and it was the medical-pharmaceutical industry that moved away from this kind of exploration of the interactions of substances, electrons, and organisms.

For Koch, antibiotics and anticancer agents weren't necessarily distinct from each other, and would be expected to have other beneficial effects as well.

But an entirely different view of the immune system was taking over the medical culture just as Koch began his research. Mechnikov's morphogenic view, in which the essential function of "the immune system" was to maintain the integrity of the organism, was submerged by Ehrlich's approach, which emphasized killing pathogens, and at the same time, the genetic theory of cancer was replacing the developmental-environmental theory.

Following the early work on the carcinogenicity of estrogens, and the estrogenicity of carcinogens such as polycyclic aromatic hydrocarbons from soot, a few German and French chemists (e.g., Schmidt and the Pullmans) began calculating the high electron densities of highly reactive regions of the anthracene molecule, showing formally why certain molecules are carcinogenic.

At that time, their work was compatible with a developmental view of cancer. But the fact that the polycyclic molecules could interact with the new model of the DNA gene caused the Pullmans' work to be reduced to nothing but a minor theory of mutagenesis.

Anthraquinones, because of the presence of several oxygen molecules, had low electron densities and were stable. The tetracyclines, with related structure, have some similar properties, and are antiinflammatory, as well as antibiotic.

When a polycyclic bacterial antibiotic, adriamycin (later called doxorubicin), was found to be too toxic to use as an antibiotic, the fact that it was toxic to cancer cells caused it to be developed as a cancer drug. It continued to be widely used even after it was found to cause heart failure in many of the "cured" patients, because of its "success" in killing cancer cells.

The fact that many kinds of cancer cells can be killed by emodin makes it slightly interesting as a cancer drug, but its simple generic nature has caused the drug industry to look for a more Ehrlichian magic bullet; for example, they are still looking for ways to keep doxorubicin from destroying the heart.

Emodin isn't a magic bullet (in fact it isn't a bullet/toxin of any sort), but when combined with all the other adaptogens, it does have a place in cancer therapy, as well as in treating many other ailments.

None of the basic metaphors of mainstream medicine--receptors, lock-and-key, membrane pores and pumps--can account for the laxative, anticancer, cell-protective effects of emodin. The new interest in it provides an opportunity to continue to investigate the effects of adjusting the electrical state of the cell substance, building on the foundations created by William F. Koch, Albert Szent-Gyorgyi, and Gilbert Ling.

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