Aspirin, brain, and cancer

From the original article in 2006. Author: Ray Peat.

Since the 1970s, aspirin has been thought of as an inhibitor of prostaglandin synthesis, but that is only part of its effect. Sometimes its effect is the opposite of the effects of other prostaglandin inhibitors.

It protects against the harmful effects of estrogen, prolactin, serotonin, cortisol, histamine, and radiation (u.v., x-rays, gamma rays).

It prevents cancer, and can cause its regression. It inhibits vascular proliferation. It inhibits interleukin 6 (and other inflammatory cytokines), which is a factor in heart disease and breast and liver cancer.

It protects the brain, and can improve learning. It's an antioxidant, prevents cataracts, and protects against glycation in diabetes.

It prevents premature birth and prevents birth defects caused by diabetes, preeclampsia, and exposure to alcohol. It prevents recurrence of neural tube defects and protects against many of the gestational problems associated with lupus.

Although aspirin protects against uncontrolled cell proliferation, as in cancer and psoriasis, salicylic acid increases normal cell division in the skin.

Aspirin protects against many forms of shock and stess, and corrects imbalances in the nervous system.

It protects against several kinds of toxins involved in brain degeneration.

"Aspirin elevated ATP levels not only in intact cortical neurons but also in isolated brain mitochondria, an effect concomitant with an increase in NADH-dependent respiration by brain submitochondrial particles."

De Cristobal, et al., 2002

"The pharmacological action of salicylate cannot be explained by its inhibition of cyclooxygenase (COX) activity." ". . . salicylate exerts its antiinflammatory action in part by suppressing COX-2 induction. . . ." XM Xu, et al., 1999

When a drug such as caffeine or aspirin turns out to have a great variety of protective effects, it's important to understand what it's doing.

Because aspirin has been abused by pharmaceutical companies that have competing products to sell, as well as by the original efforts to promote aspirin itself, people can easily find reasons why they shouldn't take it.

Early in the 20th century, people were told that fevers were very bad, and that aspirin should be used whenever there is a fever.

In the 1980s, there was a big publicity campaign warning parents that giving aspirin to a child with the flu could cause the potentially deadly Reye syndrome. Aspirin sales declined sharply, as sales of acetaminophen (Tylenol, etc.) increased tremendously. But in Australia, a study of Reye syndrome cases found that six times as many of them had been using acetaminophen as had used aspirin. (Orlowski, et al., 1987)

Until the 1950s and 1960s, when new products were being promoted, little was said about the possibility of stomach ulceration from aspirin. Lately, there has been more publicity about the damage it can do to the stomach and intestine, much of it in connection with the sale of the new "COX-2 inhibitors." (These new drugs, rather than protecting the circulatory system as aspirin does, damage it.) Aspirin rapidly breaks down into acetic acid and salicylic acid (which is found in many fruits), and salicylic acid is protective to the stomach and intestine, and other organs. When aspirin was compared with the other common antiinflammatory drugs, it was found that the salicylic acid it releases protects against the damage done by another drug. (Takeuchi, et al, 2001; Ligumsky, et al., 1985.) Repeated use of aspirin protects the stomach against very strong irritants. The experiments in which aspirin produces stomach ulcers are designed to produce ulcers, not to realistically model the way aspirin is used.

Recently, the public has been led to believe that drugs are being designed to fit certain cellular "receptors." The history of the "COX-2 inhibitors" is instructive, in a perverse way. The structures of DES and other synthetic estrogens were said to relate to "the estrogen receptor." Making these estrogenic molecules more soluble in water made them somewhat anti-estrogenic, leading to products such as Tamoxifen. But some of the molecules in this group were found to be antiinflammatory. The structure of Celecoxib and other "COX-2 inhibitors" is remarkably similar to the "designer estrogens." Considering this, it's a little odd that so few in the U.S. are openly discussing the possibility that estrogen's function is directly related to inflammation, and involves the production of many inflammatory mediators, including COX-2. (See Lerner, et al., 1975; Luo, et al., 2001; Cushman, et al, 2001; Wu, et al., 2000; Herrington, et al., 2001.)

Soot and smoke contain many chemicals that produce inflammation (Brune, et al., 1978). In the 1930s, soot was known to be both carcinogenic and estrogenic, and analysis of its components led to the production of the early commercial estrogens. Any intelligent person reading the chemical and biological publications of that time will see how closely associated cancer, inflammation, and estrogen are.

Soon after vitamin E was discovered, tocopherol was defined as a brain-protective, pregnancy protective, male fertility

protective, antithrombotic, antiestrogenic agent. But very soon, the estrogen industry made it impossible to present ideas that explained vitamin E, progesterone, vitamin A, or thyroid hormone in terms of the protection they provide against estrogenic substances. Since the polyunsaturated fats caused the same conditions that were caused by unopposed estrogen, vitamin E came to be known as an "antioxidant," because it reduced their toxicity. (Vitamin E is now known to suppress COX-2, synergizing with aspirin and opposing estrogen.)

In 1970, when I was beginning to see the ways in which unopposed estrogen and accumulated polyunsaturated fats interacted with a vitamin E deficiency during aging and in infertility, I got some prostaglandins to experiment with, since they are products of the oxidation of linoleic acid. The prostaglandins are an interesting link between estrogens and inflammation, in normal physiology as well as in disease.

I wanted to test their effects on the uterus, especially the sites where the embryos implant. There was a theory that the electrical charge of the surface of the uterus was decreased at the implantation sites, to reduce the repulsion between two negatively charged things. Although there were regions of lower surface charge along the lining of the uterus, the charge changed as waves of muscle contraction moved along the uterus, and the prostaglandins affected the contractions.

To understand the differences between the different types of prostaglandin, I tested them on my arm, and those with the most hydroxyl groups produced regions with an increased negative charge. For comparison, I exposed another spot to sunlight for an hour, and found that there was a similar increase in the negative charge in that spot. Apparently the prostaglandins were causing an injury or excitation, a mild inflammation, in the skin cells.

A few years later, aspirin was found to inactivate the enzyme that forms prostaglandins, by the transfer of the acetyl radical to the enzyme. This became the orthodox "explanation" for what aspirin does, though it neglected to explain that salicylic acid (lacking the acetyl radical) had been widely known in the previous century for its very useful antiinflammatory actions. The new theory did explain (at least to the satisfaction of editors of medical magazines) one of aspirin's effects, but it distracted attention from all the other effects of aspirin and salicylic acid.

Aspirin is an antioxidant that protects against lipid peroxidation, but it also stimulates mitochondrial respiration. It can inhibit abnormal cell division, but promote normal cell division. It can facilitate learning, while preventing excitotoxic nerve injury. It reduces clotting, but it can decrease excessive menstrual bleeding. These, and many other strangely beneficial effects of aspirin, strongly suggest that it is acting on very basic biological processes, in a coherent way.

In explaining aspirin's effects, as in explaining those of estrogen and progesterone, or polyunsaturated fats and vitamin E, I think we need concepts of a very broad sort, such as "stability and instability."

The COX (cyclooxygenase) enzymes, that make prostaglandins, are just one system among many that are activated by stress. Aromatase, that makes estrogen, enzymes that make histamine, serotonin and nitric oxide, the cytokines, and the stress-induced hormones of the pituitary and adrenal glands, are turned on in difficult situations, and have to be turned off when the threat has been overcome. The production of energy is the basis for overcoming all threats, and it has to be conserved in readiness for future needs.

The fetus produces saturated fats such as palmitic acid, and the monounsaturated fat, oleic acid, which can be turned into the Mead acid, ETrA (5,8,11-eicosatrienoic acid), and its derivatives, which are antiinflammatory, and some of which act on the "bliss receptor," or the cannibinoid receptor. In the adult, tissues such as cartilage, which are protected by their structure or composition from the entry of exogenous fats, contain the Mead acid despite the presence of linoleic acid in the blood.

At birth, the baby's mitochondria contain a phospholipid, cardiolipin, containing palmitic acid, but as the baby eats foods containing polyunsaturated fatty acids, the palmitic acid in cardiolipin is replaced by the unsaturated fats. As the cardiolipin becomes more unsaturated, it becomes less stable, and less able to support the activity of the crucial respiratory enzyme, cytochrome oxidase.

The respiratory activity of the mitochondria declines as the polyunsaturated oils replace palmitic acid, and this change corresponds to the life-long decline of the person's metabolic rate.

In old age, a person's life expectancy strongly depends on the amount of oxygen that can be used. When the mitochondria can't use oxygen vigorously, cells must depend on inefficient glycolysis for their energy.

Estrogen activates the glycolytic pathway, while interfering with mitochondrial respiration. This resembles the aged or stressed metabolism, in which lactic acid is produced instead of carbon dioxide.

Aspirin activates both glycolysis and mitochondrial respiration, and this means that it shifts the mitochondria away from the oxidation of fats, toward the oxidation of glucose, resulting in the increased production of carbon dioxide. Its action on the glycolytic enzyme, GAPDH, is the opposite of estrogen's.

The shift away from fat oxidation under the influence of aspirin doesn't lead to an accumulation of free fatty acids in the circulation, since aspirin inhibits the release of fatty acids from both phospholipids and triglycerides. Estrogen has the opposite effects, increasing fat oxidation while increasing the level of circulating free fatty acids, since it activates lipolysis, as do several other stress-related hormones.

The polyunsaturated fatty acids, such as linolenic, linoleic, arachidonic, EPA, and DHA, have many directly toxic, antirespiratory actions, apart from the production of the prostaglandins or eicosanoids. Just by preventing the release of these fatty acids, aspirin would have broadly antiinflammatory effects.

Since the polyunsaturated fats and prostaglandins stimulate the expression of aromatase, the enzyme that synthesizes

estrogen, aspirin decreases the production of estrogen. So many of aspirin's effects oppose those of estrogen, it would be tempting to suggest that its "basic action" is the suppression of estrogen. But I think it's more likely that both estrogen and aspirin are acting on some basic processes, in approximately opposite ways.

Bioelectrical functions, and the opposition between carbon dioxide and lactic acid, and the way water is handled in cells, are basic conditions that have a general or global effect on all of the other more specific biochemical and physiological processes. Originally, estrogen and progesterone were each thought to affect only one or a few biochemical events, but it has turned out that each has a multitude of different biochemical actions, which are integrated in globally meaningful ways. The salicylic acid molecule is much smaller and simpler than progesterone, but the range of its beneficial effects is similar. Because of aspirin's medical antiquity, there has been no inclination to explain its actions in terms of an "aspirin receptor," as for valium and the opiates, leaving its biochemistry, except for the inadequate idea of COX-inhibition, simply unexplained.

If we didn't eat linoleic acid and the other so-called "essential fatty acids," we would produce large amounts of the "Mead acid," n-9 eicosatrienoic acid, and its derivatives. This acid in itself is antiinflammatory, and its derivatives have a variety of antistress actions. The universal toxicity of the polyunsaturated fats that suppress the Mead fats as they accumulate, and the remarkable vitality of the animals that live on a diet deficient in the essential fatty acids, indicate that the Mead fats are important factors in the stability of our mammalian tissues. This protective lipid system probably interacts with cellular proteins, modifying the way they bind water and carbon dioxide and ions, affecting their electrons and their chemical reactivity.

If salicylic acid and the structurally similar antiinflammatories, local anesthetics, muscle relaxants, expectorants, and antihistamines, act as surrogates for the absent Mead acid family, and thereby act as defenses against all the toxic effects of the unstable fats, it would explain the breadth and apparent coherence of their usefulness. And at the same time it explains some of the ways that estrogen goes out of control, when it exacerbates the toxicity of the accumulated unstable fats.

The competition between aspirin and salicylic acid, and other antiinflammatories, for the active site on the COX enzyme (Rao, et al., 1982), shows that the structural features of these molecules are in some ways analogous to those of the polyunsaturated fatty acids. Wherever there are phospholipids, free fatty acids, fatty acid esters, ethers, etc. (i.e., in mitochondria, chromosomes, cytoskeleton, collagen networks--essentially everywhere in and around the cell), the regulatory influence of specific fatty acids--or their surrogates--will be felt.

Although it would undoubtedly be best to grow up eating foods with relatively saturated fats, the use of aspirin preventively and therapeutically seems very reasonable under the present circumstances, in which, for example, clean and well ripened fruits are not generally available in abundance. Preventing blindness, degenerative brain diseases, heart and lung diseases, and cancer with aspirin should get as much support as the crazy public health recommendations are now getting from government and foundations and the medical businesses.

When people with cancer ask for my recommendations, they usually think I'm joking when I tell them to use aspirin, and very often they don't take it, on the basis of what seems to be a very strong cultural prejudice. Several years ago, a woman whose doctors said it would be impossible to operate on her extremely painful "inflammatory breast cancer," had overnight complete relief of the pain and swelling from taking a few aspirins. The recognized anti-metastatic effect of aspirin, and its ability to inhibit the development of new blood vessels that would support the tumor's growth, make it an appropriate drug to use for pain control, even if it doesn't shrink the tumor. In studies of many kinds of tumor, though, it does cause regression, or at least slows tumor growth. And it protects against many of the systemic consequences of cancer, including wasting (cachexia), immunosuppression, and strokes.

Opiates are the standard medical prescription for pain control in cancer, but they are usually prescribed in inadequate quantities, "to prevent addiction." Biologically, they are the most inappropriate means of pain control, since they increase the release of histamine, which synergizes with the tumor-derived factors to suppress immunity and stimulate tumor growth.

It has recently become standard practice in most places to advise a person who is having a heart attack to immediately chew and swallow an aspirin tablet.

The same better-late-than-never philosophy can be applied to Alzheimer's disease, Parkinson's disease, and other degenerative nerve diseases. Aspirin protects against several kinds of toxicity, including excitotoxicity (glutamate), dopamine toxicity, and oxidative free radical toxicity. Since its effects on the mitochondria are similar to those of thyroid (T3), using both of them might improve brain energy production more than just thyroid. (By activating T3, aspirin can sometimes increase the temperature and pulse rate.) Magnesium, niacinamide, and other nerve protective substances work together.

In multiple organ failure, which can be caused by profound shock caused by trauma, infection, or other stress, aspirin is often helpful, but carbon dioxide and hypertonic glucose and sodium are more important.

Aspirin, like progesterone or vitamin E, can improve fertility, by suppressing a prostaglandin, and improving uterine circulation.

Although the animal studies that showed stomach damage from aspirin often used single doses equivalent to 10 or 100 aspirin tablets, the slight irritation produced by a normal dose of aspirin can be minimized by dissolving the aspirin in water. The stomach develops a tolerance for aspirin over a period of a few days, allowing the dose to be increased if necessary. And both aspirin and salicylic acid can be absorbed through the skin, so rheumatic problems have been treated by adding the drug to bath water.

The unsaturated (n-6 and n-3) fats that accumulate in our tissues, instead of being part of the system for reestablishing order and stability, tend to amplify the instability that is triggered by excitation, by estrogen, or by external stresses.

I think it's important that we don't allow the drug publicists to obscure the broad importance of substances such as aspirin, vitamin E, progesterone, and thyroid. For 60 years, a myth that was created to sell estrogen has harmed both science and the health of many people.

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