

Ray Peat's Newsletter

"If humanity does not opt for integrity we are through completely." Buckminster Fuller

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Progesterone, brain protection, and the "science culture"

The brain is a factor in any sickness or injury, and if the brain malfunctions, every other system is affected. This sort of complexity isn't handled well by contemporary "evidence based medicine."

200 years ago, medicine and biology relied more on lore than on theory. In the last 100 years, there has been a steady increase in the emphasis on theory, rather than lore.

The situation is analogous to the difference between the automobile mechanics of the 20th century who grew up with the developing technology and were familiar with all of the parts of most types of vehicle, and the contemporary automotive technician who needs a computer to diagnose many problems. In an earlier time, it was easy to distinguish between competence and incompetence. Now, the highly formalized system can sometimes hide incompetence, but it can also create an appearance of stupidity, and pecuniary motives can be misinterpreted as incompetence.

In the US, about 50,000 people die each year from brain injuries, and about 1.7 million people suffer medically significant brain trauma. The permanent brain damage caused by sports has been getting increased attention--for example, an autopsy study of the brains of 94 football players found that 90 of the brains showed anatomical damage. Brain injury is the main cause of death up to the age of 44, and is the most important factor leading to Alzheimer's disease and Parkinson's disease.

"Vibration sickness" has been studied for several decades, showing that prolonged vibration (working with a vibrating tool) causes nervous, hormonal, and structural changes in the affected tissues. A recent study examined the kind of vibration experienced while riding in a car, and found that a few hours per

day of that mild vibration caused measurable changes in the brains of animals, including the death of nerve cells (Yan, et al., 2015). People might be accumulating nerve damage without realizing it.

The US National Institutes of Health, NIH, has spent hundreds of millions of dollars on studies supposedly looking for drugs that will protect the brain, but in more than 60 clinical trials in traumatic brain injury, and more than 150 trials in stroke, nothing has been found effective in a "phase III clinical trial."

In 2009, a part of the NIH, National Institute of Neurological Disorders and Stroke (NINDS), funded a project to study the effect of progesterone on serious brain injury, with \$28,000,000 for six years. (The 2016 NINDS budget is \$1,696,139,000.)

Many years ago, when I asked the FDA about regulations regarding progesterone dissolved in vitamin E, they said that the first step in the process was to have a patent on the product. (Although that isn't formalized in law, it's the way they operate.) Those who invest in "clinical research" want to know that there will be a market for the product being tested, so potential FDA approval is essential, and the patented proprietary status of the material to be tested is an important factor. A century ago, such involvements would have been conflicts of interest that tainted the "patent medicine" (which formerly was a pejorative term).

On January 15, 2014, "The ProTECT trial was stopped after the independent Data and Safety Monitoring Board determined that the data indicated it was very unlikely that progesterone treatment would demonstrate better outcomes compared to a placebo control in this trial." A similar study in Europe, called SyNAPSe®, was

stopped a few months later, with a similar failure to show benefit from the treatment.

Animal studies since the 1950s have clearly showed progesterone's protective, stabilizing, restorative effects on the brain, and the direct effects of progesterone on brain cells have been demonstrated in vitro. All of the organs affected by brain injury--kidneys, lungs, intestine, heart, liver, blood vessels, thymus, bones and bone marrow, endocrine glands--are protected by progesterone.

While the effects of stress on the intestine have been recognized since Hans Selye described the general adaptation syndrome (with intestinal bleeding as an early sign of stress), that hasn't been taken into account in any of the large brain trauma or stroke studies. The phenomenon is a general feature of physiology, even in insects. When fruit flies experience closed-head brain trauma, the effects parallel those that occur in humans--they are temporarily incapacitated, lack coordination in movement, and if they don't die immediately, they experience progressive degenerative brain changes, a leaky intestine, and systemic inflammation and immune changes (Katzenberger, et al., 2015; Kux and Pitsouli, 2014).

The inflammatory, degenerative processes in the brain take a few hours to develop, and during these few hours the stress signals from the brain are causing changes in the intestine that lead to a systemic inflammatory state.

Stress signals from the brain (as in shock, generally) cause the intestine to become inflamed and leaky, and bacterial endotoxin is absorbed into the general circulation, and in the intestine it stimulates the formation of large amounts of serotonin, histamine, and nitric oxide, and systemically it increases the level of free fatty acids. In other types of shock, the condition of the intestine is known to be decisive in recovery, but the medical approach to traumatic brain injury seems to devalue the existing knowledge of how to treat shock.

Progesterone happens to protect against the inflammatory signals produced by the bowel during stress. It inhibits the synthesis of nitric oxide and prostaglandins, reduces the effects of histamine and serotonin, and reduces the formation of free fatty acids. Giving progesterone orally would seem to be appropriate for any serious stress, since the intestine

quickly becomes an amplifier of the inflammatory reactions.

In the middle of the last century, generic progesterone tablets were available, but the pharmaceutical industry developed proprietary synthetic "progestins," which they promoted in medical journals by claiming that natural progesterone was inactive when taken orally, while their product was active when used orally. The success of that false claim led doctors who wanted to administer natural progesterone to give it by injection, either suspended in water or dissolved in a solution of benzyl alcohol and vegetable oil. These preparations were hormonally effective, but they often produced bad reactions at the injection site, so their popularity was limited.

In the 1970s I found that progesterone was very soluble in vitamin E, and that this solution was effective on the skin and membranes as well as when swallowed. After an oral dose, the blood serum level increased quickly and then declined slowly over a period of several hours. When a drug is dissolved in fat it enters the bloodstream by the chylomicron route, which bypasses the liver, preventing the quick inactivation that can occur with water-soluble substances that are taken up by the portal circulation (Yáñez, et al., 2011). A small amount of vitamin E and other fat-soluble material also enters the blood bound to HDL, high density lipoprotein. These fat-soluble substances are distributed to all the other blood components, including red blood cells, from which they gradually move into the various tissues and organs.

In the European study of TBI treatment with progesterone, the drug was provided in the form of "250-ml bottles with identical appearance, containing a lipid emulsion consisting of 6% soybean oil and 1.2% egg lecithin phospholipids, with the addition of 2.0 mg of progesterone per milliliter." In the US study, an amount of progesterone (dissolved in 95% ethyl alcohol, "since progesterone is soluble only in alcohol," according to the authors) was added to a 250-ml bag of 20% Intralipid (soybean oil emulsified with egg lecithin).

The concentration of progesterone was adjusted according to the weight of the patient, so that a person weighing 122 pounds, for example, would receive a solution containing 3 mg of

progesterone per milliliter, and a person weighing 176 pounds would receive a solution with 4 mg of progesterone per milliliter, and everyone would receive the solution at the rate of 14.3 ml during the first hour, and 10 ml per hour for the next 71 hours.

In a liter of water, less than 1 mg. of progesterone can be dissolved, so in the European study, 2 mg of progesterone was present for every 60 mg. of soybean oil; that's about twice the solubility of progesterone in soybean oil, which strongly suggests that some of it would remain in the form of crystals. When a solution of progesterone in alcohol is added to an oil-in-water emulsion, the alcohol mixes with the water, causing most of the progesterone to crystalize; the crystals, insoluble in water, would normally associate with the oil droplets. However, the large amount of lecithin relative to soybean oil would coat the very small particles with a hydrophilic surface, that would tend to reduce interaction between oil and crystals.

When solid particles enter the blood circulation, they are likely to be trapped in the spleen. Ordinary "pharmacokinetic" studies measure the amount of a drug and its metabolites that appear in the urine, but I haven't seen evidence that this was done in these progesterone studies.

A common problem with prolonged intravenous infusion of drugs is inflammation of the veins. and the US study reported that the progesterone-intralipid solution caused phlebitis. The presence of crystals in an infused material can produce phlebitis.

The possibility that some of the progesterone wasn't reaching the patients' brains is a minor flaw of these studies. The real problem is that intralipid greatly increases free fatty acids in the blood, and free fatty acids, especially when they are polyunsaturated, are toxic to the brain, increasing inflammation and blocking energy metabolism.

A possible good outcome of the failure of the studies would be that it could lead to some study and thinking about physiology, but most of the published reactions to the failure indicate that those who are interested aren't even considering the possibility that simple ignorance was involved. They are suggesting that they need more refinement of their research methods, and an unstated assumption is that it will take much much more money.

Fifty years ago, government funding was already shaping university science education, but about 25

years ago the idea of "university corporate partnerships" appeared, and has normalized the idea of commercial science research. At Emory University, a professor's study of the protective effects of progesterone on rats' brains attracted the interest of a French company that specializes in "non-oral" drugs, such as topical testosterone products, in which a gram of testosterone sells for \$240. Professors patented a way to administer progesterone intravenously (the originality of which is hard to perceive), and the principal investigator began receiving royalties from the company.

The "randomized, double-blind, placebo-controlled" design of the experiment makes it ethical for the patent holder to guide the research, but the system gives life to a project that is governed by the expectation that it will make a lot of money, rather than a project to test a treatment simply because it is likely to be therapeutic. NINDS/NIH and the FDA won't support a project just because it is biologically right, the project must be the property of a corporation.

In this case, the huge system--many hospitals, a university, and two branches of the federal government--have been activated by a French corporation which acted on the advice of its ignorant medical experts.

There are people working for NIH who are aware of the effects of free fatty acids on the brain, and who have done valuable research that makes the foolishness of these studies clear, but the system isn't set up to deal with reality. Big medical science is structured the way Mussolini's fascism was structured, with government serving the interests of business. Mussolini's favorite propaganda line was that "he made the trains run on time," but in fact he didn't. Fascism justified itself on the basis of "efficiency," but the only efficiency was the accelerated flow of public money to the ruling clique. The system of big medicine is efficient in that way.

Each person with a traumatic brain injury has unique needs that aren't very compatible with the stereotyped treatments used in "clinical studies," but there are common features of any brain injury, and those overlap with the features of the various kinds of shock, and of degenerative processes of particular organs. The kind of stress involved in these conditions involves impaired energy

production, and increased mediators of inflammation.

The traditional view of the "art of medicine" was a recognition that science was required for validating general principles, and that the application of those principles to an individual case required intelligent judgment. Starting in 1990, with some articles in JAMA, there has been a campaign to promote "evidence based medicine," arguing for a statistical refinement of evidence, based on some theoretical principles of randomization. Individualization of guidelines could be achieved by treating a patient's "risk factors" statistically. This bureaucratic approach devalues the art of clinical judgment and avoids the need to see a patient as a meaningful whole, and it was developed first for the insurance industry and the American Cancer Society. Without this herd approach to medicine the opportunities for corporate control would be limited.

Progesterone (and its metabolites, including allopregnanolone) protect against the harmful changes caused by a brain injury, but there are still important ideological and commercial reasons for not using it. As the major hormone of pregnancy, produced in very large amounts by the placenta, it is able to normalize a wide variety of physiological imbalances and malfunctions. For example, it can protect against an excess or deficiency of aldosterone, the sodium-retaining hormone, and also against an excess of vasopressin, the water retaining, sodium-losing, hormone. These are common changes associated with head injury, and there are well known commercial products for treating them, and a general skepticism that the "pregnancy hormone" could be effective. Wherever there's a product, such skepticism is encouraged.

Medicine's constant public relations promotion of the idea of medical progress obscures the nature of the real changes that are occurring. Market medicine has changed some basic ideas about biology; for example, old understandings of the nervous system, and treatments that worked, based on those ideas--such as anticholinergics for dementia and antiserotonin drugs for depression--were abandoned, for marketing purposes. 50 years ago, urea was widely used to treat brain injuries, but a misunderstanding of its physical properties, and now the availability of the highly profitable "vaptans," have displaced it.

There are many substances besides progesterone and urea that are helpful for treating brain injuries and the overlapping stress and degenerative problems. Some of these are:

Acetazolamide, agmatine, amantadine, aminoguanidine, antibiotics (minocycline, tetracycline, etc.), antihistamines, aspirin, bromocriptine, DCA, emodin, glucagon, glucose, memantine, methylene blue, niacinamide, T3 (triiodothyronine), vitamin D, vitamin E.

Several of these substances inhibit the liberation of free fatty acids and prostaglandin formation, and reduce nitric oxide, lactate production, inflammation, excitation and cholinergic tone, and what they all have in common is supporting a shift away from a highly reduced condition, a shift toward an oxidized-energized balance. These are tools that are available for the practice of medicine as an art, but they are effectively invisible to big "evidence based" medicine.

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