Ray Peat's Newsletter

The proper route to an understanding of the world is an examination of our errors about it. Errol Morris

Money, progesterone & life

The flow of money through a society is the most powerful source of organization and meaning, generating real structures and the language used to describe them. By 1940, objective endocrinology had been submerged by promotional articles in medical journals.

In the 1940s, while Alexander Lipschutz was showing that progesterone could prevent cancer, and Katharina Dalton was starting to use it to treat PMS, the pharmaceutical industry was claiming that they had produced synthetic drugs more useful than progesterone during pregnancy, which they called progestogens or progestins.

In 1930 progesterone was shown to support pregnancy in animals, while estrogen was already recognized as causing breast cancer. By the mid-thirties, governments and drug companies became interested in estrogen (Nazi Germany used it in concentration camps), while only a few people continued to study progesterone. Some doctors in the 1930s were using corpus luteum extract, a rich source of progesterone, to treat pregnant women. In the 1940s, while Alexander Lipschutz was showing that progesterone could prevent cancer, and Katharina Dalton was starting to use it to treat PMS, the pharmaceutical industry was claiming that they had produced synthetic drugs more useful than progesterone during pregnancy, which they called progestogens or progestins.

In 1941, a synthetic estrogen, DES (already known to cause cancer and miscarriages) was approved for medical use in women, and in that same year Charles Huggins began using it to treat prostate cancer—a Nobel Prize winning insane idea. A few years later, DES was promoted by professors George and Olive Smith at Harvard to treat pregnant women; millions of women received the treatment, leading to deformities and cancer in following generations.

In 1942, the FDA approved Premarin (an extract of horse urine containing about 50 kinds of estrogen) for treating "menopause" symptoms, with no evidence of effectiveness, and the assurance of the manufacturer, Wyeth Ayerst, that it was safe.

Encouraged by support from the estrogen industry, thousands of articles in major medical journals falsely claimed that estrogen was effective for treating or preventing hundreds of conditions, including miscarriages, strokes, heart disease, and dementia.

The 1940s marked the end of endocrinology as an exploratory project, and the beginning of the social-economic predominance of the drug industry.

30 years after their approval of Premarin, in 1972 the FDA announced that it was effective, and in following years interacted closely with the industry to shape the way estrogen is understood and regulated. Government research was

designed to support the pharmaceutical industry, so in 2002 the medical world was shocked when the Women's Health Initiative reported that their study showed that the combination of Premarin and Provera, a synthetic progestin, contributed to dementia, strokes, clots, heart disease, and breast cancer.

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Sales of Premarin and other estrogen products decreased sharply, and millions of women began using natural progesterone. Breast cancer incidence decreased substantially during the first few years of decreased estrogen consumption. Money began flowing to researchers who would try to show that progesterone was responsible for all of the harmful effects of estrogen. My article, "Estrogen, progesterone, and cancer: Conflicts of interest in regulation and product promotion," discussed a few of the early examples.

In 1956, the FDA approved an injectable form of synthetic 17-hydroxyprogesterone (Delalutin) to prevent miscarriage. The manufacturer later asked the FDA to cancel its approval, which it did in 2000. Another company applied for accelerated approval, and that was granted in 2011 on the basis of a 2003 study, which had suggested that the drug might have increased the risk of miscarriage or stillbirth, with the provision that another study be completed. The second study clearly showed that the drug is ineffective in preventing preterm birth. On the basis of their 7 year monopoly granted by the FDA, the vendor increased the price per injection more than 100-fold. At one point, in response to criticism, the FDA said that compounding pharmacists could provide the product at a more reasonable price, but more recently they issued a statement telling pharmacists that competing with the approved drug would not be allowed, because it would undercut the regulatory process. Animal studies have demonstrated that this so-called *progestin* doesn't have progesterone's protective effects on gestation (Nelson, et al., 2017), and human observations have suggested that it appeared to have masculinizing effects on females, and feminizing effects on males.

While fraud and thuggery have had their influence on medical endocrinology, there have been subtler influences shaping thinking at the level of basic science. The receptor idea, created mainly by government and the estrogen industry, has become entrenched in the general culture, not just in the culture of endocrinology. It entered our culture just as the "field" concept in biology was disappearing, with the receptor becoming one of the essential features of reductionist mechanistic biology.

During the last 200 years there have been times when holistic thinking in biology led to important discoveries, especially in embryology and physiology, but mechanistic thinking and genetic essentialism have repeatedly submerged those approaches. Thinking about progesterone has been almost entirely confined to the mechanistic paradigm, and the result has been that it is generally miscategorized and misused. From the FDA label warnings, (based on toxic effects of ***synthetic progestins***) to California's OEHHA cancer warning and Wikipedia's definition, and common medical practice, progesterone is grotesquely misunderstood.

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The idea of "generality" is where many mistakes are made in science and medicine. To understand a substance, it's important to know, as far as possible, its general properties. For example, carbon monoxide generally interferes with oxygen's biological actions; carbon dioxide generally acidifies and stabilizes cells. It's possible to refer generically to "estrogens," "glucocorticoids," "mineralocorticoids," and "androgens," since the body makes more than one steroid in

each group with very similar biological effects. However, to say that there is a category of "progestogens," consisting of things which allow the uterus to form a deciduoma or to support pregnancy, derives from specific marketing policies of the drug industry around 1941. It was the first step in a series of misrepresentations, which effectively blocked productive exploration of the physiology of progesterone.

In 1972—30 years after approving Premarin—the FDA announced that it was effective. . . . It was another 21 years before randomized clinical trials were started under the WHI to test these beliefs about the use of synthetic hormones in women.

The drug companies and the "intelligence community" have similar attitudes toward evidence—there is a story that they want to tell, and they select concrete bits of data that form a mosaic to tell that story, ignoring the original ambiguity of each piece of the mosaic. The cultures of science and politics have become extremely authoritarian in the way they limit debate and public expression of thought. Every substance or process that affects the body or the way people live is given a mystique by these cultures.

The idea that certain lumps of tissue were "glands of internal secretion" developed in the middle of the 19th century, and for a time, some writers recognized that everything produced by the metabolism of cells and emitted into the blood stream could have an effect on all the other cells of the body. **Carbon dioxide was recognized as such an internal secretion with effects on the body's functions.** Crude extracts of the adrenal glands and thyroid gland were found to have important physiological effects. However, when a famous physiologist, Charles Edouard Brown-Sequard reported that subcutaneous injections of a testicular extract had a sexually rejuvenating effect, people were shocked, and denounced him as a quack. Later, when others reported powerfully beneficial effects from extracts of the adrenal cortex, there was a similar response—neither of those glands, they said, could contain enough hormone to produce the effects that were reported.

In 1940, Hans Selye and Christiane Dosne described the adrenal cortex extract as being "rich in the life-preserving principle." ("Effect of cortin after partial and after complete hepatectomy," American J. of Physiology 128 [1940], 729-35. "Cortin" referred to an aqueous extract of the adrenal cortex, containing many "hormonal" substances.) The corporate endocrinologists of the period disparaged Selye's work almost as virulently as they did Brown-Sequard's. The 1940s marked the end of endocrinology as an exploratory project, and the beginning of the social-economic predominance of the drug industry.

Selye, recognizing the presumptuousness of classifying hormones according to what they do, while their effects are still being explored, suggested that, until more is known, identifying them according to their tissue of origin would be more appropriate.

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In studying the physiology of stress, which he called the General Adaptation Syndrome, Selye noticed that the adrenal glands of pregnant rats could be removed, without leading to death from minor stresses, but that the usual stresses would kill them after they had given birth. Suspecting that it was progesterone produced by the placenta that made the difference, he found that the adrenalectomized rats could live a normal, stress resistant, life span, if they received a regular progesterone supplement. Since the "life-preserving principle" of the adrenal cortex extract had consisted of a complex mixture of substances, his discovery that the single substance, progesterone, could replace it should

have aroused great interest in discovering the way that substance affected every part of the organism.

In Selye's Syndrome, the adaptations are to harmful events, such as infections or traumas, and the hormones of the adrenal cortex, especially cortisol and aldosterone, allow the organism to overcome those, but with a cost—the chronic harmful effects of those hormones. For example, cortisol causes tissue atrophy, and aldosterone causes tissue fibrosis. Progesterone, besides substituting for the absence of those hormones, protects against their chronic degenerative effects, blocking, for example, both atrophy and fibrosis.

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Unfortunately, in the 1940s progesterone was still very expensive, and the drug companies were promoting the sales of their newly synthesized "progestins," by claiming that progesterone was ineffective when taken by mouth, and could be used only by intramuscular injections of an oily solution. The medical journals, as well as drug salesmen, unanimously said that it was impossible for oral progesterone to work, because "it's destroyed by stomach acid." Boiling it in hydrochloric acid doesn't harm it, but doctors were convinced that only the synthetic steroids could be used orally, and those all had unpleasant side effects, such as masculinization, clotting disorders, cancer, water retention, and blood glucose disturbances.

After I had investigated the effects of progesterone in aging animals, I met a woman who said she had read Katharina Dalton's book about the use of injected progesterone, and convinced her doctor to let her try it. She said she had recovered from optic neuritis and inability to walk as a result of the injections. I was familiar with the ease with which oily substances can pass through the skin into the blood stream, and I had noticed effects in the lab when I would get a small amount on my skin.

Dissolved in warm olive oil, its effects were immediate and dramatic, but it came out of solution when it cooled, producing fine crystals. When a particle of an oil-loving molecule contacts the surface of the intestine, it is exposed to enzymes similar to those in the liver, that prepare substances for excretion; micronized progesterone is largely absorbed in that manner. After trying many substances, I found that natural vitamin E had a great affinity for progesterone, which is reasonable, since they are both protectors of mitochondrial respiration and antagonists of estrogen, and must interact closely in stabilizing cells.

Vitamin E is more slowly absorbed through the skin than a triglyceride like olive oil, but vitamin E taken orally is absorbed, like the other oily vitamins and long chain fats, by the chylomicron pathway that carries it directly into the general blood stream, distributing it quickly through the body (Herrera and Barbas, 2001; Muller, et al., 1974; Anwar, et al., 2007). This distribution process mimics that of naturally synthesized progesterone from the ovaries.

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Although progesterone will dissolve in medium chain triglycerides, MCT, that oil isn't compatible with oral use of progesterone, because it interferes with chylomicron formation, being mainly absorbed by the direct portal pathway to the liver (Ohshima, 1977; Borel, et al., 1998; Murota, et al., 2013), where it is quickly metabolized, activating fat synthesis (Takase & Hosoya, 1986). The unique properties of this synthetic fat could lead to the development of food allergies (Li, et al., 2013).

I patented the composition of natural vitamin E, progesterone, and appropriate triglycerides, and licensed it to Kenogen, which sells it as Progest-E Complex (info@kenogen.org).

While progesterone happens to be a very convenient supplement for an individual lacking adrenal glands when confronting stresses, that doesn't explain its basic biological meaning, for example **why it's synthesized in the brain, where its concentration is much higher than in the blood, and why its synthesis and concentration rise steadily during pregnancy, and why its concentration corresponds to the size of the brain, and why birds and reptiles synthesize it.** In viviparous snakes, it is thought to be responsible for the retention of the eggs, leading to live birth, an anticipation of mammalian reproduction (Callard, et al., 1992). In plants, it supports growth.

Biological adaptation has meanings much broader than Selye's. One sense of biological adaptation was influenced by Darwinism, in which variations in inherited traits affected an organism's ability to adapt to an environment. That "genetic," relatively fixed, sense of adaptation has deflected the attention of biologists away from the changes that the organism is always undergoing in any environment. Exercise and learning involve biological changes, improving certain performances. Our daily physiological processes are continually causing small epigenetic changes, that influence how we will react to future environments.

Early in the 20th century, the embryologists Hans Driesch and Jaques Loeb were trying to explain the goal-directed behavior that could be seen in developing embryos, in which the organism could overcome imposed obstacles to continue its development. The mechanistic, neodarwinist side of the argument became the ruling dogma after Driesch's death in 1941, leading to denial of the possibility of cloning and stem cells until the end of the century.

The "entelechy" idea (the tendency to develop, realizing potential) of Driesch and Aristotle has been denounced as "vitalistic" and "metaphysical," but it simply suggested that organisms exist as organized substance with intrinsic purpose. Nothing supernatural was claimed. Embryologists had believed that if the cells of an early embryo were divided, the two halves would develop as fragments, for example front and back, of a single organism, but Driesch found that each half developed into a complete, but smaller, organism. The parts intended to become an organism. Driesch's 1885 experiment can be considered to be the first clone, or identical copy, of an organism.

The mechanistic culture in science, which finally accepted the possibility of cloning when Dolly the sheep was born in 1996, has retarded the growth of knowledge because of its insistence that there are no wholes other than the sums of the parts. The reason for its suppressive effect is that it has imposed a metaphysical definition, a definition that isn't based on evidence, of what matter is. **That metaphysical belief that the mechanists know, *a priori,* what matter is, has served as a barrier to perception and creative theorizing.** It creates a state of mind in which, for example, people think they are understanding something when they say that "progesterone is a progestogenic steroid." The premature naming of its purpose forestalls consideration of what it is, and what it is becoming.

Thinking about progesterone has been almost entirely confined to the mechanistic paradigm, i.e. the receptor theory, and the result has been that it is generally miscategorized and misused.

The sense of "adaptation" that derives from embryology doesn't deny that Selye's adaptation occurs, but it reverses the emphasis. Selye emphasized the threatening side of stress, while embryology emphasizes the constructive side of adaptation, in which the organism is assimilating what it needs from the environment, making the best use of what it encounters. Relative to the intrinsic purpose of the organism, some environments are better than others. **The organism, moment by moment, is the judge of the adequacy of the environment, contrary to the long established doctrine that inherited genes determine the needs of the growing organism.**

Experimental animals that are given enriched environments develop larger, more intelligent brains than normal. These brains consume energy at a higher rate, making new demands on the environment. An important function of intelligence is to find or to create a better environment, creating a kind of momentum by positive

feedback. These processes occur during embryonic development, during growth and education, and in the process of self actualization generally. The curiosity reflex tends to become more central to the organism's life as brain metabolism increases.

I want to suggest that the practice of calling progesterone a "hormone" has been counter-productive historically.

When needs aren't met, development stops or regresses, shutting down the most expensive functions, especially the curiosity reflex, and shifting resources to the more basic survival functions. The hormones of Selye's stress reaction—cortisol, aldosterone, and estrogen—become dominant, shrinking muscles and immune tissues, reducing oxidative metabolism, and, if the process is prolonged, increasing fibrosis, cell type reversion or dedifferentiation (EMT), inflammation, and interference with cell renewal. Even if the adrenal glands fail to produce an excess of the stress hormones, they can be produced in the brain. These anti-developmental, negatively adaptive, changes eventually lead to the various stress-related and degenerative diseases.

In Selye's *Encyclopedia of Endocrinology,* he observed that progesterone can not only compensate for an absence of the essential hormones of the adrenal cortex, it can also block the effects of an excess of those hormones. It can block the stress-related degenerative processes produced by those hormones, and it is required for the creative progression of the organism into higher states of being, supporting self-actualizing brain development.

I want to suggest that the practice of calling progesterone a hormone historically has been counterproductive. Like cholesterol, it is a cell-stabilizing substance produced by cells, especially brain cells. Its concentration in the brain, like that of cholesterol, increases with the size and quality of the brain, and corresponds to the quality of life. Its functions go beyond those of cholesterol, shifting the way the brain responds to all sorts of stimulation and stress. These functions transcend the accidents of Darwinian evolution, and are involved in the epigenetics of development, protecting against the degenerative effects of stress, preserving the higher levels of organization achieved through experience.

The basic life supporting effects of carbon dioxide are parallel to those of progesterone, and progesterone supports the production of CO2, and the brain's sensitivity to it (Awad and Alrefaie, 2014; Stekovic, et al., 2017; Szelke, et al., 2008).

The deliberate commercial slander of cholesterol over the last 70 years has done damage, bodily and financial, equivalent to a continuing war, harming people at every stage of life from conception to old age. The misclassification of progesterone has resulted in direct damage, affecting especially developing fetuses, women using oral contraceptives, and post-menopausal women, who have been exposed to substances with long-lasting toxic effects called progestins and progestogens. But besides these obvious aggressions of the drug industry, there has been the damage caused by failing to understand and treat easily correctable conditions appropriately.

The false claims and misclassification of progesterone have done great harm . . . besides the obvious aggressions of the drug industry, there has been the damage caused by failing to understand and treat easily correctable conditions appropriately.

The role of progesterone deficiency in epilepsy, depression, mania, heart failure, dementia, osteoporosis, neuropathies, myopathies, hypertension, pulmonary arterial hypertension, fibrosis, autoimmunity and glaucoma, has been neglected, because of its classification as a pregnancy hormone. Even in pregnancy, that categorical thinking has been responsible for the injury and death of large numbers of women and their children.

The behavior of the FDA in regard to progesterone and the synthetic progestins has culminated in 2019 with the approved new pregnancy-related drug, Zulpresso (for postpartum depression) and the previously approved

Makena (for premature birth prevention), treatments that are ridiculously expensive, and one of which is both ineffective and harmful. If the FDA is shamed into withdrawing its corrupt approval of Makena, the hydroxyprogesterone pregnancy treatment, this could provide an opportunity to reconsider its 78 years of approving toxic hormonal treatments and misrepresenting the effects of progesterone.

Even if the FDA should decide to put science ahead of business, there would still be the problem of the journals, and the subsidized research groups, who aren't likely to stop their campaign against progesterone. Readers and consumers have to become aware of tricks such as using estrogenic solvents such as ethanol in studies of progesterone. People who are going to have a biopsy or other surgery can be responsible for either timing the operation to coincide with the luteal phase when progesterone is high, or for using a progesterone supplement before the procedure (Badwe, et al., 2011; Vasei, et al., 2006). There are too few physicians who are conscious of the difference between progesterone and synthetic drugs, and of the importance of progesterone, so medical consumers should be cautious.

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