Ray Peat's Newsletter

I am I and my circumstance; if I don't save it, I don't save myself. José Ortega y Gasset

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Postpartum depression, brain, aging, and reductionism

There's an important trend in medicine toward an enforced conformity, based on "evidence-based guidelines for diagnosis and management," and this is associated with a campaign to change medical education, eliminating the "basic science" instruction (biochemistry, molecular biology, neuroscience, physiology) of the first two years of medical school as a waste of time. Vinay Prasad (2013) has said that those subjects are worse than a waste of time, because they "encourage a dangerous cognitive bias: subordinating evidence-based medicine to pathophysiological reasoning," which plays "a key role in popularizing unproven medical practices."

Since very large, expensive, studies (randomized, controlled trials) are the "gold standard" of medical practice, "evidence based" medicine is a way to herd individual practitioners into a way of doing medicine that maintains the profits of the corporations that are able to fund the studies that are big enough to be acceptable to those who set the standards. It's true that the "pathophysiological reasoning" based on knowledge of the basic sciences has very often been wrong, but the solution is to improve the quality of the basic science education, rather than abandoning active reason in favor of passively following guidelines established by the corporations with their interest in the most profitable treatments.

About 12% of new mothers in the US, and a higher percentage in less industrialized countries, experience serious depression in the first several months after the birth**;** when the birth is premature, the percentage is much higher. Women who previously experienced premenstrual symptoms, and who had various symptoms during pregnancy, are more likely to have serious postpartum depression. Hair loss, seizures, rapid bone loss, edema, fainting, fibromyalgia, joint pain, insomnia, and hypertension are sometimes associated with the depression.

Physiological reasoning will lead to mistaken conclusions if the properties of the factors involved are misunderstood.

The FDA has approved the first treatment for postpartum depression (PPD), and the company plans to charge $34,000 for the drug, which has to be administered intravenously in a hospital, during 60 hours. The drug is allopregnanolone, the main metabolite of progesterone in the brain. Taking progesterone reliably increases the brain content of allopregnanolone, with a small oral dose of progesterone tripling (196% increase) the concentration of allopregnanolone (Andréen, et al., 2006). Supplementing pregnenolone also increases allopregnanolone.

The approval of the "New Drug," Zulresso, was possible because of the recognized commitment of the FDA, the insurance industry, and a large part of the medical profession, to the idea that each disease can be treated by a specific drug, and that the only way to have confidence that the right drug has been chosen, is to permit a monopoly that will justify the investment needed for research. The FDA has been committed to the privatization of generic drugs for many years; for example, a cheap drug, gamma hydroxybutyrate,

Oxybate, was given a New Drug monopoly, as Xyrem, leading to an astronomical price increase. Monopoly profits are a powerful reinforcer for a reductionist approach to medicine, especially for a centralized, official, reductionism.

When some older methods of treating sickness are used instead of "Evidence-Based" treatments, doctors risk losing their license. Some doctors still prefer to use reasoning, rather than authority, to guide their practice. When medical reasoning fails, it's usually because the facts taken into account are mistaken. The basic assumption of medical reductionism is that the parts of a system can be understood and defined, and that those definitions can be trusted as a basis for pathophysiological reasoning. To the extent that the interests of the drug industry have guided research, publication, and education, the facts, the "basic sciences," have to be reconsidered.

Whenever a major industry sells a substance, with profits of billions of dollars, reasoning involving that substance should begin with a skeptical and detailed investigation of the substance, in as many different contexts as possible.

The problems that occur in the months after having a baby have, historically, been treated in a great variety of ways. Chamomile tea (Chang and Chen, 2016), massage, and counseling seem to be effective. The popularity of the "selective serotonin reuptake inhibitors," SSRI, has led to their frequent use for postpartum depression: "Despite the lack of good-quality evidence comparing SSRIs with placebo directly, SSRIs are likely to be beneficial for the treatment of postnatal depression based on evidence of their effectiveness in treating depressive disorders in general, and also in the treatment of premenstrual dysphoric disorder" (Craig, 2016).

The popularity of the SSRI antidepressants, which is heavily influenced by advertising, leads to their use for PPD despite the absence of specific evidence, and despite the clearly established harmful side effects, especially bone loss, which is already a major postpartum problem (Weaver, et al., 2019; Weaver and Hernandez, 2018; Weaver, et al,, 2018). Several studies have reported that they increase estrogen or its effects (Kempan, et al., 2011, Lupu, et al., 2017, Hansen, et al., 2017, Shea, et al., 2019), and there is evidence that they increase breast cancer mortality (Busby, et al., 2018). The pharmaceutical myth about serotonin, the "happy hormone," has led most people, even researchers, to ignore the fact that it increases inflammation and activates the stress system, while reducing the efficiency of energy production.

Drug company manipulation of information about estrogen has been more extreme than its treatment of serotonin. Activated by stress, along with serotonin, it is one of the major activators of the corticotropin release hormone, CRH, which activates the pituitary and adrenal glands, and promotes inflammation, and is a major factor in PPD (Glynn and Sandman, 29014, Hahn-Holbrook, 2016), as well as in other types of depression, and aging, and Alzheimer's disease. CRH activates aromatase, creating a potential vicious circle, but progesterone can prevent that effect (Roy, et al., 1999). CRH inhibits progesterone production, while increasing estrogen (Jeschke, et al., 2005; Yang, et al., 2006; Stamatelou, et al., 2009; Gao, et al., 2012).

Estrogen increases the brain's capacity to synthesize serotonin (Hiroi, et al., 2006). If it weren't for the advertising culture, it would probably be generally recognized that both estrogen and serotonin have important roles in causing depression, migraine, and Alzheimer's disease, all of which occur much more often in women than in men.

Physiological reasoning will lead to mistaken conclusions if the properties of the factors involved are misunderstood. Whenever a major industry sells a substance, with profits of billions of dollars, reasoning involving that substance should begin with a skeptical and detailed investigation of the substance, in as many different contexts as possible.

In the 1960s, Fritz Verzar found that treating animals with estrogen accelerated the aging of their connective tissues, modifying their collagen.

Later, A.V. Everitt reviewed studies in rabbits showing that the endogenous estrogen of pregnancy increased the stiffness of their connective tissues, but that the continuing increased production of progesterone between litters reversed that effect. They found that the connective tissues of animals that had borne many litters seemed to be younger than the tissues of animals of the same age that had never been mated.

In women, MRI images show (Hoekzema, et al., 2017) that the grey matter of the brain shrinks considerably during pregnancy, similar to the changes of advanced aging, and in some women these changes were still present after two years. However, another study has found a very rapid restoration of brain structure in the second postpartum month. In these healthy women, the brain restoration in that two month period was equivalent to five years of rejuvenation (Luders, et al., 2018).

In healthy women, progesterone in the postpartum period is much higher than before pregnancy—seven times higher in the plasma, three times higher in the cerebrospinal fluid (Datta, et al., 1986). This corresponds to the time of brain restoration. Many studies over the last 60 years have shown the positive effects of progesterone on brain development—increasing the size of the brain, the thickness of the cortex, the resistance to injury, and the quality of functioning.

For at least as long, the opposite effects of estrogen on the brain have been shown in a great variety of situations. Prenatally, an excess of estrogen inhibits cell growth, resulting in a smaller brain at birth, with a thinner cortex. In mature animals, it can cause seizures and excitotoxic cell death.

Despite the fact that hundreds of millions of women have been treated for decades with estrogens, only a few studies have bothered to see whether its effects on the human brain are similar to the effects seen in the animal studies. In a variety of situations, they have reported that estrogen treatment causes reduction of grey matter in the brain; as the grey matter volume decreases, the fluid volume increases.

For example: “HT users had significantly less gray matter and more cerebrospinal fluid than nonusers,” Greenberg, et al., 2006); “We found a highly significant negative correlation of regional gray matter volume in the anterior cingulate cortex with estradiol concentrations,” De Bondt, et al., 2013; people currently receiving hormone treatment “had significantly smaller ratios of gray matter to ICV and increased atrophy (CSF/ICV ratio),” Ryan, et al., 2014; “HT [hormone therapy] had adverse effects on GM [grey matter] volumes and risk for cognitive impairment and dementia in older women,” Zhang, et al., 2016. Espelund, et al, 2015, observed shrinkage in the brains of older diabetic women receiving hormone therapy, and Seiger, et al., 2016, reported that in male to female transexuals receiving estrogen and anti-androgens, there was shrinkage in the hippocampal region, with enlargement of the ventricles, i.e., more fluid.

Cholesterol is the precursor to pregnenolone, progesterone, and the other neurosteroids, and its own properties include stabilizing effects similar to progesterone’s. Normally, cholesterol, like progesterone, is higher during the postpartum months. Several studies have observed an association of lower postpartum cholesterol with symptoms of anxiety and depression (Ploeckinger, et al., 1996, Nasta, et al., 2002, Troisi, et al., 2002, Troisi, et al., 2018). With insufficient cholesterol, the normally high postpartum concentration of progesterone isn’t likely to be maintained, and instead of brain restoration, the various pro-inflammatory effects of serotonin and estrogen will predominate, with effects such as depression, joint pain, anxiety, and brain edema.

Stress is experienced when processes that are normally adaptive begin to have maladaptive effects. That happens when the organism’s resources aren’t adequate to meet the demands of the situation. The stimulation of CRH production by histamine, serotonin, endorphins, IL-1, nitric oxide, and/or estrogen in good health leads to the activation of complex and appropriate antistress reactions. When stress is very intense or prolonged, or if nutrition hasn’t been adequate, all of the activating signals, CRH itself, and the antistress glucocorticoids, can produce effects that aren’t integrated into the organism’s functions as it confronts its problems, and that produce symptoms and, eventually, degenerative processes and aging. That failure of integration is almost always the result of insufficient metabolic energy.

In pregnancy, the placenta serves as a large antistress organ that increases the mother's adaptability, but it and the growing fetus increase the mother's nutritional needs. The role of nutrition in preventing toxemia of pregnancy was shown clearly by Tom Brewer, Douglas Shanklin, and Jay Hodin, but there has been less attention to the adaptational problems of the mother following the birth. Tom Brewer emphasized the importance of protein and salt, but he generally recommended drinking two quarts of milk daily during pregnancy, and three quarts daily during lactation. A study in Japan asked women during pregnancy how much milk they had drunk in the preceding month. Based on that small amount of information, they saw a 49% reduction of the incidence of postpartum depression in those who drank the most milk (Miyake, et al., 2016).

The importance of salt and calcium in pregnancy relates to their effects on the respiratory energy system, and the fact that these effects aren't widely known has led most doctors to believe that a diet that supplies "all the required nutrients" is adequate for pregnancy and lactation. Despite the presence of all the required nutrients, that would be adequate for someone with a generally supportive environment, a "good" diet won't necessarily be adequate for someone with a problematic environment, or a history of stressful experiences.

The levels of aldosterone and parathyroid hormone are increased by stress, with serotonin acting on the adrenal cortex and the parathyroid gland to increase their secretion. All three of those hormones act on the mitochondria to lower oxidative energy production. Increasing the amount of sodium and calcium (and vitamin D, which also helps to lower parathyroid hormone and aldosterone) in the diet can lower the secretion of aldosterone and parathyroid hormone, with a resulting increasing in oxidative energy production.

The use of SSRI antidepressants has increased greatly in the last 20 years. Recently, doctors, fearing that the strange new drug, allopregnanolone, could appear in the mother's milk and affect the baby, have said that breast feeding would have to be stopped during the treatment, so they prefer, as "first line treatment" for postpartum depression, the standard SSRIs. Used during pregnancy, those chemicals increase birth defects, but the benefit is usually considered to be worth the harm.That has seemed to be the only medical consideration; the effect on the mother's health seems to be of no interest. The activation of the stress system by serotonin affects the mother's ability to support the gestation; there is evidence that use of the SSRI in the 2nd and 3rd trimesters increases premature delivery (Huybrechts, et al., 2014). Those same changes contribute to postpartum depression.

In this situation, the people who say medicine should be guided by authoritative studies, rather than by so-called pathophysiologcal reasoning, might seem to have a case, since a progesterone metabolite, even when it's dissolved with a cyclodextrin and administered intravenously, is likely to be more helpful than the usual antidepressants. But the use of antidepressant drugs isn't guided by biological reasoning, it's guided by advertising, and the anti-biological beliefs associated with serotonin.

Physiological reasoning would use the available knowledge about the nature of pregnancy and the nature of stress, and would identify the most important factors that can be optimized with existing resources. Healthier pregnancies will result in healthier and happier postpartum life.

Some of these factors would be sunlight, vitamin D, milk, cheese, eggs, fruits and well cooked vegetables, fibrous foods, and optimizing thyroid function and pregnenolone and progesterone (which support mitochondrial function, protecting against aldosterone, parathyroid hormone, excess serotonin, CRK, and cortisol, besides increasing allopregnanolone), and using the safest antiinflammatory and antiserotonin drugs, such as aspirin and cyproheptadine, when they are needed.

REFERENCES

Maturitas. 2006 Jun 20;54(3):238-44. **Pharmacokinetics of progesterone and its metabolites allopregnanolone and pregnanolone after oral administration of low-dose progesterone.** Andréen L, Spigset O, Andersson A, Nyberg S, Bäckström T.

J Card Fail. 2014 May;20(5):334-42. T**he effect of vitamin d on aldosterone and health status in patients**

with heart failure. Boxer RS, Hoit BD, Schmotzer BJ, Stefano GT, Gomes A, Negrea L.

Breast Cancer Res. 2018 Jan 19;20(1):4. **Selective serotonin reuptake inhibitor use and breast cancer survival: a population-based cohort study.** Busby J, Mills K, Zhang SD, Liberante FG, Cardwell CR.

J Adv Nurs. 2016 Feb;72(2):306-15. **Effects of an intervention with drinking chamomile tea on sleep quality and depression in sleep disturbed postnatal women: a randomized controlled trial.** Chang SM, Chen CH.

BMJ Clin Evid. 2016; 2016: 1407. **Postnatal depression: drug treatments**. Craig MC.

Anesth Analg. 1986 Sep;65(9):950-4. **Plasma and cerebrospinal fluid progesterone concentrations in pregnant and nonpregnant women.** Datta S, Hurley RJ, Naulty JS, Stern P, Lambert DH, Concepcion M, Tulchinsky D, Weiss JB, Ostheimer GW.

Brain Res. 2013 Sep 12;1530:22-31. **Regional gray matter volume differences and sex-hormone correlations as a function of menstrual cycle phase and hormonal contraceptives use.** De Bondt T(1), Jacquemyn Y, Van Hecke W, Sijbers J, Sunaert S, Parizel PM.

Neurology. 2015 Sep 29;85(13):1131-8. **Postmenopausal hormone therapy, type 2 diabetes mellitus, and brain volumes.** Espeland MA, Brinton RD, Manson JE, Yaffe K, Hugenschmidt C, Vaughan L, Craft S, Edwards BJ, Casanova R, Masaki K, Resnick SM.

Endocrinology. 2012 Oct;153(10):4918-28. **Regulation of estradiol and progesterone production by CRH-R1 and -R2 is through divergent signaling pathways in cultured human placental trophoblasts.** Gao L, Tao Y, Hu T, Liu W, Xu C, Liu J, You X, Gu H, Ni X.

Psychosom Med. 2014 Jun;76(5):355-62. **Evaluation of the association between placental corticotrophin-releasing hormone and postpartum depressive symptoms.** Glynn LM, Sandman CA.

Psychiatry Res. 2006 Oct 30;147(2-3):127-34. **Differences in brain volumes among males and female hormone-therapy users and nonusers.** Greenberg DL, Payne ME, MacFall JR, Provenzale JM, Steffens DC, Krishnan RR.

J Clin Endocrinol Metab. 2016 Feb; 101(2): L5–L6. Letter to the Editor: Demonstration of Elevated **Cerebrospinal Fluid CRH Levels During Pregnancy Provides Support for (Not Against) the Link Between CRH and Postpartum Depression.** Hahn-Holbrook J, Fox M, Glynn LM.

Toxicol In Vitro. 2017 Jun;41:1-11. **The six most widely used selective serotonin reuptake inhibitors decrease androgens and increase estrogens in the H295R cell line.** Hansen CH, Larsen LW, Sørensen AM, Halling-Sørensen B, Styrishave B.

Biol Psychiatry. 2006 Aug 1;60(3):288-95. **Estrogen Selectively Increases Tryptophan Hydroxylase-2 mRNA Expression in Distinct Subregions of Rat Midbrain Raphe Nucleus: Association between Gene Expression and Anxiety Behavior in the Open Field** Hiroi R, McDevitt RA, Neumaier JF.

Nat Neurosci. 2017 Feb;20(2):287-296. **Pregnancy leads to long-lasting changes in human brain structure.** Hoekzema E, Barba-Müller E, Pozzobon C, Picado M, Lucco F, García-García D, Soliva JC, Tobeña A, Desco M, Crone EA, Ballesteros A, Carmona S, Vilarroya O.

Arch Gynecol Obstet. 2005 Jun;272(1):7-12. **Regulation of progesterone production in human term trophoblasts in vitro by CRH, ACTH and cortisol (prednisolone).** Jeschke U, Mylonas I, Richter DU, Höcker I, Briese V, Makrigiannakis A, Friese K.

Behav Neurosci. 2010 Oct;124(5):695-700. **The plasticity of human maternal brain: longitudinal changes in brain anatomy during the early postpartum period.** Kim P, Leckman JF, Mayes LC, Feldman R, Wang X, Swain JE.

Placenta. 2011 Sep;32(9):651-6. **Stimulation of serotonergic 5-HT2A receptor signaling increases placental aromatase (CYP19) activity and expression in BeWo and JEG-3 human choriocarcinoma cells.** Klempan T, Hudon-Thibeault AA, Oufkir T, Vaillancourt C, Sanderson JT.

Neuroscience. 2018 Aug 21;386:309-314. **Potential Brain Age Reversal after Pregnancy: Younger Brains at 4-6 Weeks Postpartum.** Luders E, Gingnell M, Poromaa IS, Engman J, Kurth F, Gaser C.

Clujul Med. 2017;90(4):420-424. **Fluoxetine modulates sex steroid levels in vitro.** Lupu D, Sjödin MOD, Varshney M, Lindberg J, Loghin F, Rüegg J.

Nutr Res. 2016 Sep;36(9):907-913. **Milk intake during pregnancy is inversely associated with the risk of postpartum depressive symptoms in Japan: the Kyushu Okinawa Maternal and Child Health Study.**

Miyake Y, Tanaka K, Okubo H, Sasaki S, Furukawa S, Arakawa M.

J Psychosom Res. 2002 Feb;52(2):61-3. **Cholesterol and mood states at 3 days after delivery.** Nasta MT, Grussu P, Quatraro RM, Cerutti R, Grella PV.

BMJ. 1996 Sep 14;313(7058):664. **Rapid decrease of serum cholesterol concentration and postpartum depression.** Ploeckinger B, Dantendorfer K, Ulm M, Baischer W, Derfler K, Musalek M, Dadak C.

Perspect Med Educ. 2013 Nov; 2(5-6): 335–339. **Persistent reservations against the premedical and medical curriculum.** Vinay Prasad.

Endocrinology. 1999 May;140(5):2191-8. **The effects of estrogen and progesterone on corticotropin-releasing hormone and arginine vasopressin messenger ribonucleic acid levels in the paraventricular nucleus and supraoptic nucleus of the rhesus monkey.** Roy BN, Reid RL, Van Vugt DA.

Neurobiol Aging. 2014 Mar;35(3):645-54. **Brain volumes in late life: gender, hormone treatment, and estrogen receptor variants.** Ryan J, Artero S, Carrière I, Scali J, Maller JJ, Meslin C, Ritchie K, Scarabin PY, Ancelin ML.

Psychoneuroendocrinology. 2016 Dec;74:371-379. **Subcortical gray matter changes in transgender subjects after long-term cross-sex hormone administration.** Seiger R, Hahn A, Hummer A, Kranz GS, Ganger S, Woletz M, Kraus C, Sladky R, Kautzky A, Kasper S, Windischberger C, Lanzenberger R.

Climacteric. 2019 May 7:1-4. **The effect of serotonin reuptake inhibitors on the vaginal epithelium in postmenopausal women.** Shea AK, Meschino D, Wolfman W.

Ann Acad Med Singapore. 2009 Nov;38(11):1011-6. **Abnormal progesterone and corticotropin releasing hormone levels are associated with preterm labour.** Stamatelou F, Deligeoroglou E, Farmakides G, Creatsas G.

Psychiatry Res. 2002 Apr 15;109(3):213-9. **Serum cholesterol levels and mood symptoms in the postpartum period.** Troisi A(1), Moles A, Panepuccia L, Lo Russo D, Palla G, Scucchi S.

Psychiatry Res. 2018 Nov;269:394-398. **Normal cholesterol levels in the immediate postpartum period: A risk factor for depressive and anxiety symptoms?** Troisi A, Croce Nanni R.

Sci Rep. 2019 Jan 18;9(1):238. **In utero and lactational exposure to the Selective Serotonin Reuptake Inhibitor fluoxetine compromises pup bones at weaning.** Weaver SR, Xie C, Charles JF, Hernandez LL.

J Mammary Gland Biol Neoplasia. 2018 Jun;23(1-2):5-25. **Could use of Selective Serotonin Reuptake Inhibitors During Lactation Cause Persistent Effects on Maternal Bone?** Weaver SR, Hernandez LL.

Endocrinology. 2018 Aug 1;159(8):2850-2862. **Peripartum Fluoxetine Reduces Maternal Trabecular Bone After Weaning and Elevates Mammary Gland Serotonin and PTHrP.** Weaver SR, Fricke HP, Xie C, Lipinski RJ, Vezina CM, Charles JF, Hernandez LL.

J Mol Endocrinol. 2006 Dec;37(3):533-40. **Corticotropin-releasing hormone inhibits progesterone production in cultured human placental trophoblasts.** Yang R, You X, Tang X, Gao L, Ni X.

PLoS One. 2016 Mar 14;11(3):e0150834. **Effects of Hormone Therapy on Brain Volumes Changes of Postmenopausal Women Revealed by Optimally-Discriminative Voxel-Based Morphometry.** Zhang T, Casanova R, Resnick SM, Manson JE(, Baker LD, Padual CB, Kuller LH, Bryan RN, Espeland MA, Davatzikos C.

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