



ARTICLE

Tissue-bound estrogen in aging

The "Estrogen Replacement" industry is based on the doctrine that a woman's tissues are depleted of estrogen after menopause. This doctrine is false.

The concentration of a hormone in the blood doesn't directly represent the concentration in the various organs.

The amount of estrogen in tissue is decreased when progesterone is abundant. In the absence of progesterone, tissues retain estrogen even when there is little estrogen circulating in the blood.

Many things suggest an increased estrogenic activity at menopause. For example, melatonin decreases sharply at puberty when estrogen increases, and then it decreases again at menopause. Prolactin (stimulated by estrogen) increases around puberty, and instead of decreasing at menopause, it often increases, and its increase is associated with osteoporosis and other age-related symptoms.

Estrogen is produced in many tissues by the enzyme aromatase, even in the breast and endometrium, although these are considered "target tissues" rather than endocrine glands. Aromatase increases with aging.

Estrogen is inactivated, mainly in the liver and brain, by being made water soluble by the attachment of glucuronic acid and/or sulfuric acid.

Estrogen's concentration in a particular tissue depends on many things, including its affinity or binding strength for components of that tissue, relative to its affinity for the blood; the activity in that tissue of the aromatase enzyme, which converts androgens to estrogen; the activity of the glucuronidase enzyme, that converts water-soluble estrogen glucuronides into the oil soluble active forms of estrogen; and the sulfatases and several other enzymes that modify the activity and solubility of the estrogens. The "estrogen receptors," proteins which bind estrogens in cells, are inactivated by progesterone, and activated by many physical and chemical conditions.

Inflammation activates beta-glucuronidase, and antiinflammatory substances such as aspirin reduce many of estrogen's effects.

Doctrines are admitted into the "scientific canon" by those who have the power of censorship. In astronomy, Halton Arp's discovery of "anomalous" galactic red-shifts is practically unknown, because the journal editors say the observations are "just anomalies," or that the theories which could explain them are unconventional; but the actual problem is that they are strong evidence against The Big Bang, Hubble's Law, and the Expanding Universe. American science, since the 1940s, has probably been the most censored and doctrinaire in the world.

Gilbert Ling's revolution in cell biology remains outside the canon, despite the profound influence of MRI, which grew directly out of his view of the cell, because his work provided conclusive evidence that cells are not regulated by "semipermeable membranes and membrane pumps." Every field of science is ruled by a doctrinaire establishment.

Charles E. Brown-Séquard (1817-94) was a physiologist who pioneered scientific endocrinology, but who was ridiculed because of his claim that extracts of animal glands had an invigorating effect when injected. His place in the scientific canon is mainly as an object of ridicule, and the details of his case are perfectly representative of the way our "canon" has been constructed. The argument for dismissing his observations was that he used a water extract of testicles, and, according to the 20th century American biologists, testosterone is not water soluble, and so the water extract would have "contained no hormone." The argument is

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foolish, because living organs contain innumerable substances that will solublize oily molecules, but also because Brown-Séquard was describing an effect that wasn't necessarily limited to a single chemical substance. (The transplanting of living cells to repair tissues is finally being accepted, but the pioneers in promoting tissue regeneration or repair with the transplantation of living, dead, or stressed cells--V. Filatov, L.V. Polezhaev, W.T. Summerlin, for example--were simply written out of history.)

If Brown-Séquard's extract couldn't work because testosterone isn't soluble in water, then what are we to think of the thousands of medical publications that talk about "free hormones" as the only active hormones? ("Free hormone" is defined as the hormone that isn't bound to a transporting protein, with the more or less explicit idea that it is dissolved in the water of the plasma or extracellular fluid.) Brown-Séquard's tissue extracts would have contained solubilizing substances including proteins and phospholipids, so the oily hormones would certainly be present (and active) in his extracts. But the thousands of people who ridiculed him committed themselves to the fact that steroid hormones are insoluble in water. By their own standard, they are selling an impossibility when they do calculations to reveal the amount of "free hormone," as something distinct from the protein bound hormone, in the patient's blood.

The immense Hormone Replacement Therapy industry--which Brown-Séquard's experiments foreshadowed--is based on the fact that the concentrations of some hormones in the blood serum decrease with aging.

At first, it was assumed that the amount of the hormone in the blood corresponded to the effectiveness of that hormone. Whatever was in the blood was being delivered to the "target tissues." But as the idea of measuring "protein bound iodine" (PBI) to determine thyroid function came into disrepute (because it never had a scientific basis at all), new ideas of measuring "active hormones" came into the marketplace, and currently the doctrine is that the "bound" hormones are inactive, and the active hormones are "free." The "free" hormones are supposed to be the only ones that can get into the cells to deliver their signals, but the problem is that "free hormones" exist only in the imagination of people who interpret certain lab tests, as I discussed in the newsletter on thyroid tests (May, 2000).

In the 1960s and 1970s, when the PBI test was disappearing, there was intense interest in--a kind of mania regarding--the role of "membranes" in regulating cell functions, and the membrane was still seen by most biologists as the "semipermeable membrane" which, "obviously," would exclude molecules as large as albumin and the other proteins that carry thyroid and other hormones in the blood. (In reality, and experimental observations, albumin and other proteins enter cells more or less freely, depending on prevailing conditions.) The membrane doctrine led directly to the "free hormone" doctrine.

This issue, of arguing about which form of a hormone is the "active" form, has to do with explaining how much of the blood-carried hormone is going to get into the "target tissues." If the membrane is a "semipermeable" barrier to molecules such as hormones, then specific receptors and transporters will be needed. If the concentration of a hormone inside the cell is higher than that in the blood, a "pump" will usually be invoked, to produce an "active transport" of the hormone against its concentration gradient.

But if the membrane regulates the passage of hormones from blood to tissue cells, and especially if pumps are needed to move the hormone into the cell, how relevant is the measurement of hormones in the blood?

Within the blood, progesterone and thyroid hormone (T3) are much more concentrated in the red blood cells than in the serum. Since it isn't likely that red blood cells are "targets" for the sex hormones, or for progesterone or even thyroid, their concentration "against their gradient" in these cells suggests that a simple distribution by solubility is involved. Oily substances just naturally tend to concentrate inside cells because of their insolubility in the watery environment of the plasma and extracellular fluid. Proteins that have "oily" regions effectively bind oily molecules, such as fats and steroids. Even red blood cells have such

proteins.

In the case of oil soluble molecules, such as progesterone and estrogen, it's important to explain that most of their "binding" to proteins or other oil-loving molecules is really the nearly passive consequence of the molecules' being forced away from the watery phase--they are hydrophobic, and although it would take a great amount of energy to make these insoluble substances enter the watery phase, the attractive force between them and the cell is usually small. This means that they can be freely mobile, while "bound" or concentrated within the cell. The oxygen atoms, and especially the phenolic group of estrogen, slightly reduce the hormones' affinity for simple oils, but they interact with other polar or aromatic groups, giving estrogen the ability to bind more strongly and specifically with some proteins and other molecules. Enzymes which catalyze estrogen's oxidation-reduction actions are among the specific estrogen-binding proteins.

Many proteins and lipoproteins bind steroids, but some intracellular proteins bind them so strongly that they have been--in a very teleological, if not anthropomorphic, way--considered as the switch by which the hormone turns on the cellular response. In the popular doctrine of the Estrogen Receptor, a few molecules of estrogen bind to the receptors, which carry them to the nucleus of the cell, where the activated receptors turn on the genes in charge of the female response. (Or the male response, or the growth response, or the atrophy response, or whatever genetic response estrogen is producing.) Once the switch has been thrown, the estrogen molecules have fulfilled their hormonal duty, and must get lost, so that the response isn't perpetuated indefinitely by a few molecules.

Although the Estrogen Receptor doctrine is worse than silly, there are real proteins which bind estrogen, and some of these are called receptors. The uterus, breast, and brain, which are very responsive to estrogen, bind, or concentrate, estrogen molecules.

When I was working on my dissertation, I tried to extract estrogens from hamster uteri, but the chemical techniques I was using to measure estrogen weren't accurate for such small quantities. A few years later, S. Batra was able to extract the estrogen from human tissue in quantities large enough for accurate analysis by radioimmunoassay. (Batra, 1976.)

His crucial observation was that the difference in estrogen concentration between tissue and blood was lowest in the luteal phase, when progesterone is high:

"The tissue/plasma ratio of E2 [estradiol] ranged from 1.45 to 20.36 with very high values in early follicular phase and the lowest in mid-luteal phase." This means that progesterone prevents the tissue from concentrating estrogen. He made similar observations during pregnancy, **with tissue estrogen decreasing as blood progesterone increased, so that there is less estrogen in the tissue than in the plasma.** But in women who aren't pregnant, and when their progesterone is low, the tissues may contain 20 to 30 times more estrogen than the plasma (in equal volumes).

In aging, the sharply decreased progesterone production creates a situation resembling the follicular phase of the menstrual cycle, allowing tissues to concentrate estrogen even when the serum estrogen may be low.

"In postmenopausal women, the tissue concentration of E2 was not significantly lower than in menstruating women in follicular phase. . . ." (Akerlund, et al., 1981.)

Besides the relatively direct actions of progesterone on the estrogen receptors, keeping their concentration low, and its indirect action by preventing prolactin from stimulating the formation of estrogen receptors, there are many other processes that can increase or decrease the tissue concentration of estrogen, and many of these influences change with aging.

There are two kinds of enzyme that produce estrogen. Aromatase converts male hormones into estrogen. Beta-glucuronidase converts the inactive estrogen-glucuronides into active estrogen. The healthy liver inactivates practically all the estrogen that reaches it, mostly by combining it with the "sugar acid," glucuronic acid. This makes the

estrogen water soluble, and it is quickly eliminated in the urine. But when it passes through inflamed tissue, these tissues contain large amounts of beta-glucuronidase, which will remove the glucuronic acid, leaving the pure estrogen to accumulate in the tissue.

Many kinds of liver impairment decrease its ability to excrete estrogen, and estrogen contributes to a variety of liver diseases. The work of the Biskinds in the 1940s showed that a dietary protein deficiency prevented the liver from detoxifying estrogen. Hypothyroidism prevents the liver from attaching glucuronic acid to estrogen, and so increases the body's retention of estrogen, which in turn impairs the thyroid gland's ability to secrete thyroid hormone. Hypothyroidism often results from nutritional protein deficiency.

Although we commonly think of the ovaries as the main source of estrogen, the enzyme which makes it can be found in all parts of the body. Surprisingly, in rhesus monkeys, aromatase in the arms accounts for a very large part of estrogen production. Fat and the skin are major sources of estrogen, especially in older people. **The activity of aromatase increases with aging, and under the influence of prolactin, cortisol, prostaglandin, and the pituitary hormones, FSH (follicle stimulating hormone) and growth hormone. It is inhibited by progesterone, thyroid, aspirin, and high altitude.** Aromatase can produce estrogen in fat cells, fibroblasts, smooth muscle cells, breast and uterine tissue, pancreas, liver, brain, bone, skin, etc. Its action in breast cancer, endometriosis, uterine cancer, lupus, gynecomastia, and many other diseases is especially important. Aromatase in mammary tissue appears to increase estrogen receptors and cause breast neoplasia, independently of ovarian estrogen (Tekmal, et al., 1999).

Women who have had their ovaries removed are usually told that they need to take estrogen, but animal experiments consistently show that removal of the gonads causes the tissue aromatases to increase. The loss of progesterone and ovarian androgens is probably responsible for this generalized increase in the formation of estrogen. In the brain, aromatase increases under the influence of estrogen treatment.

Sulfatase is another enzyme that releases estrogen in tissues, and its activity is inhibited by antiestrogenic hormones.

In at least some tissues, progesterone inhibits the release or activation of beta-glucuronidase (which, according to Cristofalo and Kabakjian, 1975, increases with aging). Glucaric acid, which inhibits this enzyme, is being used to treat breast cancer, and glucuronic acid also tends to inhibit the intracellular release of estrogen by beta-glucuronidase.

Although there is clearly a trend toward the rational use of antiestrogenic treatments for breast cancer, in other diseases the myth of estrogen deficiency still prevents even rudimentary approaches.

Ever since Lipshutz' work in the 1940s, it has been established that the **uninterrupted** effect of a little estrogen is more harmful than larger but intermittent exposures. But after menopause, when progesterone stops its cyclic displacement of estrogen from the tissues, the tissues retain large amounts of estrogen continuously.

The menopause itself is produced by the prolonged exposure to estrogen beginning in puberty, in spite of the monthly protection of the progesterone produced by cycling ovaries. The unopposed action of the high concentration of tissue-bound estrogen after menopause must be even more harmful.

The decline of the antiestrogenic factors in aging, combined with the increase of pro-estrogenic factors such as cortisol and prolactin and FSH, occurs in both men and women. During the reproductive years, women's cyclic production of large amounts of progesterone probably retards their aging enough to account for their greater longevity. Childbearing also has a residual antiestrogenic effect and is associated with increased longevity.

Being aware of this pervasive increase in estrogen exposure with aging should make it possible to marshal a comprehensive set of methods for opposing that trend toward degeneration.

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Contraception 1981 Apr;23(4):447-55. **Comparison of plasma and myometrial tissue concentrations of estradiol-17 beta and progesterone in nonpregnant women.** Akerlund M, Batra S, Helm G Plasma and myometrial tissue concentrations of estradiol (E2) and progesterone (P) were measured by radioimmunoassay techniques in samples obtained from women with regular menstrual cycles and from women in pre- or postmenopausal age. In women with regular cycles, the tissue concentration of E2 ranged from 0.13 to 1.06 ng/g wet weight, with significantly higher levels around ovulation than in follicular or luteal phases of the cycle. The tissue concentration of P ranged from 2.06 to 14.85 ng/g wet weight with significantly higher level in luteal phase than in follicular phase. The tissue/plasma ratio of E2 ranged from 1.45 to 20.36 with very high values in early follicular phase and the lowest in mid-luteal phase. The ratio for P ranged from 0.54 to 23.7 and was significantly lower in the luteal phase than in other phases of the cycle. One woman in premenopausal age with an ovarian cyst was the only case with a tissue/plasma ratio of E2 Less Than 1, since her plasma E2 levels were exceptionally high. In postmenopausal women, the tissue concentration of E2 was not significantly lower than in menstruating women in follicular phase, and the tissue concentration of P was not significantly lower than in fertile women in any of the phases. Neither in these women nor in menstruating women was there a close correlation between tissue and plasma levels. The present data indicate that the myometrial uptake capacity for ovarian steroids may be saturated, and also that a certain amount of these steroids is bound to tissue even if plasma levels are low.

Biokhimiia 1984 Aug;49(8):1350-6. **[The nature of thyroid hormone receptors. Translocation of thyroid hormones through plasma membranes].** Azimova ShS, Umarova GD, Petrova OS, Tukhtaev KR, Abdugarimov A **The in vivo translocation of thyroxine-binding blood serum prealbumin (TBPA) was studied. It was found that the TBPA-hormone complex penetrates-through the plasma membrane into the cytoplasm of target cells. Electron microscopic autoradiography revealed that blood serum TBPA is localized in ribosomes of target cells as well as in mitochondria, lipid droplets and Golgi complex. Negligible amounts of the translocated TBPA is localized in lysosomes of the cells insensitive to thyroid hormones (spleen macrophages). Study of T4- and T3-binding proteins from rat liver cytoplasm demonstrated that one of them has the antigenic determinants common with those of TBPA. It was shown autoimmunoradiographically that the structure of TBPA is not altered during its translocation.**

Biokhimiia 1985 Nov;50(11):1926-32. **[The nature of thyroid hormone receptors. Intracellular functions of thyroxine-binding prealbumin]** Azimova ShS; Normatov K; Umarova GD; Kalontarov AI; Makhmudova AA **The effect of thyroxine-binding prealbumin (TBPA) of blood serum on the template activity of chromatin was studied. It was found that the values of binding constants of TBPA for T3 and T4 are 2×10^{-11} M and 5×10^{-10} M, respectively. The receptors isolated from 0.4 M KCl extract of chromatin and mitochondria as well as hormone-bound TBPA cause similar effects on the template activity of chromatin. Based on experimental results and the previously published comparative data on the structure of TBPA, nuclear, cytoplasmic and mitochondrial receptors of thyroid hormones as well as on translocation across the plasma membrane and intracellular transport of TBPA, a conclusion was drawn, which suggested that TBPA is the "core" of the true thyroid hormone receptor. It was shown that T3-bound TBPA caused histone H1-dependent conformational changes in chromatin. Based on the studies with the interaction of the TBPA-T3 complex with spin-labeled chromatin, a scheme of functioning of the thyroid hormone nuclear receptor was proposed.**

Biokhimiia 1984 Sep;49(9):1478-85 **[The nature of thyroid hormone receptors. Thyroxine- and triiodothyronine-binding proteins of mitochondria]** Azimova ShS; Umarova GD; Petrova OS; Tukhtaev KR; Abdugarimov A. **T4- and T3-binding proteins of rat liver were studied. It was found that the external mitochondrial membranes and matrix contain a protein whose electrophoretic mobility is similar to that of thyroxine-binding blood serum prealbumin (TBPA) and which binds either T4 or T3. This protein is precipitated by monospecific antibodies against TBPA. The internal mitochondrial membrane has two proteins able to bind thyroid hormones, one of which is localized in the cathode part of the gel and binds only T3, while the second one capable of binding T4 rather than T3 and possessing the electrophoretic mobility similar to that of TBPA. Radioimmunoprecipitation with monospecific antibodies against TBPA revealed that this protein also the antigenic determinants common with those of TBPA. The in vivo translocation of ¹²⁵I-TBPA into submitochondrial fractions was studied. The analysis of densitograms of submitochondrial protein fraction showed that both TBPA and hormones are localized in the same protein fractions. Electron microscopic autoradiography demonstrated that ¹²⁵I-TBPA enters the cytoplasm through the external membrane and is localized on the internal mitochondrial membrane and matrix.**

Biokhimiia 1984 Aug;49(8):1350-6. **[The nature of thyroid hormone receptors. Translocation of thyroid hormones through plasma membranes]** Azimova ShS; Umarova GD; Petrova OS; Tukhtaev KR; Abdugarimov A **The in vivo translocation of thyroxine-binding blood serum prealbumin (TBPA) was studied. It was found that the TBPA-hormone complex penetrates-through the plasma membrane into the cytoplasm of target cells. Electron microscopic autoradiography revealed that blood serum TBPA is localized in ribosomes of target cells as well as in mitochondria, lipid droplets and Golgi complex. Negligible amounts of the translocated TBPA is localized in lysosomes of the cells insensitive to thyroid hormones (spleen macrophages). Study of T4- and T3-binding proteins from rat liver cytoplasm demonstrated that one of them has the antigenic determinants common with those of TBPA. It was shown autoimmunoradiographically that**

the structure of TBPA is not altered during its translocation.

Probl Endokrinol (Mosk), 1981 Mar-Apr, 27:2, 48-52. **[Blood estradiol level and G2-chalone content in the vaginal mucosa in rats of different ages]** Anisimov VN; Okulov VB. **"17 beta-Estradiol level was higher in the blood serum of rats aged 14 to 16 months with regular estral cycles during all the phases as compared to that in 3- to 4-month-old female rats.** The latter ones had a higher vaginal mucosa G2-chalone concentration. The level of the vaginal mucosa G2-chalone decreased in young rats 12 hours after subcutaneous benzoate-estradiol injection. . . .". "Possible role of age-associated disturbances of the **regulatory cell proliferation stimulant (estrogen) and its inhibitor (chalone) interactions in neoplastic target tissue transformation is discussed."**

Clin Endocrinol (Oxf) 1979 Dec;11(6):603-10. **Interrelations between plasma and tissue concentrations of 17 beta-oestradiol and progesterone during human pregnancy.** Batra S, Bengtsson LP, Sjoberg NO Oestradiol and progesterone concentration in plasma, decidua, myometrium and placenta obtained from women undergoing Caesarian section at term and abortion at weeks 16-22 of pregnancy were determined. There was a significant increase in oestradiol concentration (per g wet wt) both in placenta, decidua and myometrium from mid-term to term. **Both at mid-term and term oestradiol concentrations in decidua and myometrium were much smaller than those in the plasma (per ml).** Progesterone concentration in placenta and in myometrium did not increase from mid-term to term where it increased significantly in decidua. **Decidual and myometrial progesterone concentrations at mid-term were 2-3 times higher than those in plasma,** but at term the concentrations in both these tissues were lower than in plasma. The ratio **progesterone/oestradiol in plasma, decidua, myometrium and placenta at mid-term was 8.7, 112.2, 61.4 and 370.0,** respectively, and it decreased significantly in the myometrium and placenta but was nearly unchanged in plasma and decidua at term. The general conclusion to be drawn from the present study is **the lack of correspondence between the plasma concentrations and the tissue concentrations of female sex steroids during pregnancy.**

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Am J Obstet Gynecol 1980 Apr 15;136(8):986-91. **Female sex steroid concentrations in the ampullary and isthmic regions of the human fallopian tube and their relationship to plasma concentrations during the menstrual cycle.** Batra S, Helm G, Owman C, Sjoberg NO, Walles B. The concentrations of estradiol-17 beta (E2) and progesterone (P) were measured in the ampullary and isthmic portions of the fallopian tube of nonpregnant menstruating women and the cyclic fluctuations were related to the concentrations of these hormones in plasma. The steroid concentrations were determined by radioimmunoassays. There was no significant difference in the isthmic and ampullary concentrations of either steroid in any of the menstrual phases. The mean value for E2 was highest in the ovulatory phase and for P during the luteal phase. The tissue (per gm)/plasma (per ml) ratio for the steroid concentrations was above unity in all measurements. The ratio for E2 was highest (isthmus:12, ampulla:8) in the follicular phase and for P (isthmus:26, ampulla:18) during ovulation. Since **these highest ratios were attained when plasma steroid concentrations were relatively low they were interpreted as reflections of a maximal receptor contribution.**

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ARO, presumably at the transcriptional level."

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Biol Reprod, 1993 Oct, 49:4, 647-52. **Pathologic effect of estradiol on the hypothalamus**. Brawer JR; Beaudet A; Desjardins GC; Schipper HM. Estradiol provides physiological signals to the brain throughout life that are indispensable for the development and regulation of reproductive function. In addition to its multiple physiological actions, we have shown that estradiol is also selectively cytotoxic to beta-endorphin neurons in the hypothalamic arcuate nucleus. The mechanism underlying this neurotoxic action appears to involve the conversion of estradiol to catechol estrogen and subsequent oxidation to o-semiquinone free radicals. The estradiol-induced loss of beta-endorphin neurons engenders a compensatory increment in mu opioid binding in the medial preoptic area rendering this region supersensitive to residual beta-endorphin or to other endogenous opioids. The consequent persistent opioid inhibition results in a cascade of neuroendocrine deficits that are ultimately expressed as a chronically attenuated plasma LH pattern to which the ovaries respond by becoming anovulatory and polycystic. This neurotoxic action of estradiol may contribute to a number of reproductive disorders in humans and in animals in which aberrant hypothalamic function is a major component.

Mech Ageing Dev, 1991 May, 58:2-3, 207-20. **Exposure to estradiol impairs luteinizing hormone function during aging**. Collins TJ; Parkening TA Department of Anatomy and Neurosciences, University of Texas Medical Branch, Galveston 77550. "This work evaluated the anterior pituitary (AP) component of the H-P axis by determining the ability of perfused AP to release LH following sustained but pulsatile LHRH stimulation. The normal dual discharge profile of LH was affected by age." **"The role of estradiol (E2) in AP aging was further tested as AP from ovariectomized (OVXed) mice, deprived of E2 since puberty, responded as well as the mature proestrous group. In contrast, aged mice subjected to long-term E2 exposure (cycling or OVXed plus E2 replacement) failed to produce the dual response pattern."** "Furthermore, E2 is a major factor in altering LH function and appears to act before middle age."

Mech Ageing Dev 1975 Jan-Feb;4(1):19-28. **Lysosomal enzymes and aging in vitro: subcellular enzyme distribution and effect of hydrocortisone on cell life-span**. Cristofalo VJ, Kabakjian J. "The acid phosphatase and beta glucuronidase activities of four subcellular fractions (nuclear, mitochondrial-lysosomal, microsomal, supernatant) of WI-38 cells were compared during in vitro aging. All of the fractions showed an age-associated increase in activity."

Endocrinology, 1992 Nov, 131:5, 2482-4. **Vitamin E protects hypothalamic beta-endorphin neurons from estradiol neurotoxicity**. Desjardins GC; Beaudet A; Schipper HM; Brawer JR. Estradiol valerate (EV) treatment has been shown to result in the destruction of 60% of beta-endorphin neurons in the hypothalamic arcuate nucleus. Evidence suggests that the mechanism of EV-induced neurotoxicity involves the conversion of estradiol to catechol estrogen and subsequent oxidation to free radicals in local peroxidase-positive astrocytes. In this study, we examined whether treatment with the antioxidant, vitamin E, protects beta-endorphin neurons from the neurotoxic action of estradiol. Our results demonstrate that chronic vitamin E treatment prevents the decrement in hypothalamic beta-endorphin concentrations resulting from arcuate beta-endorphin cell loss, suggesting that the latter is mediated by free radicals. Vitamin E treatment also prevented the onset of persistent vaginal cornification and polycystic ovarian condition which have been shown to result from the EV-induced hypothalamic pathology.

Exp Gerontol, 1995 May-Aug, 30:3-4, 253-67. **Estrogen-induced hypothalamic beta-endorphin neuron loss: a possible model of hypothalamic aging**. Desjardins GC; Beaudet A; Meaney MJ; Brawer JR. Over the course of normal aging, all female mammals with regular cycles display an irreversible arrest of cyclicity at mid-life. Males, in contrast, exhibit gametogenesis until death. **Although it is widely accepted that exposure to estradiol throughout life contributes to reproductive aging, a unified hypothesis of the role of estradiol in reproductive senescence has yet to emerge.** Recent evidence derived from a rodent model of chronic estradiol-mediated accelerated reproductive senescence now suggests such a hypothesis. It has been shown that chronic estradiol exposure results in the **destruction of greater than 60% of all beta-endorphin neurons in the arcuate nucleus** while leaving other neuronal populations spared. This loss of opioid neurons is prevented by treatment with antioxidants indicating that it results from **estradiol-induced formation of free radicals. Furthermore, we have shown that this beta-endorphin cell loss is followed by a compensatory upregulation of mu opioid receptors in the vicinity of LHRH cell bodies.** The increment in mu opioid receptors presumably renders the opioid target cells supersensitive to either residual beta-endorphin or other endogenous mu ligands, such as met-enkephalin, thus resulting in chronic opioid **suppression of the pattern of LHRH release, and subsequently that of LH.** Indeed, prevention of the neuroendocrine effects of estradiol by antioxidant treatment also **prevents the cascade of neuroendocrine aberrations resulting in anovulatory acyclicity.** The loss of beta-endorphin neurons along with the paradoxical opioid supersensitivity which ensues,

provides a unifying framework in which to interpret the diverse features that characterize the reproductively senescent female.

Geburtshilfe Frauenheilkd 1994 Jun; 54(6):321-31. **Hormonprofile bei hochbetagten Frauen und potentielle Einflussfaktoren.** Eggert-Kruse W, Kruse W, Rohr G, Muller S, Kreissler-Haag D, Klinga K, Runnebaum B. **[Hormone profile of elderly women and potential modifiers].** Eggert-Kruse W, Kruse W, Rohr G, Muller S, Kreissler-Haag D, Klinga K, Runnebaum B. "In 136 women with a median age of 78 (60-98) years the serum concentrations of FSH, LH, prolactin, estradiol-17 beta, testosterone and DHEA-S were determined completed by GnRH and ACTH stimulation tests in a subgroup. This resulted in median values for FSH of 15.8 ng/ml, LH 6.4 ng/ml, prolactin 6.9 ng/ml, estradiol 16 pg/ml, testosterone 270 pg/ml and 306 ng/ml for DHEA-S. **No correlation with age in this population was found for gonadotropins as well as the other hormones for an age level of up to 98 years."**

Acta Physiol Hung 1985;65(4):473-8. **Peripheral blood concentrations of progesterone and oestradiol during human pregnancy and delivery.** Kauppila A, Jarvinen PA To evaluate the significance of progesterone and estradiol in human uterine activity during pregnancy and delivery the blood concentrations of these hormones were monitored weekly during the last trimester of pregnancy and at the onset of labour in 15 women, and before and 3 hours after the induction of term delivery in 83 parturients. Neither plasma concentrations of progesterone or estradiol nor the ratio of progesterone to estradiol changed significantly during the last trimester of pregnancy or at the onset of delivery. After the **induction of delivery parturients with initial progesterone dominance (ratio of progesterone to estradiol higher than 5 before induction) demonstrated a significant fall in serum concentration of progesterone and in the ratio of progesterone to estradiol while estradiol concentration rose significantly. In estrogen dominant women (progesterone to estradiol ratio equal to or lower than 5) the serum concentration of progesterone and the ratio of progesterone to estradiol rose significantly during the 3 hours after the induction of delivery.** Our results suggest that the peripheral blood levels of progesterone and estradiol do not correlate with the tissue biochemical changes which prepare the uterine cervix and myometrium for delivery. The observation that the ratio of progesterone to estradiol decreased in progesterone-dominant and increased in estrogen-dominant women stresses the importance of a well balanced equilibrium of these hormones for prostaglandin metabolism during human delivery.

Am J Obstet Gynecol 1984 Nov 1;150(5 Pt 1):501-5. **Estrogen and progesterone receptor and hormone levels in human myometrium and placenta in term pregnancy.** Khan-Dawood FS, Dawood MY. Estradiol and progesterone receptors in the myometrium, decidua, placenta, chorion, and amnion of eight women who underwent elective cesarean section at term were determined by means of an exchange assay. The hormone levels in the peripheral plasma and cytosol of these tissues were measured by radioimmunoassays. Maternal plasma and the placenta had high concentrations of estradiol and progesterone, with the placenta having 12 times more progesterone **than in maternal plasma but only half the concentrations of estradiol in maternal plasma.** The decidua and placenta had detectable levels of cytosol and nuclear estradiol receptors, but the myometrium had no measurable cytosol estradiol receptors, **whereas the chorion and amnion had neither cytosol nor nuclear estradiol receptors. However, the chorion and amnion had significantly higher concentrations of estradiol** in the cytosol than those in the decidua and myometrium. Only the decidua and myometrium had cytosol and nuclear progesterone receptors, but the placenta, amnion, and chorion had neither cytosol nor nuclear progesterone receptors. In contrast, progesterone hormone levels were significantly higher in the placenta, amnion, and chorion than in the decidua and myometrium. The findings indicate that, in the term pregnant uterus, (1) the placenta, amnion, and chorion are rich in progesterone, estradiol, and nuclear estradiol receptors but have no progesterone receptors, (2) the decidua and myometrium have nuclear estradiol and progesterone receptors, and (3) **the myometrium has a higher progesterone/estradiol ratio than that of the peripheral plasma, thus suggesting a highly progesterone-dominated uterus.**

Biochem Biophys Res Commun 1982 Jan 29;104(2):570-6. **Progesterone-induced inactivation of nuclear estrogen receptor in the hamster uterus is mediated by acid phosphatase.** MacDonald RG, Okulicz WC, Leavitt, W.W.

Steroids 1982 Oct;40(4):465-73. **Progesterone-induced estrogen receptor-regulatory factor is not 17 beta-hydroxysteroid dehydrogenase.** MacDonald RG, Gianferrari EA, Leavitt WW These studies were done to determine if the progesterone-induced estrogen receptor-regulatory factor (ReRF) in hamster uterus is 17 beta-hydroxysteroid dehydrogenase (17 beta-HSD), i.e. that rapid loss of nuclear estrogen receptor (Re) might be due to enhanced estradiol oxidation to estrone catalyzed by 17 beta-HSD. Treatment of proestrous hamsters with progesterone (approximately 25 mg/kg BW) for either 2 h or 4 h had no effect on 17 beta-HSD activity measured as the rate of conversion of [6,7-³H]estradiol to [3H]estrone by whole uterine homogenates at 35 degrees C. During this same time interval, progesterone treatment increased the rate of inactivation of the occupied form of nuclear Re as determined during a 30 min incubation of uterine nuclear extract in vitro at 36 degrees C. Since we previously demonstrated that such in vitro Re-inactivating activity represents ReRF, the present studies show that ReRF is not 17 beta-HSD or a modifier of that enzyme.

Am J Obstet Gynecol 1987 Aug; 157(2):312-317. **Age-related changes in the female hormonal environment during reproductive life.** Musey VC, Collins DC, Musey PI, Martino-Saltzman D, Preedy JR Previous studies have indicated that serum levels of

follicle-stimulating hormone rise with age during the female reproductive life, but the effect on other hormones is not clear. We studied the effects of age, independent of pregnancy, by comparing serum hormone levels in two groups of nulliparous, **premenopausal women aged 18 to 23 and 29 to 40 years. We found that increased age during reproductive life is accompanied by a significant rise in both basal and stimulated serum follicle-stimulating hormone levels. This was accompanied by an increase in the serum level of estradiol-17 beta and the urine levels of estradiol-17 beta and 17 beta-estradiol-17-glucosiduronate.** The serum level of estrone sulfate decreased with age. Serum and urine levels of other estrogens were unchanged. The basal and stimulated levels of luteinizing hormone were also unchanged. There was a significant decrease in basal and stimulated serum prolactin levels. Serum levels of dehydroepiandrosterone and dehydroepiandrosterone sulfate decreased with age, but serum testosterone was unchanged. It is concluded that significant age-related changes in the female hormonal environment occur during the reproductive years.

Endocrinology 1981 Dec;109(6):2273-5. **Progesterone-induced estrogen receptor-regulatory factor in hamster uterine nuclei: preliminary characterization in a cell-free system.** Okulicz WC, MacDonald RG, Leavitt WW. **"In vitro studies have demonstrated a progesterone-induced activity associated with the uterine nuclear fraction which resulted in the loss of nuclear estrogen receptor."** "This progesterone-dependent stimulation of estrogen receptor loss was absent when nuclear extract was prepared in phosphate buffer rather than Tris buffer. In addition, sodium molybdate and sodium metavanadate (both at 10 mM) inhibited this activity in nuclear extract. These observations support the hypothesis that progesterone modulation of estrogen action may be accomplished by induction (or activation) of an estrogen receptor-regulatory factor (Re-RF), and this factor may in turn **act to eliminate the occupied form of estrogen receptor from the nucleus**, perhaps through a hypothetical dephosphorylation-inactivation mechanism."

American Journal of Human Biology, v.8, n.6, (1996): 751-759. **Ovarian function in the latter half of the reproductive lifespan.** O'Rourke, M T; Lipson, S F; Ellison, P T. "Thus, ovarian endocrine function over the course of reproductive life represents a process of change, but not one of generalized functional decline."

J Gerontol, 1978 Mar, 33:2, 191-6. **Circulating plasma levels of pregnenolone, progesterone, estrogen, luteinizing hormone, and follicle stimulating hormone in young and aged C57BL/6 mice during various stages of pregnancy.** Parkening TA; Lau IF; Saksena SK; Chang MC Young (3-5 mo of age) and senescent (12-15 mo of age) multiparous C57BL/6 mice were mated with young males (3-6 mo of age) and the numbers of preimplantation embryos and implantation sites determined on days 1 (day of plug), 4, 9, and 16 of pregnancy. The numbers of viable embryos were significantly lower (p less than 0.02 to p less than 0.001) in senescent females compared with young females on all days except day 1 of pregnancy. Plasma samples tested by radioimmunoassay indicated circulating estradiol-17B was significantly lower (P less than 0.05) on day 1 and **higher (p less than 0.05) on day 4** in older females, whereas FSH was higher on days 4, 9, and 16 (p less than 0.02 to p less than 0.001) in senescent females when compared with samples from young females. Levels of pregnenolone, progesterone, estrone, and LH were not significantly different at any stage of pregnancy in the two age groups. From the hormonal data it did not appear that degenerating corpora lutea were responsible for the declining litter size in this strain of aged mouse.

Biol Reprod, 1985 Jun, 32:5, 989-97. **Orthotopic ovarian transplantations in young and aged C57BL/6J mice.** Parkening TA; Collins TJ; Elder FF. "Orthotopic ovarian transplantations were done between young (6-wk-old) and aged (17-mo-old) C57BL/6J mice. The percentages of mice mating following surgery from the four possible ovarian transfer combinations were as follows: young into young, 83%; **young into aged, 46%**; aged into young, 83%; and aged into aged, 36%." **"The only statistical differences found between the transfer groups occurred in FSH concentrations. Plasma FSH was markedly elevated (P less than 0.005) in young recipients with ovaries transplanted from aged donors, in comparison to young recipients with ovaries from young donors.** These data indicate that the aging ovary and uterus play a secondary role in **reproductive failure and that the aging hypothalamic-hypophyseal complex is primarily responsible for the loss of fecundity in older female C57BL/6J mice.**"

J Endocrinol, 1978 Jul, 78:1, 147-8. **Postovulatory levels of progestogens, oestrogens, luteinizing hormone and follicle-stimulating hormone in the plasma of aged golden hamsters exhibiting a delay in fertilization.** Parkening TA; Saksena SK; Lau IF.

Biology of Reproduction, v.49, n.2, (1993): 387-392. **Controlled neonatal exposure to estrogens: A suitable tool for reproductive aging studies in the female rat.** Rodriguez, P; Fernandez-Galaz, C; Tejero, A. "The present study was designed to determine whether the modification of exposure time to large doses of estrogens provided a reliable model for early changes in reproductive aging." "Premature occurrence of vaginal opening was observed in all three estrogenized groups independently of EB exposure. However, females bearing implants for 24 h had first estrus at the same age as their controls and cycled regularly, and neither histological nor gonadal alterations could be observed at 75 days. Interestingly, they failed to cycle regularly at 5 mo whereas controls continued to cycle." "On the other hand, the increase of EB exposure (Ei5, EI) resulted in a gradual and significant delay in the onset of first estrus and in a high number of estrous phases, as frequently observed during reproductive decline. At 75 days, the ovaries of these last two groups showed a reduced number of corpora lutea and

an increased number of large follicles. According to this histological pattern, ovarian weight and progesterone (P) content gradually decreased whereas both groups showed higher estradiol (E-2) content than controls. This resulted in a **higher E-2:P ratio, comparable to that observed in normal aging rats.** The results allow us to conclude that the exposure time to large doses of estrogens is critical to the gradual enhancement of reproductive decline. Furthermore, exposures as brief as 24 h led to a potential early model for aging studies that will be useful to verify whether neuroendocrine changes precede gonadal impairment."

J Clin Endocrinol Metab 1996 Apr;81(4):1495-501. **Characterization of reproductive hormonal dynamics in the perimenopause.** Santoro N, Brown JR, Adel T, Skurnick JH. "Overall mean estrone conjugate excretion was greater in the perimenopausal women compared to that in the younger women [76.9 ng/mg Cr (range, 13.1-135) vs. 40.7 ng/mg Cr (range, 22.8-60.3); P = 0.023] and was similarly elevated in both follicular and luteal phases. Luteal phase pregnanediol excretion was diminished in the perimenopausal women compared to that in younger normal subjects (range for integrated pregnanediol, 1.0-8.4 vs. 1.6-12.7 microg/mg Cr/luteal phase; P = 0.015)." "We conclude that altered ovarian function in the perimenopause can be observed as early as age 43 yr and include hyperestrogenism, hypergonadotropism, and decreased luteal phase progesterone excretion. These hormonal alterations may well be responsible for the increased gynecological morbidity that characterizes this period of life."

Brain Res, 1994 Jul 25, 652:1, 161-3. **The 21-aminosteroid antioxidant, U74389F, prevents estradiol-induced depletion of hypothalamic beta-endorphin in adult female rats.** Schipper HM; Desjardins GC; Beaudet A; Brawer JR. "A single intramuscular injection of 2 mg estradiol valerate (EV) results in neuronal degeneration and beta-endorphin depletion in the hypothalamic arcuate nucleus of adult female rats." "The present findings support the hypothesis that the toxic effect of estradiol on hypothalamic beta-endorphin neurons is mediated by free radicals."

Clin Exp Obstet Gynecol 2000;27(1):54-6. **Hormonal reproductive status of women at menopausal transition compared to that observed in a group of midreproductive-aged women.** Sengos C, Iatrakis G, Andreacos C, Xygakis A, Papapetrou P. **CONCLUSION: The reproductive hormonal patterns in perimenopausal women favor a relatively hypergonadotropic hyper-estrogenic milieu.**

Endocr Relat Cancer 1999 Jun;6(2):307-14. **Aromatase overexpression and breast hyperplasia, an in vivo model-continued overexpression of aromatase is sufficient to maintain hyperplasia without circulating estrogens, and aromatase inhibitors abrogate these preneoplastic changes in mammary glands.** Tekmal RR, Kirma N, Gill K, Fowler K "To test directly the role of breast-tissue estrogen in initiation of breast cancer, we have developed the aromatase-transgenic mouse model and demonstrated for the first time that increased mammary estrogens resulting from the overexpression of aromatase in mammary glands lead to the induction of various preneoplastic and neoplastic changes that are similar to early breast cancer." "Our current studies show aromatase overexpression is sufficient to induce and maintain early preneoplastic and neoplastic changes in female mice without circulating ovarian estrogen. Preneoplastic and neoplastic changes induced in mammary glands as a result of aromatase overexpression can be completely abrogated with the administration of the aromatase inhibitor, letrozole. Consistent with complete reduction in hyperplasia, we have also seen downregulation of estrogen receptor and a decrease in cell proliferation markers, suggesting aromatase-induced hyperplasia can be treated with aromatase inhibitors. Our studies demonstrate that **aromatase overexpression alone, without circulating estrogen, is responsible for the induction of breast hyperplasia and these changes can be abrogated using aromatase inhibitors.**"

J Steroid Biochem Mol Biol 2000 Jun;73(3-4):141-5. **Elevated steroid sulfatase expression in breast cancers.** Utsumi T, Yoshimura N, Takeuchi S, Maruta M, Maeda K, Harada N. In situ estrogen synthesis makes an important contribution to the high estrogen concentration found in breast cancer tissues. Steroid sulfatase which hydrolyzes several sulfated steroids such as estrone sulfate, dehydroepiandrosterone sulfate, and cholesterol sulfate may be involved. In the present study, we therefore, assessed steroid sulfatase mRNA levels in breast malignancies and background tissues from 38 patients by reverse transcription and polymerase chain reaction. The levels in breast cancer tissues were significantly increased at 1458.4+/-2119.7 attomoles/mg RNA (mean +/- SD) as compared with 535.6+/-663.4 attomoles/mg RNA for non-malignant tissues (P<0.001). Thus, increased steroid sulfatase expression may be partly responsible for local overproduction of estrogen and provide a growth advantage for tumor cells.

Ann N Y Acad Sci 1986;464:106-16. **Uptake and concentration of steroid hormones in mammary tissues.** Thijssen JH, van Landeghem AA, Poortman J In order to exert their biological effects, steroid hormones must enter the cells of target tissues and after binding to specific receptor molecules must remain for a prolonged period of time in the nucleus. Therefore the endogenous levels and the subcellular distribution of estradiol, estrone, DHEAS, DHEA and 5-Adiol were measured in normal breast tissues and in malignant and nonmalignant breast tumors from pre- and postmenopausal women. For estradiol the highest tissue levels were found in the malignant samples. **No differences were seen in these levels between pre- and postmenopausal women despite the largely different peripheral blood levels.** For estrone no differences were found between the tissues studied. Although the estradiol concentration was higher in the estradiol-receptor-positive than in the receptor-negative tumors, no correlation was

calculated between the estradiol and the receptor consent. Striking differences were seen between the breast and uterine tissues for the total tissue concentration of estradiol, the ratio between estradiol and estrone, and the subcellular distribution of both estrogens. **At similar receptor concentrations in the tissues these differences cannot easily be explained.** Regarding the androgens, the tissue/plasma gradient was higher for DHEA than for 5-Adiol, and for DHEAS there was very probably a much lower tissue gradient. The highly significant correlation between the androgens suggests an intracellular metabolism of DHEAS to DHEA and 5-Adiol. **Lower concentrations of DHEAS and DHEA were observed in the malignant tissues compared with the normal ones and the benign lesions.** For 5-Adiol no differences were found and therefore these data do not support our original hypothesis on the role of this androgen in the etiology of breast abnormalities. Hence the way in which adrenal androgens express their influence on the breast cells remains unclear.

Clin Endocrinol (Oxf) 1978 Jul;9(1):59-66. **Sex hormone concentrations in post-menopausal women.** Vermeulen A, Verdonck L. "Plasma sex hormone concentrations (testosterone, (T), androstenedione (A), oestrone (E1) and oestradiol (E2) were measured in forty post-menopausal women more than 4 years post-normal menopause." **"Sex hormone concentrations in this group of postmenopausal women (greater than 4YPM) did not show any variation as a function of age,** with the possible exception of E2 which showed a tendency to decrease in the late post-menopause. E1 and to a lesser extent E2 as well as the E1/A ratio were significantly correlated with degree of obesity or fat mass, suggesting a possible role of fat tissue in the aromatization of androgens. Neither the T/A nor the E2/E1 ratios were correlated with fat mass, suggesting that the reduction of 17 oxo-group does not occur in fat tissue. The E1/A ratio was significantly higher than the reported conversion rate of A in E1."

J Steroid Biochem 1984 Nov;21(5):607-12. **The endogenous concentration of estradiol and estrone in normal human postmenopausal endometrium.** Vermeulen-Meiners C, Jazmann LJ, Haspels AA, Poortman J, Thijssen JH The endogenous estrone (E1) and estradiol (E2) levels (pg/g tissue) were measured in 54 postmenopausal, atrophic endometria and compared with the E1 and E2 levels in plasma (pg/ml). The results from the tissue levels of both steroids **showed large variations and there was no significant correlation with their plasma levels. The mean E2 concentration in tissue was 420 pg/g, 50 times higher than in plasma and the E1 concentration of 270 pg/g was 9 times higher.** The E2/E1 ratio in tissue of 1.6, was higher than the corresponding E2/E1 ratio in plasma, being 0.3. **We conclude that normal postmenopausal atrophic endometria contain relatively high concentrations of estradiol and somewhat lower estrone levels.** These tissue levels do not lead to histological effects.

J Clin Endocrinol Metab 1998 Dec; 83(12):4474-80. **Deficient 17beta-hydroxysteroid dehydrogenase type 2 expression in endometriosis: failure to metabolize 17beta-estradiol.** Zeitoun K, Takayama K, Sasano H, Suzuki T, Moghrabi N, Andersson S, Johns A, Meng L, Putman M, Carr B, Bulun SE. "Aberrant aromatase expression in stromal cells of endometriosis gives rise to conversion of circulating androstenedione to estrone in this tissue, whereas aromatase expression is absent in the eutopic endometrium. In this study, we initially demonstrated by Northern blotting transcripts of the reductive 17beta-hydroxysteroid dehydrogenase (17betaHSD) type 1, which catalyzes the conversion of estrone to 17beta-estradiol, in both eutopic endometrium and endometriosis. **Thus, it follows that the product of the aromatase reaction, namely estrone, that is weakly estrogenic can be converted to the potent estrogen, 17beta-estradiol, in endometriotic tissues. It was previously demonstrated that progesterone stimulates the inactivation of 17beta-estradiol through conversion to estrone in eutopic endometrial epithelial cells."** **"In conclusion, inactivation of 17beta-estradiol is impaired in endometriotic tissues due to deficient expression of 17betaHSD-2, which is normally expressed in eutopic endometrium in response to progesterone."**

Biochem Biophys Res Commun 1999 Aug 2;261(2):499-503. **Piceatannol, a stilbene phytochemical, inhibits mitochondrial F0F1-ATPase activity by targeting the F1 complex.** Zheng J, Ramirez VD.

Eur J Pharmacol 1999 Feb 26;368(1):95-102. **Rapid inhibition of rat brain mitochondrial proton F0F1-ATPase activity by estrogens: comparison with Na+, K+ -ATPase of porcine cortex.** Zheng J, Ramirez VD. "The data indicate that the ubiquitous mitochondrial F0F1-ATPase is a specific target site for estradiol and related estrogenic compounds; however, under this in vitro condition, the effect seems to require pharmacological concentrations."

J Steroid Biochem Mol Biol 1999 Jan;68(1-2):65-75. **Purification and identification of an estrogen binding protein from rat brain: oligomycin sensitivity-conferring protein (OSCP), a subunit of mitochondrial F0F1-ATP synthase/ATPase.** Zheng J, Ramirez VD. "This finding opens up the possibility that estradiol, and probably other compounds with **similar structures, in addition to their classical genomic mechanism, may interact with ATP synthase/ATPase by binding to OSCP, and thereby modulating cellular energy metabolism."**