PROGESTERONE IN ORTHOMOLECULAR MEDICINE

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PROGESTERONE IN ORTHOMOLECULAR MEDICINE
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PROGESTERONE'S BIOLOGICAL GENERALITY

1. Intrinsic general properties.

All of the steroid functions, except those of estrogen and testosterone, are included, though weakly, in the progesterone molecule itself. These include lysosome stabilization, salt regulation, blood sugar elevation, and anesthesia (or, in physiological amounts, modulation of nerve functions). It is unusual among the steroids in promoting enlargement, rather than atrophy, of the thymus gland. Progesterone, like testosterone is anti-estrogenic.

A weak hormone activity in the absence of the stronger hormone will act as a substitute, but in the presence of the stronger hormone will weaken the strong hormone's effect by competition or "dilution" at the point of action, and possibly by suppressing the trophic pituitary agent which regulates synthesis. By thus opposing both deficiencies and excesses, such a hormone will tend to protect against pathological extremes. There is, for example, supposed to be competition between progesterone and aldosterone for the "aldosterone receptors" which cause water retention by the kidneys, so that in many situations, progesterone will relieve edema; but when the adrenal cortex is removed or fails to function (as in Addison's disease), progesterone will promote relatively normal retention of sodium and water, keeping the individual alive as long as large doses are given regularly.

Some hormones which are both progestins and anti-testosterones seem to work both at the tissue "receptor" level, and at the pituitary level. Though progesterone itself will suppress menopausal pituitary gonadotrophins, and (my observations) reduces excessive facial hair, it has not been found to have anti-testosterone effects in men when used in low doses, and in appropriate doses it can improve sexual functions in some impotent men who are deficient in progesterone. Pregnenolone (produced from cholesterol in the mitochondria), which is the precursor to progesterone and other steroids, has been used successfully to restore fertility (sperm count and motility, and, according to the wives--libido) in men.

All of the natural steroids have functions that overlap to some extent--e.g., testosterone has some progestational function--but progesterone's generality is the most remarkable.

2. Steroid precursor function.

The second aspect of progesterone's biological generality, besides its intrinsic hormonal activity, is its role as precursor for all of the other steroid hormones (see chart). When consumed in food (e.g., butter, brains, milk, ovaries--some cultures eat pork ovaries, many eat sea-urchin ovaries), it, like cholesterol, only more efficiently, enters the cycle of steroid synthesis near the beginning, so that it is a raw material, allowing normal amounts of the other hormones to be produced. This aspect of progesterone distinguishes it most strongly from the other progestins (e.g., medroxyprogesterone), which have had atoms introduced at unusual positions to inhibit metabolism and prolong activity (as well as to create a patentable and thus highly profitable substance). When we eat protein, we support the production of all the peptide

hormones; likewise, natural progesterone (and pregnenolone, which is also found in brains, endocrine glands, and probably skin) serves to allow the body to produce an appropriate and balanced amount of all the other steroid hormones.

3. Anti-estrogen functions.

A third aspect of progesterone's generality is a little less clear than its intrinsic generality and its function as a general steroid precursor, because this third form has to do with its overall antagonism to estrogen, and gains significance only to the extent that we see estrogen as having a very broad physiological role--for males as well as for females. I will just mention some of the many effects of estrogen, and some reasons for its ubiquity.

Estrogen causes water retention, even when dietary salt is restricted; hyposmotic blood has been observed under estrogen influence.

Estrogen causes "erasure" of memory, as does prolactin, which is formed under the influence of estrogen.

Estrogen promotes the formation of prolactin, which normally increases with aging and stress, and which is a known contributor to osteoporosis.

Estrogen causes hypoxia at many levels--pulmonary diffusion, intracellular metabolism, and various points between.

Estrogen synergizes with insulin, lowering blood sugar, promoting fat synthesis.

Estrogen opposes actions of thyroxin, elevates the bound proportion, and blocks its secretion from the gland.

Estrogen causes reproductive aging, by exhausting neurons which regulate the pituitary.

Estrogen contributes to the risk of miscarriage and infertility.

Estrogen retards prenatal brain growth.
Estrogen promotes histamine release.
Estrogen shifts the balance of prostaglandins and cyclic nucleotides, important cellular regulators.
Estrogen and its metabolites are carcinogenic, in every sense of the word.
Estrogen promotes development of fibroids and many other kinds of tumor, including pituitary prolactin-secreting tumor.
Estrogen promotes blood clotting and increases embolism incidence.
Estrogen synergizes with adrenaline in causing vascular spasm.
Estrogen alters blood lipids and promotes gall bladder disease.
Estrogen accelerates the aging of collagen.
Estrogen mimics the shock phase of the stress reaction.
Estrogen is produced by many tissues--possibly by every tissue under certain circumstances. Stress hormones promote liver synthesis of estrogen.
Estrogen lowers the seizure threshold of nerve cells, increasing susceptibility to epileptic convulsions.
Estrogen shrinks the thymus, and contributes to many auto-immune conditions and tissue alterations including osteoarthritis.
Men and women, especially as they age, are susceptible to liver damage from toxins which can cause elevated estrogen levels by interfering with metabolism and excretion.
Malnutrition can cause signs of high estrogen.
Various physical factors, including ionizing radiation, mimic estrogen actions.
Many environmental pollutants--phenolic compounds, dioxins, PCBs, polycyclic hydrocarbons, chlorinated hydrocarbons, DDT, etc.--are estrogenic.

Estrogen promotes the retention of iron, which accumulates with aging and promotes the free-radical damage caused by stress.

In relating progesterone's effects to those of estrogen, we should avoid being misled by the opinions expressed in many textbooks, describing symptoms of the luteal phase of the menstrual cycle as symptoms "caused by progesterone." For example, many medical books promote the erroneous idea that progesterone causes edema, because edema often occurs during the luteal phase of the cycle, which is too often conceptualized as "the progesterone dominance phase." Actually, this is the time when the estrogen/progesterone ratio frequently reaches its pathological height, for four common reasons:

1. failure to eliminate estrogen;
2. failure to produce enough progesterone;
3. overproduction of estrogen;
4. excessive metabolism of progesterone.

Failure of the liver to metabolize or detoxify estrogen is equivalent to the older idea of an "elevated kidney threshold for estrogen," which was proposed as the cause of the "pre-menstrual syndrome."[1] Probably the main reason for liver sluggishness (apart from the direct action of estrogen itself, discussed in liver monographs, and often noticed in the post-ovulatory increase of susceptibility to intoxication by alcohol or other chemicals) is low thyroid, which itself is related to estrogen--about five times more women have thyroid abnormalities than men. Protein deficiency has been shown to cause the liver to fail to detoxify estrogen.[2]

Thyroid therapy normally increases assimilation of nutrients and stimulates synthesis of steroids though it

lowers estrogen by promoting its metabolism in the liver. However, it increases metabolic activity systemically and can exacerbate a nutritional deficiency or a failure of steroidogenic tissue, so thyroid therapy should always be accompanied by nutritional optimization, and sometimes should be used with a steroid, preferably progesterone, to promote adrenal and other glandular function. Thyroid hormone is one of the essential factors for the conversion of cholesterol to progesterone. Progesterone promotes its own synthesis, and provides stability during adaptation.

Failure of the corpus luteum to produce adequate quantities of progesterone has been observed under various circumstances. A lack of vitamin A, and reduced circulation resulting from the prostaglandin F_2 (resulting from estrogen action, or from uterine irritation) have been proposed as causes of luteal failure.[3] There is no doubt that vitamin A is essential for the conversion of cholesterol to progesterone; its action can be competitively blocked by an excess of carotene. Luteolysis has been demonstrated to result from uterine irritation by a foreign object.[4] A uterine infection probably would have the same effect. (Penicillin has been found to relieve PMS, but the mechanism by which it increases progesterone and decreases estrogen and cortisone isn't clear, and probably involves endotoxin and the liver.) The IUD often causes the same kind of symptoms as the oral contraceptive pill--obesity, depression, etc., and this seems to be the result of progesterone deficiency from luteolysis. An excess of prolactin, which is now recognized as a sequel to use of the estrogen contraceptive pill (estrogen induces mitoses in the prolactin secreting pituitary cells) has been found to block progesterone synthesis. (Incidentally, Korenchevsky demonstrated 50 years ago that progesterone would cause regression of the estrogen-induced pituitary tumor.) Logically, since it isn't desirable to get pregnant during stress, the stress hormones ACTH and cortisone inhibit

progesterone production. Lack of sunlight, short photoperiod, or staying indoors can probably contribute to a progesterone deficiency, since both progesterone and testosterone synthesis (the latter in men) are increased in summer.

Excessive production of estrogen can result from a large mass of adipose tissue, or from a sick liver.[5] Olfactory stimuli seem to increase estrogen production in female mice, sufficient to induce spontaneous abortion; pheromonal activation of estrogen synthesis in humans might be another possible cause of estrogen excess.[6] Stress is probably a common cause of elevated estrogen especially when it is prolonged enough to cause significant protein loss. Stress also stimulates liver estrogen synthesis.[7]

Excessive metabolism of progesterone, e.g., by its conversion to cortisol and other anti-stress hormones, can probably explain the increasingly common observations of "athlete's amenorrhea" and the development of excess facial hair in some women working under pressure (the alternate hormonal disturbance in stress appears to result in obesity).[8] Besides losing the effects of progesterone on the endometrium, pituitary gonadotrophins would be increased, and would drive various synthetic pathways at a higher rate, shifting the ratio of progesterone to other hormones, but I do not think the ovaries have been studied very much during ordinary stress. (In the stress of ionizing radiation, the ovaries produce excessive estrogen; with the stress of high levels of gonadotrophins, they tend to be cancerized.)
While large doses of progesterone have been shown to have anti-stress effects without harming the adrenals (and probably protecting them, by lowering the demand for adrenal hormones), large doses of estrogen were found to destroy certain areas of the adrenal cortex,[9] possibly in a reaction similar to luteolysis by estrogen.

4. Effects on development.

The three aspects of progesterone's biological generality discussed above disregard the time dimension, i.e., the effect of progesterone on the developing organism, which is, according to popular belief (deriving largely from its name), its only role. All of the points discussed above are relevant to the developing organism. For example, the fetus is highly dependent on glucose for growth--especially brain growth--and the oxygen supply and maternal metabolism both affect the glucose supply.

Animal studies have shown that an excess of estrogen, late in the gestation period, like oxygen deprivation and insulin-induced hypoglycemia, can cause brain damage, in the form of reduced cell number and brain weight. Stress during pregnancy can produce (apparently hormonal) defects in the offspring.[10] L. C. Strong showed transgenerational effects, apparently acting through hormone balance, in his cancer-prone (high-estrogen) mice which were treated with a liver extract (personal communication). Many older studies showed transgenerational effects which I believe can be traced to gestational hormonal modification, affecting metabolism at a variety of levels, including the liver. For example, feeding thymus to rats for several generations caused each generation to be more precocious in development. The known transgenerational influences of starvation (Zamenhoff, et al.,[11] with rats, and more recently--1978--in human studies) are similar to the first generation effects of estrogen or hypoglycemia. I suspect that these effects are part of a general system of physiologically adjusting the metabolism of offspring to the availability of nutrients.

One of the physiological effects of progesterone is its support of the thymus (opposing the effects of glucocorticoids and sex steroids). In animal experiments (dog and rat), results so far indicate that the same types of precocity are induced by progesterone in these animals as were reported for thymus feeding.[12] Dalton's (and others') studies in humans show the same generalized precocity, except that in humans the intellectual precocity is the most noticeable. Rat studies show that increased prenatal exposure to progesterone increases rats' learning ability and the thickness of their cerebral cortex, but the scientific community's lack of interest in these studies has been great. The owner of an afghan dog which gestated with extra progesterone commented that the dog had learned to retrieve a stick by watching another dog, while "normal" afghans dislike learning anything, especially retrieving (though they have a remarkable geographic memory).

Since the brain is dependent on glucose for its growth, the ability of progesterone to promote maternal fat metabolism and to spare glucose (elevating blood glucose) for fetal use is a logical part of its role as a gestational hormone. Other pregnancy hormones, including "placental lactogen," also promote elevation of blood glucose.

I propose that there is a "developmental trajectory" (analogous to a ballistic trajectory) which is set by the availability of biological energy during gestation, and that we could, by measuring brain weight and the ratio of brain weight to body weight during gestation, predict (given stable post-natal conditions for growth) such things as the ages at puberty, full growth, and approximate lifespan. Good prenatal conditions would increase the rate of development (IQ, etc.), but would delay maturity, allowing achievement of a higher level of development by the rapid and prolonged development of higher abilities. Bright

people develop faster than dull people, but bright monkeys, at first, develop even faster (see chart). Our species characteristics would include setting the angle of our developmental trajectory, but the availability of biological energy during gestation determines the rate of ascent and the "altitude" achieved, as the explosive charge determines velocity and altitude of a ballistic trajectory. The effect of nutrition on brain size is known, as are the relationships between relative brain weight and life-span[13] and between rate of sexual development and life-span (Strong, and others), so what I am suggesting is simply that the amount of energy early in life might organize in an orderly way the timing of, and quality of, development throughout the rest of one's life.

A "Medical News" item in a 1976 issue of the J.A.M.A.[14] reports a study showing that progesterone probably plays a critical role in preventing rejection of the fetus by the mother. In reviewing the scientific and medical literature, I have found no side effects attributed to natural progesterone, except for sometimes altering the menstrual rhythm temporarily. Its use before and during pregnancy is associated with a reduced incidence of birth defects. (Since all of the drugs used to treat epilepsy are known to cause birth defects, it would certainly seem reasonable to take advantage of progesterone's anti-seizure effect, especially during pregnancy. It wouldn't be hard to ascribe liability for the prenatal injury of thousands of people, to the pharmaceutical industry and regulatory agencies, who seem to conspire to keep this information away from the medical profession.) Some publications fail to distinguish between natural progesterone and the frequently harmful synthetic progestins.

Some recent animal studies are showing that prenatal progesterone increased body size, but even more, it

increased brain size, for an improved brain/body ratio. First, it was established that good prenatal nutrition produced big, healthy babies with big heads, high intelligence, and good disposition. Then, experiments with rats showed that prenatal treatment with prolactin, which stimulates progesterone synthesis in that species (but blocks it in humans) produced large brained, intelligent animals (95th percentile for brain size and intelligence). It has since been established that a large brain is associated with a long life span.

Prenatal stress produces many minor physical "stigmata," and these have been shown to be associated with hyperactivity. Excess estrogen (and other toxins, and associated deficiencies) reduces brain size and damages behavior. (In animals, the effects of prenatal stress can be passed on to the third generation.)

Progesterone opposes estrogen, and promotes prenatal nutrition. Dalton's studies of babies whose mothers received natural progesterone showed greatly improved intelligence.[15] Another researcher, deliberately attempting to improve intelligence (Dalton simply intended to treat PMS and toxemia of pregnancy) claims "his" babies have a 200 IQ. Other investigators find that progesterone babies have strong, serene, independent characters.

There is increasing recognition that prenatal conditions, whether good or bad, can be passed on to at least one subsequent generation. A reduced ability to produce progesterone is probably often a consequence of prenatal stress, which can lead to pregnancy difficulties, and another stress-injured generation. I feel that progesterone can reverse the trend toward more hyperactive and brain damaged children, and that it can make a great contribution to the mental and physical health of future generations.

5. Progesterone and magnesium.

In considering the general biological effects of progesterone, it is interesting to compare some of its functions with those of the magnesium ion, and to contrast them with the effects of calcium and estrogen.[16] Uptake of magnesium is promoted by thyroid, and progesterone promotes thyroid function, while tending to block the stress-induced loss of magnesium. Estrogen increases the uptake of calcium.

Blood clotting (especially excessive): promoted by estrogen and calcium, restrained by magnesium and progesterone.

Blood sugar: depressed by estrogen and calcium, sustained by progesterone and magnesium.

Kidney function, diuresis: promoted by magnesium and progesterone, decreased by estrogen; excess calcium appears to damage kidneys.

Histamine release: decreased by progesterone and magnesium, increased by estrogen, and calcium probably facilitates it.

Phagocytosis and other immune functions: increased by magnesium and progesterone, decreased by estrogen; calcium is involved in triggering thymocyte death.

Glucagon: magnesium promotes, calcium inhibits.

Insulin: magnesium and progesterone restrain its secretion, calcium and estrogen promote it.

Vascular spasms: decreased by progesterone and magnesium, promoted by estrogen and calcium.

Vascular tone: stabilized by progesterone and magnesium, often decreased by estrogen, possibly acting through histamine, leading to the tendency of blood to pool in the legs. Estrogen is believed to contribute to varicose veins.

Nerve stabilization or anesthesia: magnesium and progesterone are anesthetic in very large amounts, and are

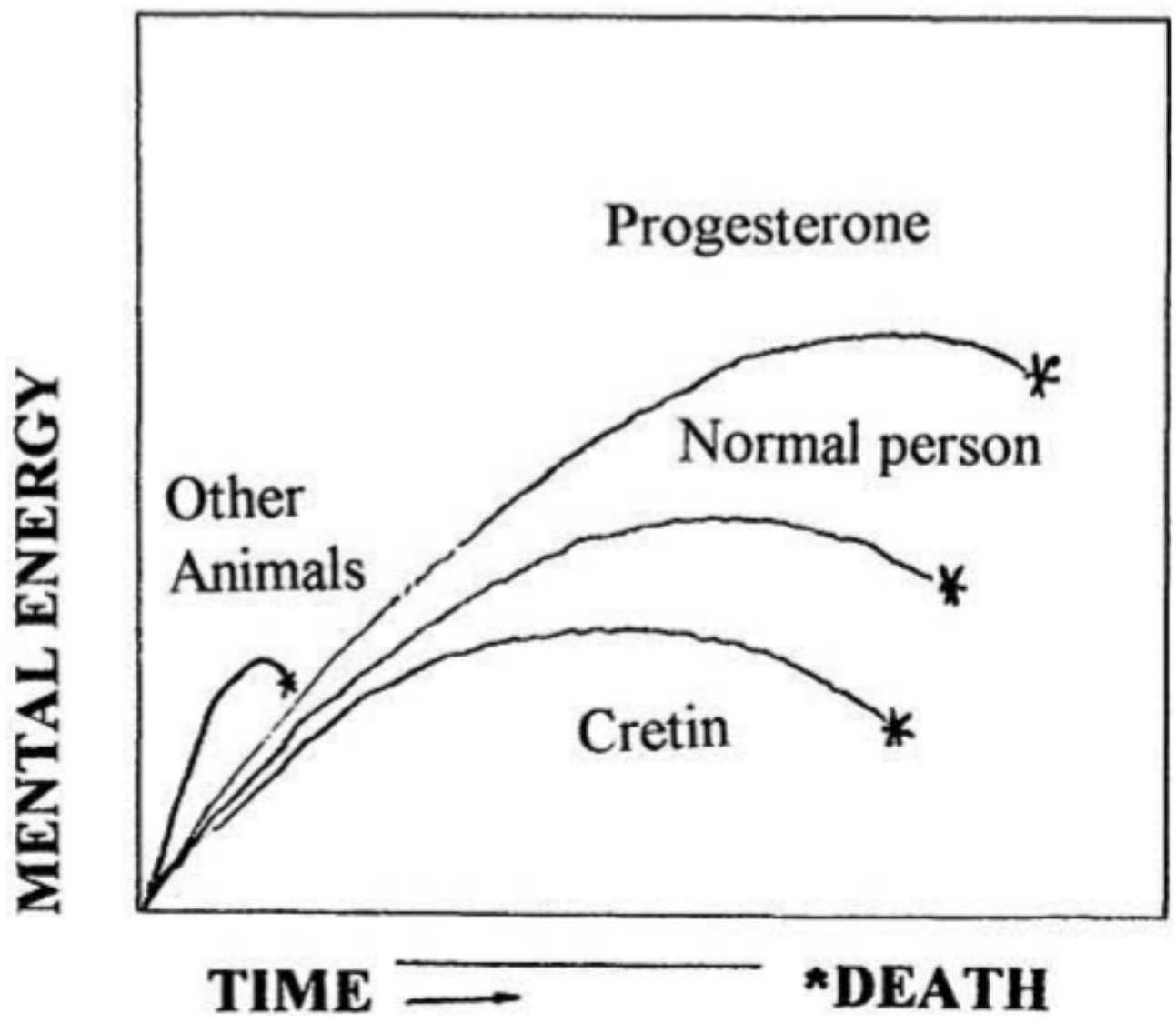
protective inhibitors in physiological amounts. Calcium opposes the anesthetic effect of magnesium, and is always involved in toxic or excitotoxic cell death. Estrogen even in physiological amounts is nerve-exciting, and eventually contributes to the excitotoxic death of brain cells.

Hans Selye demonstrated that calcification of various tissues (kidneys, blood vessels, and skin, for example) could be produced by interactions of stress and hormones. Selye and his associates, and F. Z. Meerson's group in Russia, have demonstrated numerous toxic interactions of iron, calcium, and unsaturated fats. Magnesium, vitamin E, thyroid, and progesterone tend to protect against those toxic effects.

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STEROIDS

This type of molecule might be the most common carbon compound in the universe. It is made by single celled organisms, by plants, and by animals, and has many kinds of function. The steroid hormones are involved in all aspects of animal physiology, and overlap with control functions of the nervous system, peptide hormones, metabolites, prostaglandins, cyclic nucleotides, etc. (I suspect that their ubiquity reflects a special kind of physical influence on biological water.) Sometimes people speak of "steroids" when they mean glucocorticoids such as cortisol or a synthetic like dexamethasone, or, among athletes, when they mean anabolic steroids or synthetic androgens; and so it is common to associate "steroids" with harmful side effects. All foods contain steroids and sterols (a major type, containing an alcohol group and a side-chain) some of which are beneficial and some of which are toxic or allergenic.

In animals, cholesterol is the basic sterol molecule, which is massively converted into other substances, including the steroid hormones. (In plants, cholesterol in very small amounts appears to serve as a hormone.) Thyroid hormone and vitamin A are required for this conversion. The first step occurs in the energy-producing mitochondrion, where cholesterol loses its side-chain and is slightly oxidized, producing pregnenolone. Being less fat soluble than cholesterol, pregnenolone leaves the mitochondrion, so it tends not to inhibit its own synthesis. Rather, it seems to stimulate its own synthesis, though this isn't as clearly established as in the case of progesterone.

Depending on the tissue, pregnenolone will be converted by enzymes in the cytoplasm into either

progesterone or DHEA (dehydroepiandrosterone). The fact that progesterone (and probably pregnenolone) stimulates its own synthesis means that taking it does not suppress the body's ability to synthesize it, as happens with cortisol. Sometimes, one dose or a few doses can restore the body's ability to produce enough of its own.

Progesterone also allows the thyroid gland to secrete its hormones, especially when the thyroid function has been inhibited by estrogen. Since the thyroid hormone is needed to produce progesterone, a supplement of either tends to normalize both thyroid and progesterone production.

Progesterone and DHEA are the precursors for the other more specialized steroid hormones, including cortisol, aldosterone (sodium-retaining hormone), estrogen, and testosterone. The formation of these other hormones is tightly regulated, so that taking the precursor will correct a deficiency of a specialized hormone, but will not create an excess. At least in the case of progesterone, an excess tends to balance or neutralize an excess of the specialized hormone, so it has been described as having anti-androgenic, anti-estrogen, anti-aldosterone, and anti-cortisol functions.

Many steroids have a protective ("catatoxic") action against a wide variety of poisons. Some of the quick effects (e.g., within 10 minutes) of progesterone and pregnenolone probably represent a catatoxic action, as well as a neutralizing or balancing of excessive estrogen or cortisol. Improved metabolic efficiency, sparing oxygen and glucose, will have a quick effect in reducing edema.

During pregnancy, very large amounts of progesterone are made. It protects and stabilizes practically

all functions of both the mother and the fetus.

Progesterone, glucose and the thyroid hormones powerfully influence the brain development and intelligence of the baby, probably by influencing both the number and the size of brain cells, and the quality of their functioning.

Part of progesterone's protective effect is a result of its quieting effect on cells. For example, it tends to prevent seizure activity in brain cells. During childbirth, its normal function is to act as an anesthetic. When the level of estrogen is too high, progesterone can't achieve this effect. In a non-pregnant person, it is important to determine the minimum effective dose by taking only a few drops at a time, and repeating this small dose about every 20 minutes until symptoms have been controlled. Otherwise, serious "drunkenness" can be produced, with loss of coordination, and even unconsciousness.

The only solvent for progesterone which isn't toxic and which will dissolve an effective quantity, is vitamin E. In this form, it can be absorbed through the skin or other membranes, or can be taken orally. Taken orally, it is absorbed as chylomicrons, going into the general circulation (as vitamin E does), instead of to the liver where it would be prepared for excretion. In this form, therefore, it is fully and quickly available to all tissues. It is approximately 20 times more powerful in its action than other preparations, so it is important to use it in physiological quantities, rather than in the huge doses commonly given rectally or by injection. Ten or 20 mg. is often an effective dose, though people with low thyroid or high estrogen sometimes use 50 to 100 mg. per day. In the customary 10% solution, one drop contains about 3 mg. progesterone, and 1 ml. (1/4 tsp.) contains 100 mg. The first dose should never be more than 15 mg.

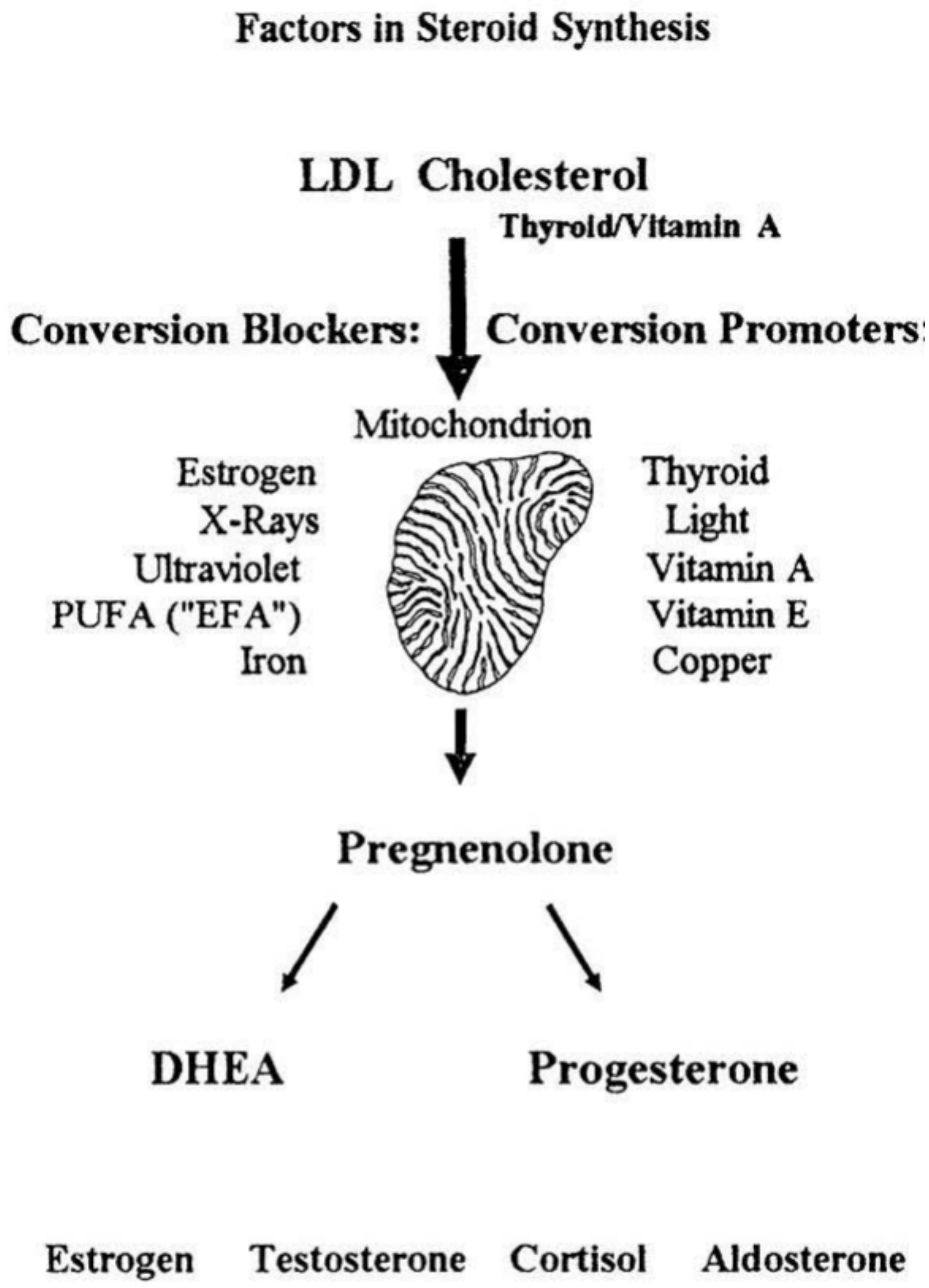
Pregnenolone, taken orally, does nothing noticeable to a healthy animal or person, but if the stress-related hormones are elevated, they return to normal when pregnenolone is taken. The brain contains much more pregnenolone, DHEA, and progesterone than do other organs or the blood, and these levels decrease progressively with age. Older people are more likely to feel an effect from pregnenolone, than are young people. A tenth of a gram is a reasonable first dose, though some people seem to need as much as 1 gram per day, possibly because of poor absorption. (The amount produced daily in a healthy young adult is roughly 30 mg.)

Normalizing the stress hormones with pregnenolone often seems to have the effect of correcting the function of the thyroid gland, probably because it is suppressed by stress. Since pregnenolone is the precursor for progesterone and DHEA (and all the other steroid hormones), it often has the same effects as progesterone or DHEA, and it has the advantage that it allows the body to produce just an optimum amount of those hormones. In very old people, or people with special enzyme deficiencies, it might be necessary to supplement all three to achieve their normal physiological concentration in the tissues.

Pregnenolone and progesterone are known to protect nerves against the damaging effects of the "excitotoxins," which activate nerve cells to the point of cumulative injury during stress and fatigue. The need for pregnenolone is probably what is described as "agitated depression," in which the person feels unable to cope with ordinary life, and when the body is unable to produce enough pregnenolone, the nervous-physiological distress leads to increased production of cortisol. The clinical depression, which so typically involves elevated cortisol production, is probably primarily a pregnenolone deficiency.

The active fraction of the thyroid hormone, triiodothyronine, or liothyronine (T_3), is essential for the conversion of cholesterol to pregnenolone, as is the retinol form of vitamin A. Butyric acid is known to facilitate the entry of T_3 into the mitochondrion.

Since progesterone and pregnenolone protect against the excitotoxins which damage neurons, and estrogen and cortisol promote excitotoxic damage, it seems reasonable to see this opposition as relating to their known physiological actions. For example, estrogen damages memory, and pregnenolone restores memory in old animals. Although the excitotoxins might not be involved in other organs, I suspect that something analogous (possibly the cyclic nucleotide ratio) is involved in the opposite effects of these substances on, for example, the thymus, vascular tone, and liver function.



Structural integrity of the mitochondria is essential for functional respiration and steroid synthesis. Coconut oil, thyroid hormone, pregnenolone, and progesterone stabilize mitochondrial structure.

THYROID

Measuring the amount of thyroid in the blood isn't a good way to evaluate adequacy of thyroid function, since the response of tissues to the hormone can be suppressed (for example, by unsaturated fats).

In the 1930s accurate diagnosis was made by evaluating a variety of indications, including basal oxygen consumption, serum cholesterol level, pulse rate, temperature, carotenemia, bowel function, and quality of hair and skin. A good estimate can be made using only the temperature and pulse rate. (Pulse rate should be thought of as an indicator of the rate of blood circulation, meaning that the strength of the pulse should increase with the rate; a rapid but weak, shock-like pulse gives useful information, but has a different meaning.)

Oral or armpit temperature, in the morning before getting out of bed, should be around 98 degrees F, and it should rise to 98.6° by mid-morning. This is not valid if you sleep under an electric blanket, or if the weather is hot and humid. A person who is hypothyroid produces heat at a low rate, but doesn't lose it at the normal rate, since there is less sweating, and the skin is relatively cool. Many hypothyroid people compensate with high adrenalin production (sometimes 40 times higher than normal), and this tends to keep the skin cool, especially on the hands, feet, and nose. The high adrenalin is the consequence of low blood glucose, so a feeding of carbohydrate, such as a glass of orange juice, will sometimes lower the pulse rate momentarily. Since thyroid is essential for producing progesterone, and progesterone is "thermogenic" in the sense of setting the temperature control system higher, the

body sometimes maintains a subnormal temperature even in warm weather, Healthy populations have an average resting pulse rate of about 85 per minute. Especially in hot weather it is useful to consider both temperature and pulse rate.

The Achilles tendon reflex is another quick way to estimate thyroid function. This reflex is used because of the insignificant weight of the toes in relation to contraction of the gastrocnemius muscle. The T (repolarization) wave on the electrocardiogram is a similar indicator of the rate of energy production. Thumping the Achilles tendon causes the muscle to contract (unless it is already in a semi-contracted state, which isn't uncommon). The contraction consumes energy, and the muscle can't relax until enough energy has been produced to restore the threshold and the readiness for a new contraction. (Creatinine levels are a vague indicator of the activity of this system, and are often a little low in hypothyroidism.)

If energy production is efficient, relaxation is faster than the passive return motion of the foot, so the foot swings freely back to its original position, and over-shoots slightly, causing a slight swinging action. In hypo-thyroidism, the foot returns as if controlled by a pneumatic door-closer, and settles slowly and precisely into its relaxed position, sometimes with a hesitating, intermittent motion. This slow replenishment of energy, and slow relaxation, can cause muscles to cramp easily. The aching leg muscles of children at the end of an active day are often a sign of hypothyroidism, and sometimes the gastrocnemius muscle become very swollen and hypertrophied in hypothyroid children. The same process, of slow energy regeneration, can cause rhythm disturbance in the heart, and often causes insomnia and restless sleep.

The thyroid gland secretes about 3 parts of thyroxin to one part of triiodothyronine, and this allows the liver to regulate thyroid function, by converting more of the T_4 to the active T_3 when there is an abundance of energy. Glucose is essential for the conversion, so during fasting there is a sharp decrease in metabolic rate, and in experiments, 200 or 300 calories of carbohydrates can be added to the diet without causing fat storage.

When the liver is the main cause of hypothyroidism, your temperature (and especially the temperature of your nose, hands and feet) will fall when you are hungry, and will rise when you eat carbohydrates. If a hypothyroid person has a very slow pulse, and feels lethargic, it seems that there is little adrenalin; in this case, a feeding of carbohydrate is likely to increase both the pulse rate and the temperature, as the liver is permitted to form the active T_3 hormone.

Women often have above-average thyroxin, with symptoms of hypothyroidism. This is apparently because it isn't being converted to the active form (T_3). Before using a Cytomel (T_3) supplement, it might be possible to solve the problem with diet alone. A piece of fruit or a glass of juice or milk between meals, and adequate animal protein (or potato protein) in the diet is sometimes enough to allow the liver to produce the hormone. If Cytomel is used, it is efficient to approximate the physiological rate of T_3 formation, by nibbling one (10 or 15 mcg.) tablet during the day. When a large amount is taken at one time, the liver is likely to convert much of it to the inactive reverse-T_3 form, in a normal defensive response.

Women normally have less active livers than men do. Estrogen can have a directly toxic effect on the liver, but the normal reason for the difference is probably that temperature and thyroid function strongly influence the

liver, and are generally lower in women than in men. Estrogen inhibits the secretion of hormone by the thyroid gland itself, probably by inhibiting the proteolytic enzyme which dissolves the colloid. Progesterone has the opposite effect, promoting the release of the hormones from the gland. At puberty, in pregnancy, and at menopause, the thyroid gland often enlarges, probably as a result of estrogen dominance.

Thyroid function stimulates the liver to inactivate estrogen for secretion, so estrogen dominance can create a vicious circle, in which excess estrogen (or deficient progesterone) blocks thyroid secretion, causing the liver to allow estrogen to accumulate to even higher levels. Progesterone (even one dose, in some cases) can break the cycle. However, if the gland is very big, the person can experience a few months of hyperthyroidism, as the gland returns to normal. It is better to allow the enlarged gland to shrink more slowly by using a thyroid supplement. If an enlarged gland does begin to secrete too much thyroid hormone, it can be controlled with tablets of propylthiouracil, or even with raw cabbage or cabbage juice, and cysteine-rich meats, including liver.

Besides fasting, or chronic protein deficiency, the common causes of hypothyroidism are excessive stress or "aerobic" (i.e., anaerobic) exercise, and diets containing beans, lentils, nuts, unsaturated fats (including carotene), and undercooked broccoli, cauliflower, cabbage, or mustard greens. Many health conscious people become hypothyroid with a synergistic program of undercooked vegetables, legumes instead of animal proteins, oils instead of butter, carotene instead of vitamin A, and breathless exercise instead of a stimulating life.

A good diet, plus a supplement of either thyroid or progesterone, can often break the cycle of hormonal imbalance.

If a person has at least a normal level of cholesterol, it is very likely that a progesterone deficiency can be corrected by normalizing the thyroid function, since thyroid, vitamin A, and cholesterol are the main factors in the synthesis of progesterone. If the problem is that the ratio of estrogen to progesterone is too high, though progesterone might itself be at a reasonable level, thyroid becomes crucial, to bring the estrogen level down to normal. In hypothyroidism there is a tendency to develop cystic ovaries, and low thyroid function normally leads to estrogen dominance, even if the ovaries seem normal.

WARBURG'S CANCER THEORY, CACHEXIA AND THYROID THERAPY

Otto Warburg[1] demonstrated that all cancers have defective respiration, by which he meant that glucose is consumed too rapidly, even when there is adequate oxygen. The excessive consumption of glucose in the presence of oxygen is called aerobic glycolysis, and is typical of cancer. Oxygen may be consumed, but it does not result in the production of sufficient ATP to inhibit glycolysis (by the Pasteur effect). This generally means that excess lactate will be produced and will leave the cell, will be detected by other tissues, and will be processed by the liver into glucose. Lactate is a sufficient stimulus to trigger the stress reaction, and in many people causes an anxiety syndrome. Since resynthesis of glucose from lactate by the liver requires much more energy than is derived from conversion of glucose to lactate, the tumor's formation of lactate constitutes a large burden to the organism. Total energy consumption would increase, because of intense but inefficient metabolism in the tumor and in the liver, and also possibly because of stress-induced brain excitation and the catabolism of muscle and other tissue proteins. Cortisol elevates blood glucose and would inhibit the thyroid. Since there is evidence of thyroid deficiency in various cancers, and since thyroid supplementation reduces the incidence of spontaneous tumors in animal studies, thyroid therapy would be desirable in cancer, especially if there is cachexia. Gerson,[2] Tallberg,[3] and others have reported good results from using thyroid as part of supportive therapy.

The stereotype of the hypothyroid person as over-weight will lead the typical physician to believe that metabolic stimulation by thyroid would be exactly the

opposite of what the cachectic patient needs. The relevant effects of thyroid (especially with progesterone, to promote tissue response to thyroid, to block cortisol production, and to provide general anti-stress physiological support) however, are stimulation of protein synthesis and the prevention of lactate formation--or the stimulation of its oxidation, either by the tumor itself or by other tissues, to prevent its entry into the Cori cycle, for gluconeogenesis. Cachexia strumipriva, the wasting disease that used to result following removal of the thyroid gland when the thyroid hormone wasn't replaced, should be kept in mind, since it is a situation in which thyroid cures cachexia, stimulating anabolic processes.

There has been publicity in recent decades about various substances produced by cancers that induce the growth of blood vessels, providing the tumors with the circulation needed for growth. Since lactic acid is an adequate stimulus for such growth, and is produced by tumors, it is remarkable that it has been so consistently ignored as a reasonable point of intervention for limiting tumor growth. Thyroid and magnesium make respiration efficient, in the sense of producing ATP, which is required for the Pasteur effect to turn off glycolysis. Lactic acid can't be made (in humans) from fats or alcohol, a point which is often overlooked by biochemists who work with bacteria, and so the use of acetic acid, butyric acid, and other fatty acids (as in coconut oil, for example), combined with adequate thyroid hormone and magnesium, should make a significant contribution toward removing the lactate stimulus for increased blood supply to the tumor.

Progesterone and pregnenolone, by reducing the cancer-induced excess of the glucocorticoid hormones, would also make a contribution to decreasing the supply of glucose to the tumor.

Warburg believed that a riboflavin deficiency was an important contributor to the development of defective respiration, but he also pointed out that the simple lack of oxygen would promote the development of cancer. I have emphasized the role of estrogen in creating an oxygen deficiency. Since it inhibits the secretion of thyroxin at the glandular level, and antagonizes thyroxin at the cellular level, estrogen is a good candidate for the main cause of the respiratory defect. It also antagonizes other respiratory factors, such as magnesium and vitamin E, and excess estrogen actually impedes oxygenation of the blood. (Both low thyroid and high estrogen are known to cause an emphysema-like interference with diffusion of oxygen into the lung capillaries.)

Radioactive estrogen has been shown to accumulate selectively in (liver) cancer cells, which is remarkable since that behavior is so untypical of liver cells. One of my first research projects had to do with the fact that estrogen promotes the formation of beta-glucuronidase, an enzyme which can reverse the reaction which normally occurs in the liver, detoxifying estrogen by combining it with glucuronic acid. Irritated tissues, and all cancers, contain beta-glucuronidase, with the capacity to "re-toxify" estrogen in the irritated or cancerous site, depositing it locally and negating the liver's protective function. More recently, breast cancer cells have been found to contain sulfatase enzymes, with the same kind of function, since the liver's other main route of estrogen detoxication is by combining it with sulfate. A systematic anti-estrogen program (including adequate protein to sustain liver function) would help to minimize the cancer-promoting action of this locally deposited estrogen. I think of the appearance of these estrogen-releasing enzymes in irritated tissue as part of a system for promoting regeneration. In the uterus, estrogen

promotes simple growth, and progesterone promotes differentiation. I think something analogous happens in other tissues, with a variety of substances supporting differentiation.

Once we accept Warburg's thesis, that damaged respiration is the prime cause of cancer, the therapeutic use of thyroid in cancer seems obvious. Aging and estrogen-dominance are other states in which cells seem to be relatively insensitive to thyroid hormones. (Unsaturated fats are involved in resistance to thyroid, and promote the incidence of cancer in a variety of ways.) If the liver is a main site of T_4's conversion to T_3, cancer patients may require very large doses of thyroid hormone, or else direct use of T_3 (possibly in large doses), since the liver is so likely to be inefficient. Incidentally, thyroid's ability to improve digestion and peristalsis is important for liver function; endotoxin absorbed from the intestine can be a serious burden to the liver, and it is known to cause a large increase in the blood estrogen level.

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THE CERVICAL CANCER SCARE

Many women with abnormal Pap smears, even with a biopsy showing the so-called "carcinoma in situ," have returned to normal in just two months with a diet including the following: 90 grams of protein, 500 mg. of magnesium as chloride, 100,000 units of vitamin A, 400 units of vitamin E, 5 mg. folic acid, 100 mg. pantothenic acid, 100 mg. of B_6 and niacinamide, and 500 mg. of vitamin C, with progesterone and thyroid as needed. Liver should be eaten once a week, because of its high B-vitamin content. Some of the women apply vitamin A (not carotene) directly to the cervix.

Estrogen is known to cause uterine cancer, but the pervasive marketing of estrogen led to solving that problem by the mass removal of American uteruses. The evidence is clear, however, that many tissues have estrogen receptors, and can be cancerized by exposure to estrogen. Breast, lung, brain, and liver are coming to be widely recognized as sites of estrogen-induced cancers in humans, 50 years after Lipschutz demonstrated the extensive nature of estrogen carcinogenesis in animals. The pancreas, which has estrogen receptors, is another organ that I believe is significantly cancerized by estrogen.

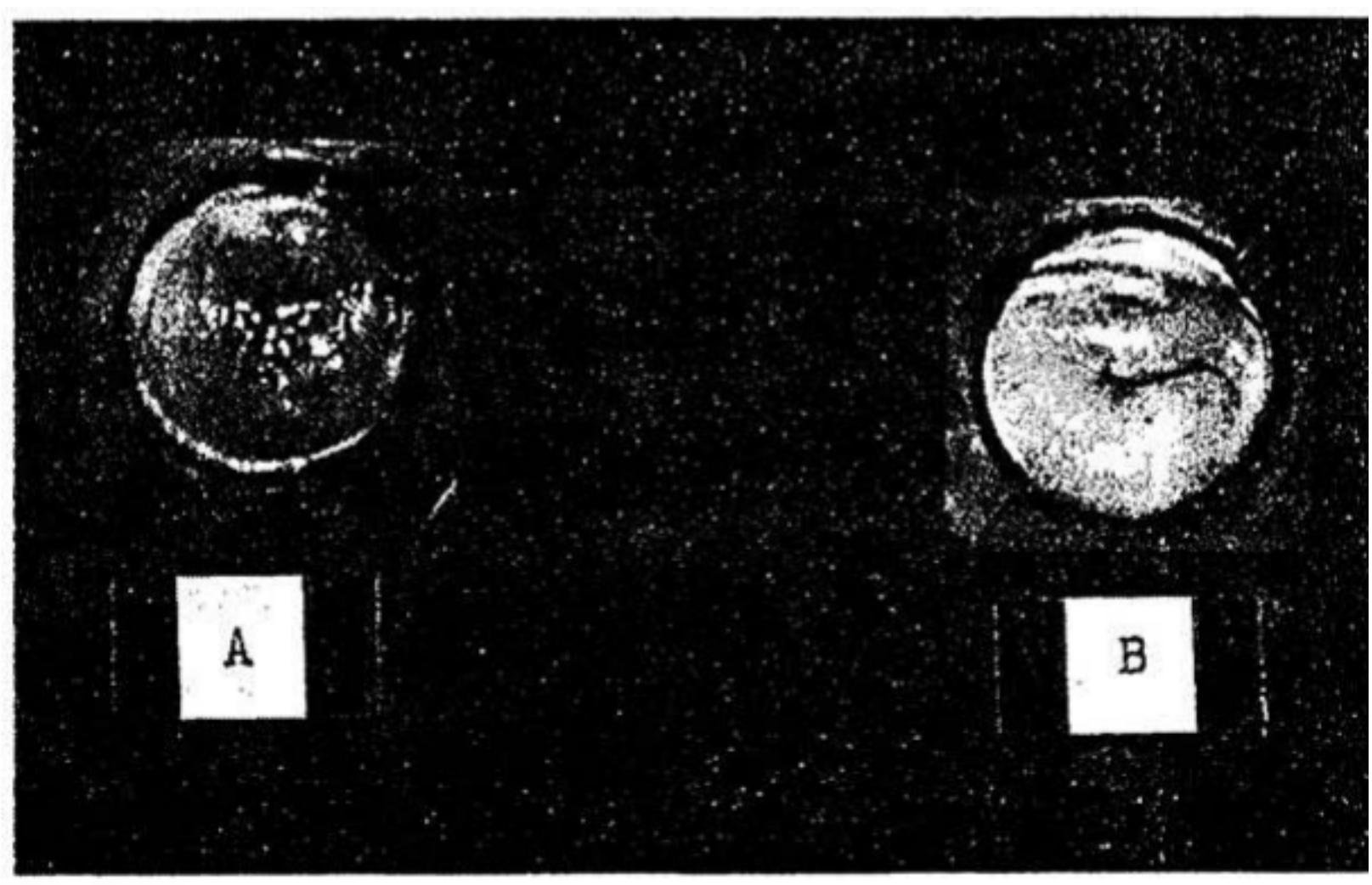
Progesterone's anti-estrogen effect has been successfully used to treat some uterine and breast cancers, but the doses were never high enough to duplicate the levels that exist in late pregnancy. I believe it is irrational to use less than the maximum physiological level, in attempting to reverse a condition which resulted from years of severe deficiency. When progesterone dissolved in benzyl alcohol

with sesame oil is injected, progesterone crystals are deposited, inertly, in the tissue. Even this limited approach has produced some visible results.

I believe the fact that the cancer death rate keeps rising disproves the claim that there has been progress in the cure of cancer. Everyone over 50 contains some tissue that can be diagnosed as cancer. Though not everyone dies from cancer, it could be diagnosed in everyone, if a sufficient diagnostic effort were made. Then, 75% of "all cancers" could be "cured," though just as many people would die from it. The cancer situation is so thoroughly unscientific that I am not convinced that it is worthwhile to make any effort to diagnose cancer. At a cancer conference, a very high proportion of the male physicians, when asked what they would do if they had prostate cancer, said they would do nothing; that response seems to be justified by the evidence accumulated for several decades, that treatment for prostate cancer hasn't clearly prolonged life. More aggressive diagnosis will certainly improve the "cure rate," but until the population's death rate from prostate cancer decreases, it is hard to have confidence in therapies based on fundamentally confused notions of the biology of cancer. If something harms your vitality, and is just as toxic to your immune system, your liver, and your brain, as it is to cancer cells, the medical situation seems analogous to that of the army that destroys a town to save it.

Benign breast disease, breast cancer and pre-cancerous conditions have been found to be associated with a progesterone deficiency and excess estrogen. Some references are given in Nutrition for Women. Since progesterone deficiency and excess estrogen can be caused by either a thyroid deficiency or a protein deficiency, the most important cause of the steroid imbalance, and of the hormone related cancers, is hypothyroidism. Broda Barnes

has discussed this issue in his books. (Protein deficiency is one cause of hypothyroidism.) Vitamin A, vitamin E, and thyroid have all been used effectively to relieve benign breast disease. Caffeine actually has been repeatedly shown to protect against cancer. Minton's so-called study which led to a generalized fear of coffee as a cause of breast disease was based on confused reasoning. I believe anti-inflammatory drugs such as aspirin or prostaglandin inhibitors such as indomethacin have a rational place in cancer therapy, especially if (like aspirin) they have some antihistamine activity. Estrogen tends to be deposited in inflamed tissues, and in that sense those drugs might be considered as part of an anti-estrogenic program.



(A) initial appearance of lesion, (B) after 31 days on progesterone.

MENOPAUSE AND ITS CAUSES

When I was in graduate school at the University of Oregon, everyone in our lab was working on the problem of reproductive aging. Previously, people in the lab had established that the ovaries didn't "run out of eggs." There was never really any basis for that ridiculous belief. Many people just said it, they way they said "old eggs" (but never old sperms) were responsible for birth defects, or that "estrogen is the female hormone," a deficiency of which is the cause of menopausal infertility.

I knew, from talking with L. C. Strong, that early reproductive maturity was associated with early death; in his strains of cancer-prone mice, he showed that high estrogen was the cause of early puberty and high cancer incidence. In my work with hamsters, I found that the infertility that developed at middle age was caused by a high rate of oxygen consumption in the uterus, causing the oxygen needed by the developing embryo to be consumed by uterine tissues, and causing suffocation of the embryo. This is the central mechanism by which the estrogen-containing contraceptives work: at any stage of pregnancy, a sufficient dose of estrogen kills the embryo.

Polvani and Nencioni, among others, found that in women, the onset of menopause (the first missed period, bone loss, nervous symptoms) corresponds to the failure to produce progesterone, while estrogen is produced at normal levels. This results in a great functional excess of estrogen, because it is no longer opposed by progesterone. Typically, it takes about 4 years for the monthly estrogen excess to disappear. They suggested that the bone loss sets in

immediately when progesterone fails because cortisol then is able to dominate, causing bone catabolism; progesterone normally protects against cortisol. Other researchers have pointed out that estrogen dominance promotes mitosis of the prolactin-secreting cells of the pituitary, and that prolactin causes osteoporosis; by age 50, most people have some degree of tumefaction of the prolactin-secreting part of the pituitary. But estrogen dominance (or progesterone deficiency) also clearly obstructs thyroid secretion, and thyroid governs the rate of bone metabolism and repair. Correcting the thyroid and progesterone should take care of the cortisol/prolactin/osteoporosis problem.

P. M. Wise[1] has demonstrated that the "menopausal" pituitary hormones, high levels of LH and FSH, are produced because the regulatory nerves in the hypothalamus have lost their sensitivity to estrogen, not because estrogen is deficient. In fact, he showed that the nerves are desensitized precisely by their cumulative exposure to estrogen. If an animal's ovaries are removed when it is young, the regulatory nerves do not atrophy, and if ovaries are transplanted into these animals at the normally infertile age, they are fertile. But if animals are given larger doses of estrogen during youth, those nerves atrophy prematurely, and they become prematurely infertile.

The mechanism by which estrogen desensitizes and kills brain cells is now recognized as the "excitotoxic" process, in which the excitatory transmitter glutamic acid is allowed to exhaust the nerve cells. (This explains the older observations that glutamic acid, or aspartic acid, or aspartame, can cause brain damage and reproductive failure.) Cortisol also activates the excitotoxic system, in other brain cells, causing stress-induced atrophy of those cells.[2] Progesterone and pregnenolone are recognized as inhibitors of this excitotoxic process.

It was established in the 1950s that estrogen "erases" memories in well trained animals. I suppose that acute effect is related to the chronic toxicity that leads to cell death. (In the 1940s, DES was sold to prevent miscarriages, though it was already known that it caused them; then there was the argument that it slowed aging of the skin, despite the Revlon studies at the University of Pennsylvania showing that it accelerates all aspects of skin aging; lately there has been talk of promoting estrogen to improve memory; I guess there is some weird homeopathic reasoning involved here.)

Estrogen's nerve-exciting action is known to lower seizure thresholds; premenstrual epilepsy is probably another acute sign of the neurotoxicity of estrogen.

When fatigue and lethargy are associated with aging, the brain stimulating action of estrogen can make a woman feel that she has more energy. (Large doses given to rats will make them run compulsively; running wheels with odometers have shown that they will run over 30 miles a day from the influence of estrogen.) Estrogen inhibits one of the enzymic routes for inactivating brain amines, and so it has more general effects on the brain than just the glutamate system. This generalized effect on brain amines is more like the effects of cocaine or amphetamine. If that is a woman's basis for wanting to use estrogen, a monoamine oxidase inhibitor would be safer.

The reason for the menopausal progesterone deficiency is a complex of stress-related causes. Free-radicals interfere with progesterone synthesis, as do prolactin, ACTH, estrogen, cortisol, carotene, and an imbalance of gonadotropins. A deficiency of thyroid, vitamin A, and LDL-cholesterol can also prevent the

synthesis of progesterone. Several of the things which cause early puberty and high estrogen, also tend to work against progesterone synthesis. The effect of an intra-uterine irritant is to signal the ovary to suppress progesterone production, to prevent pregnancy while there is a problem in the uterus. The logic by which ACTH suppresses progesterone synthesis is similar, to prevent pregnancy during stress.

Since progesterone and pregnenolone protect brain cells against the excitotoxins, anything that chronically lowers the body's progesterone level tends to accelerate the estrogen-induced excitotoxic death of brain cells.

Chronic constipation, and anxiety which decreases blood circulation in the intestine, can increase the liver's exposure to endotoxin. Endotoxin (like intense physical activity) causes the estrogen concentration of the blood to rise. Diets that speed intestinal peristalsis might be expected to postpone menopause. Penicillin treatment, probably by lowering endotoxin production, is known to decrease estrogen and cortisone, while increasing progesterone.

Finally, long hours of daylight are known to increase progesterone production, and long hours of darkness are stressful. Annually, our total hours of day and night are the same regardless of latitude, but different ways of living, levels of artificial illumination, etc., have a strong influence on our hormones. In some animal experiments, prolonged exposure to light has delayed some aspects of aging.

General aging contributes to the specific changes that lead to menopause, but the animal experiments show that fertility can be prolonged to a much greater age by preventing excitotoxic exhaustion of the hypothalamic nerves. The question that still needs to be more clearly

answered is, to what extent can general aging be prevented or delayed by protecting against the excitotoxins? Minimizing estrogen (and cortisone) with optimal thyroid activity, and maximizing pregnenolone and progesterone to prevent excitotoxic cell fatigue, can be done easily. A diet low in iron and unsaturated fats protects the respiratory apparatus from the damaging effects of excessive excitation, and--since pregnenolone is formed in the mitochon-drion--also helps to prevent the loss of these hormones.

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DOSAGE OF PROGESTERONE

Since progesterone is not known to have any harmful side effects (except for alteration of the menstrual cycle if it is taken at the wrong time of month), the basic procedure should be to use it in sufficient quantity to make the symptoms disappear, and to time its use so that menstrual cycles are not disrupted. This normally means using it only between ovulation and menstruation unless symptoms are sufficiently serious that a missed period is not important. The basic idea of giving enough to stop the symptoms can be refined by some information on a few of the factors that condition the need for progesterone.

If a person has an enlarged thyroid gland, progesterone promotes secretion and unloading of the stored "colloid," and can bring on a temporary hyperthyroid state. A thyroid supplement should be used to shrink the goiter before progesterone is given. Normal amounts of progesterone facilitate thyroid secretion, while a deficiency, with unopposed estrogen, causes the thyroid to enlarge. The production of euphoria has been mentioned as a side effect, but I think euphoria is simply an indication of a good physiological state. Very large doses that are given in vitamin E solution, allowing complete absorption, can reach the level that is sometimes achieved late in pregnancy, producing both euphoria and a degree of anesthesia. To avoid unexpected anesthesia, the correct dose should be determined by taking about 10 mg. at a time, allowing it to spread into the membranes of the mouth, and repeating the dose after 10 minutes until the symptoms are controlled.

An excessive estrogen/progesterone ratio is more generally involved in producing or aggravating symptoms

than either a simple excess of estrogen or a deficiency of progesterone, but even this ratio is conditioned by other factors, including age, diet, other steroids, thyroid, and other hormones. The relative estrogen excess seems to act by producing tissue hypoxia (as reported in my dissertation, University of Oregon, 1972), and this is the result of changes induced by estrogen in alveolar diffusion, peripheral vascular changes, and intracellular oxygen wastage.

Hypoxia in turn produces edema (as can be observed in the cornea when it is deprived of oxygen, as by a contact lens) and hypoglycemia (e.g., diminished ATP acts like insulin), because glycolysis must increase greatly for even a small deficiency of oxygen. Elevated blood lactic acid is one sign of tissue hypoxia. Edema, hypoglycemia, and lactic acidemia can also be produced by other "respiratory" defects, including hypothyroidism, in which the tissue does not use enough oxygen. In hypoxia, the skin will be bluer (in thin places, such as around the eyes), than when low oxygen consumption is the main problem. Low thyroid is one cause of excess estrogen, and when high estrogen is combined with low thyroid, the skin looks relatively bloodless.

Symptoms in cycling women are most common around ovulation and in the premenstrual week, when the estrogen/progesterone ratio is normally highest. At puberty, in the early twenties and in the late thirties and menopause are the ages when the ratio is most often disturbed--and these are also the ages when thyroid disorders are commonest in women.

The individual who suffers from one aspect of the progesterone (and/or thyroid) deficiency will tend to develop other problems at different times. With cyclic depressions or migraine headaches at age 22, there will

possibly be breast disease later, and often there will be problems with pregnancy. These people with a history of severe symptoms are the ones most likely to have severe problems around menopause. Prenatal exposure to poorly balanced hormones seems to predispose the child to later hormone problems.

Excess stress (which can block progesterone synthesis and elevate estrogen) may bring on symptoms in someone who never had them. Spending a summer in Alaska, with an unusually long day, may relieve the symptoms of a chronic sufferer. Dark cloudy winters in England or the Pacific Northwest are powerful stressors, and cause lower production of progesterone in women, and testosterone in men. Toxins can produce similar symptoms, as can nutritional deficiencies. A very common cause of an estrogen excess is a dietary protein deficiency--the liver simply cannot detoxify estrogen when it is under-nourished.

With a diet high in protein (e.g., 70-100 grams per day, including eggs) and vitamin A (not carotene), I have found that the dose of progesterone can be reduced each month. Using thyroid will usually reduce the amount of progesterone needed. Occasionally, a woman won't feel any effect even from 100 mg. of progesterone; I think this indicates that they need to use thyroid and diet, to normalize their estrogen, prolactin, and cortisol.

Progesterone stimulates the ovaries and adrenals to produce progesterone, and it also activates the thyroid, so one dose can sometimes have prolonged effects. shouldn't be necessary to keep using progesterone indefinitely, unless the ovaries have been removed. In slender post-menopausal women, 10 mg. per day is usually enough to prevent progesterone deficiency symptoms.

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Figure 1

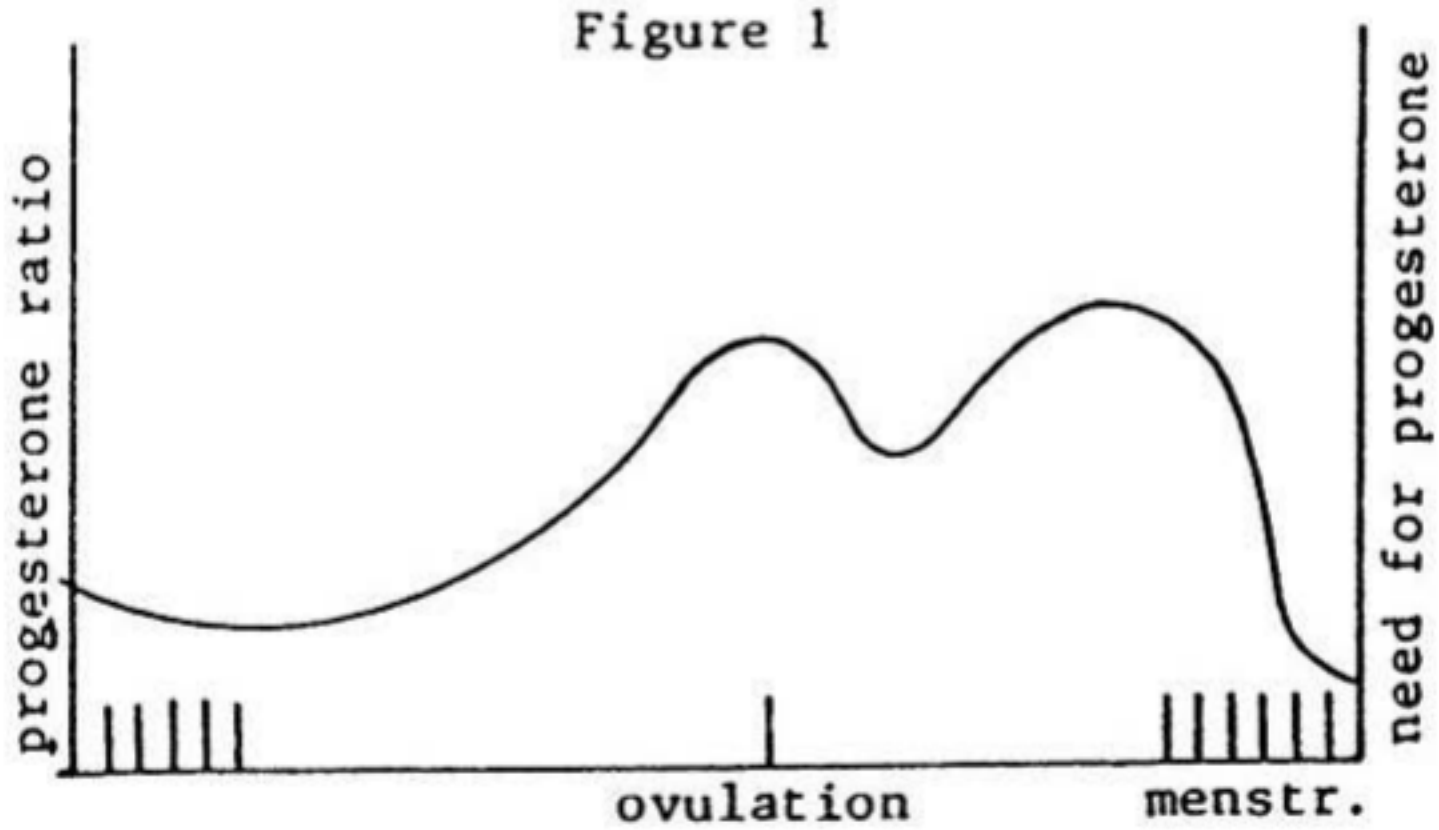
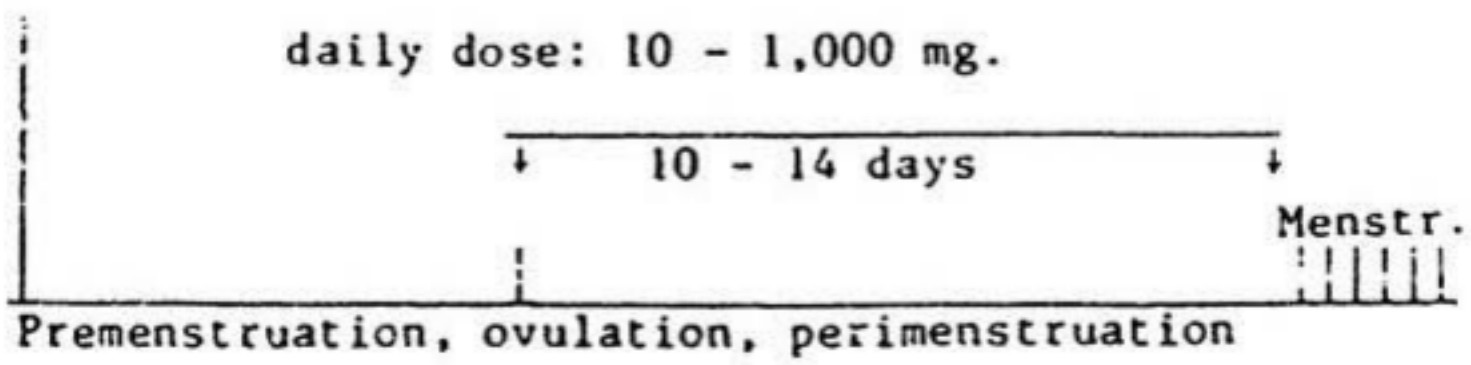


Figure 2



THE PROGESTERONE DECEPTIONS

In the 1930s, it was demonstrated that estrogen, even in small doses, produced abortions, and that when it is given early enough, even a very small dose will prevent implantation of the fertilized embryo. Progesterone was known, by the early 1940s, to protect against the many toxic effects of estrogen, including abortion, but it was also known as nature's contraceptive, since it prevents pregnancy without harmful side-effects, by different mechanisms, including prevention of sperm entry into the uterus. That is, progesterone prevents the miscarriages which result from excess estrogen,(1,2) but if used before intercourse, it prevents conception, and thus is a true contraceptive, while estrogen is an abortifacient, not a contraceptive.

In the 1950s, there was a search for chemicals which would prevent ovulation. According to Carl Djerassi,(3) drug companies were extremely reluctant to risk a religious backlash against their other products, and so hesitated to market contraceptives. Obviously, the induction of monthly abortions would have been even harder to sell.

According to Djerassi,(3) "Until the middle 1940s it was assumed that progesterone's biological activity was extremely specific and that almost any alteration of the molecule would diminish or abolish its activity." This would obviously discourage interest from the drug companies, who could patent a substance which they had chemically modified, but could not patent a simple natural substance. However, many substances--even non-steroidal chemicals--turned out to have estrogenic action.(4)

By 1942, Hans Selye had demonstrated that natural steroids retain their activity when administered orally. But every drug company with a steroid patent had an obvious interest in having the public believe that there is a reason that the natural steroids cannot be conveniently used. The doctrine that natural steroids are destroyed by stomach acid appeared, was promoted, and was accepted. In the manufacture of progesterone, the precursor steroid is boiled in hydrochloric acid to free it from its glucose residue; no one seriously believed that stomach acid hurts progesterone, except the public.

The real issue is solubility. Hydrocortisone is reasonably soluble in water, but progesterone is extremely insoluble in water, and, though it is vastly more soluble in vegetable oil than in water, it does not stay in solution at room temperature even at the low concentration of 1 part in 1000 parts of vegetable oil.

When people speak of an allergy to progesterone (or even to penicillin) they generally are not aware of the presence of a very toxic solvent.(5) A few years ago, progesterone was often sold dissolved in benzyl benzoate; the Physician's Desk Reference warned of possible allergic reaction to progesterone. Now, it is supposedly sold dissolved in vegetable oil, with about 10% benzyl alcohol as a bacteriostatic agent. Bacteriostatic water contains 0.9% to 1.9% benzyl alcohol, and can irreversibly harm nerves.(7) Awareness of benzyl alcohol's toxicity goes back to 1918 at least; it was proposed as an effective insecticide, and was found to be toxic to many animal systems. The safe systemic dose(7) is exceeded with an injection of 150 mg. of progesterone, yet the local concentration is far higher. It can cause a severe reaction even when used at a lower concentration, in bacteriostatic water.(5)

Other alcohols, including ethanol, have been used as solvents, but since they (ethanol even more than benzyl alcohol) have an affinity for water, the solution decomposes in contact with tissue water.

In spite of the toxicity of the vehicle, several beneficial effects can be obtained with injected progesterone, in serious conditions such as epilepsy or cancer of the breast or uterus. Many researchers have commented on the very obvious difficulty of giving very large amounts of progesterone.(8) My comparisons of oral progesterone in tocopherol with other forms and methods of administration show a roughly similar efficiency for oral and injected progesterone, and about 1/20 the effect for suppositories. Crystals of progesterone are visible in the suppositories I have examined, and this material is obviously wasted.

An old theory of vitamin E's mechanism of action in improving fertility was that it spares progesterone.(9) It is established that some of the effects of vitamin E and progesterone are similar; for example, both prevent oxygen waste and appear to improve mitochondrial coupling of phosphorylation with respiration. I suspected that if they actually both work at the same mitochondrial site, then they must have a high mutual solubility. Knowing the long-standing problem of administering large doses of progesterone without a toxic solvent, I applied for and was granted a patent for the composition of progesterone in tocopherol. One of my reasons for publishing in the form of patents is that I have had many years of experience in having my discoveries taken up by others without acknowledgment. My dissertation research, which established that an estrogen excess kills the embryo by suffocation, and that progesterone protects the embryo by promoting the delivery of both oxygen and glucose, didn't

strike a responsive chord in the journals which are heavily influenced by funds from the drug industry.

According to a consultant for a major medical journal, the idea "...of dissolving progesterone, a fat soluble steroid hormone, in vitamin E which is then incorporated into chylomicrons absorbed via the lymphatics, and thus avoids the liver on the so called first pass... ...is so simple it is amazing that the pharmaceutical companies have not jumped on it."

In the powder form, direct and intimate contact with a mucous membrane allows lipid phase to lipid phase transfer of progesterone molecules. Instead of by-passing the liver, much of the progesterone is picked up in the portal circulation, where a major part of it is glucuronidated, and made water soluble for prompt excretion. Since this glucuronide form cross-reacts to some extent with ordinary progesterone in the assay process, and since 50% of the ordinary free progesterone is carried inside the red blood cells,(10) and 50% is associated with proteins in the plasma, while the glucuronide hardly enters the red blood cells at all, it is better to judge by clinical efficacy when comparing different oral forms. My comparisons show several times higher potency in the tocopherol composition than in powder form.

Since progesterone's use as a drug antedates the 1938 law requiring special federal approval, its legal status is similar to that of thyroid hormone. Unfortunately, for both thyroid and progesterone, there is a tendency to cut corners for the sake of a bigger profit margin.

For example, steroid acetates are generally a little cheaper than the simple natural steroid. Some people

assume that an acetate or butyrate can be substituted for the steroid itself. This can cause dangerous reactions.

Medroxyprogesterone acetate is considered a progestin, because it modifies the uterus in approximately the way progesterone does, but it is luteolytic, and lowers the ovaries' production of progesterone while progesterone itself has a positive effect on the corpus luteum, stimulating progesterone synthesis. Defining "progestin" in a narrow way allows many synthetics to be sold as progestagens, though some of them are strongly estrogenic, allowing them to function as contraceptives--it is odd that contraceptives and agents which suppress progesterone synthesis should be officially called "supporters of pregnancy." It is probably partly the acetate group in the medroxyprogesterone acetate molecule which makes it bind firmly to receptors, yet causes it to block the enzymes which would normally be involved in progesterone metabolism. (I think testosterone, even, might be a safer progestin than medroxyprogesterone acetate.) Pregnenolone acetate similarly blocks the enzymes which normally metabolize pregnenolone.(11) In aspirin, it has been found that it is the acetyl group which (by a free radical action) blocks an enzyme involved in prostaglandin synthesis.

If the category called "progestogens" or "progestins" is to be defined on the basis of a single tissue reaction, then it is possible to classify progesterone with the toxic synthetic substances, but then it becomes highly deceptive to imply that progesterone is just a progestin, or that it has any of the other properties of the toxic synthetics, but this continues to be done. The warnings about "progestins causing birth defects," for example, cause epileptic women to use conventional anti-seizure drugs (all of which cause birth defects) during pregnancy, and to avoid natural progesterone, which generally could control their seizures.

Thus, a false message attached to progesterone creates precisely the harm it claims to want to prevent. In my communications with the regulatory agencies, I have concluded that their attempts to deceive are too blatant to ascribe to incompetency. Whether it's the Forest Service or the FDA, the principle is the same: the regulatory agencies have been captured by the regulated industries.

Another place to cut costs is in the tocopherol. Tocopherol acetate does have vitamin E activity, but since it is only about half as efficiently absorbed as the simple tocopherol,(12) it is a mistake to save a few dollars an ounce, at the expense of losing half of the therapeutic effect. People who have compared natural progesterone in natural tocopherols with other compositions have insisted that the other compositions must not contain progesterone.

The taste of natural vitamin E is stronger than that of the synthetic forms, but since the mixture is absorbed by any tissue it contacts, including various parts of the bowel, it can be taken in a capsule. If a small amount of olive oil is used with it, absorption through the skin is very rapid. Many women use it vaginally, spread onto a diaphragm, to hold it in contact with the membranes. The efficiency of absorption by all routes is so high that patients should be warned against its anesthetic effect, until their dosage requirement is known approximately. Some physicians prefer concentrations higher than 10%, but the risk of accidental drunkenness or anesthesia is higher with the stronger solutions.

It is an indication of the tocopherol solution's high availability that medical researchers such as Roy Hertz,(8) who thought they were administering maximal doses by combining injections with suppositories, never mentioned the problem of an anesthetic effect from an overdose.

Similarly, it is evidence of the extremely poor availability of the micropulverized progesterone that the researchers have administered hundreds of milligrams per day, without mentioning the symptoms of an overdose. Because of the difficulties involved in scientifically studying the clinical effectiveness of various formulations, I think the most practical way of evaluating the effectiveness of different progesterone formulations is to measure the amount extractable from the red blood cells, a few hours after the peak serum level has been reached. This will reasonably reflect the amounts reaching brain cells, adrenal glands, and the various other cells on which progesterone has its therapeutic action.

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ORIGINS OF PROGESTERONE THERAPY

By the beginning of the 20th century, the idea of extracting regulatory substances from animal tissues was coming into general acceptance in Western medicine. J. A. Lebreton, in Paris, was one of the first to argue for the therapeutic use of an extract of the corpus luteum. Around 1904, C. F. Burnam, of Baltimore, began using corpus luteum of the sow, administered orally, to treat the nervous symptoms associated with menopause or with the menstrual cycle, and also to treat functional amenorrhea, obesity, sterility, and habitual miscarriage. (1912 edition of New and Nonofficial Remedies, and J.A.M.A., Aug. 31, 1919, lix, p. 698.) By the 1920s, tablets of desiccated corpus luteum were generally available, and the daily dosage recommended (representing 6 to 18 grams of fresh tissue) contained a very substantial quantity of progesterone.

The chemical structure of pure crystalline progesterone was determined in 1934 (by Butenandt), and within 2 years many publications were reporting the beneficial effects of injections of the purified material. By 1935, animal research was confirming that the therapeutic work previously done with the crude extract had been on the right track. Although the early research showed that progesterone was very beneficial in threatened miscarriage, arthritis, infertility, cancer and functional diseases of the nervous system, interest in this generic, public-domain material faded as the pharmaceutical industry found methods for converting it into proprietary synthetic glucocorticoids, estrogens, and progestins.

Animals are generally more sensitive to progesterone than humans are, and in animals no toxic level has been found,

except that in the highest doses it is anesthetic. In humans, even this effect has never been reported in the medical literature, and it is clearly anti-toxic in nature. Besides preventing acute poisoning of many kinds, it also reduces the incidence of birth defects and cancer.

Progesterone, the Protective Substance of Youth

In 1971, I discovered that vitamin E and progesterone work together to sustain efficient production and use of biological energy. (1) In the mid-1970s, I found that progesterone is the most powerful order-preserving substance (anti-chaotropic) on the cellular level, and that this explains its range of protective actions, from anti-toxic to anti-stress. (2,3)

Around 1980, I discovered that vitamin E, with its crucial effect on the mitochondrial respiratory enzymes, is a uniquely powerful, stable, and biologically compatible solvent for progesterone.(4) Their intimate association at certain cellular sites requires mutual solubility. This property of mutual affinity extends to all biological areas, meaning that the solution of progesterone in vitamin E can be administered with exceptional efficiency by application to the skin or other membranes, or by ingestion, where normal digestive processes convert it into chylomicrons and distribute it to all tissues, allowing it to escape the tendency of the liver to convert it rapidly to an excretory form, as occurs when progesterone is administered in other forms.

Because of its profound biological compatibility, the progesterone-vitamin E solution permits otherwise impossibly high doses to be given, increasing by as much as 2,000% progesterone's already dramatic effects in a wide range of major biological problems, including epilepsy,

habitual miscarriages, auto-immune diseases, and cancer of the uterus, breast, and kidney.

Some Aspects of Basic Progesterone Research

By 1945, Hans Selye had demonstrated that progesterone in itself has the full spectrum of regulatory and anti-stress functions of the adrenal steroids. A little later, Albert Szent-Gyorgyi showed that progesterone is able to regulate the heart, in a manner similar to digitalis. In the 1970s, I demonstrated that it acts similarly on vascular smooth muscle, regulating its tone and preventing venous pooling of blood, and maintaining normal filling of the heart, opposing shock. The immediate improvement in circulation can have dramatic effects, which include restoration of kidney function, elimination of fluid from the lungs, restoration of sensation in the feet, and healing of gangrenous toes. It restores normal tone to other smooth muscles, including the gall bladder, urinary bladder, intestine, sphincters, and uterus.

Progesterone's ability to regulate thresholds of cellular excitation operates in nerves, as well as in smooth and cardiac muscle. It sensitizes nerves that regulate respiration, and has been used to treat infant apnea, sleep apnea in adults, and polycythemia vera in men.

In cases of specific progesterone deficiency in men, small doses can cure impotence. It has been used effectively to treat benign prostatic enlargement.

It normalizes fluid pressure, as in bursitis and glaucoma treatment. This effect on tissue fluid content is probably involved in its ability to improve oxygenation in emphysematous lungs, and to normalize swollen cartilage.

It restores many of the functions of aged skin, and is the normal defense against calcium loss from bones. It is one of the few essential requirements, besides nutrients, for nerve (brain) cell growth and survival. In young people of both sexes, the brain contains more progesterone than other organs do.

It is reasonable that progesterone, the dominant hormone in pregnancy, should have a full range of protective functions to protect the vulnerable organism during its intra-uterine life.

Practical Issues

A typical dose of progesterone/vitamin E, 20mg./day for 10 consecutive days, costs about $1.00 per month, at the present retail price. Pharmacists have the authority to compound drugs as they choose, just as physicians can prescribe the formulation they prefer. (And beyond that principle, is the fact natural hormones have never been legally even prescription drugs. Even potentially deadly injectable insulin is available everywhere without a prescription. The FDA acknowledged that they had erroneously been listing insulin as a prescription drug, when it wasn't. Federal law prohibits labeling a non-prescription drug as a prescription drug. When I asked for a copy of their policy discussions regarding natural hormones, they claimed the records were "old," and unavailable, then they said that those policy discussions were done elsewhere, so they couldn't get access to the record. It's a touchy subject; the Freedom of Information office claimed they couldn't find those old documents, and some related things they sent me were incomplete, with no explanation for the missing pages.)

Neither progesterone nor vitamin E has any toxicity when used orally. Under federal law, a prescription is

needed for a dosage form of a drug that is potentially harmful. The very dangerous injectable insulin is always sold without need for a prescription, because something overrides the principle of danger, presumably that its use is conceived as akin to nutrition, providing an essential natural substance to restore a natural function of the body. By analogy with insulin, the infinitely less dangerous progesterone should not require a prescription. The most useful terms for regulatory obfuscation are "Approved New Drug," and "not an approved drug." Most legal drugs under the 1938 FDA law have not been under the special category of "Approved New Drugs," but that is a subject the regulators just won't talk about. They talk about what they control, and hope people will assume they control everything.

Economic Questions

Because of its absorption by a natural digestive route which distributes it to all of the tissues, progesterone dissolved in vitamin E is almost 100% absorbed when taken orally. Less than 1% is absorbed from some types of suppositories, and less than 5% absorption is typical. Taken orally as a micronized powder, pharmaceutical efficiency is only slightly better.

Most of the valid human research before 1981 used intramuscular injections of progesterone dissolved in vegetable oil and benzyl alcohol. Benzyl alcohol has a high affinity for water, and in contact with the tissue fluid, it leaves the mixture, causing progesterone crystals to form, since vegetable oil is a poor solvent for progesterone. Therapeutic blood levels of progesterone can be achieved by intramuscular injections, but at the cost of leaving toxic debris at the site of injection. Benzyl alcohol is a powerful neuro-toxin, but its harm is reduced by progesterone's

anti-toxic action. The cost of the injectable progesterone, and of the injection itself, has been the main factor preventing wider acceptance of this form of progesterone in the United States.

Natural progesterone, and closely related steroids, occur in a wide variety of organisms. Up to the present, the cheapest source of the raw material has been the wild Dioscorea yam of tropical Mexico, but soybeans have also been used as the source of a steroid for production of progesterone. Since the soybean is a major source of vitamin E, the finished product can be made anywhere the bean is produced. Fenugreek, a quick-growing plant, contains the same substance as the Mexican yam, and can also be use as a source of vitamin E.

The chemistry for converting crude diosgenin into pregnenolone, and for converting pregnenolone into progesterone, is very simple, and can be done with little capital, at the site of production of the raw material.

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TRANSDERMAL PROGESTERONE FOR PREMENSTRUAL SYNDROME

For many years, Katharina Dalton has studied the use of progesterone therapy for the premenstrual syndrome. A typical patient may require ten or more progesterone injections per month, more or less permanently. While this is feasible (at least in some countries) it is not comfortable or convenient, in some cases leads to serious reactions at the injection sites, and in the United States would be too expensive for general use. When the syndrome is dasabling, even the burden of frequent and expensive injections is usually seen as a welcome alternative. However, a less expensive and more pleasant form of administration could make the therapy available to millions of women who are now disabled for one or more days each month. A satisfactory alternative to injections for many women is to use a dissolved form of progesterone in a lotion or cold cream base for transdermal use.

After animal experiments revealed that progesterone in vegetable oil was absorbed effectively through the skin, in 1977 I began experiments with women who suffered with the premenstrual syndrome. The first three were completely disabled by epilepsy, suicidal depression, and optical neuritis.

The effectiveness of the transdermal absorption route of administration varies with the individual, but compares favorably with injections in the amount assimilated. Thickness of skin or degree of circulation in the skin (these can be very abnormal in hypothyroidism, for example) and the amount of adipose tissue apparently make some difference in the rate of absorption and response. When a small daily dose (e.g., 5 or 10 mg.) is sufficient, this can be

taken as about 1/2 to 1 gram of a three percent cream rubbed into the front of the neck, where it leaves little oiliness after a few minutes. For large doses, the appropriate amount can be applied to a larger area of skin after a hot bath, once or twice a day if necessary.

Over the years I have seen transdermal progesterone used in hundreds of women suffering from the full range of perimenstrual symptoms, including migraine, acne, depression, mastalgia, edema, and lethargy. Nearly all the women, applying the lotion themselves, are able to find the appropriate dosage for controlling their symptoms. Often thyroid therapy or a change in diet or light-exposure or amount of activity is necessary for complete relief from symptoms. It is necessary to be clear in describing the amounts that can be used, while leaving it up to the patient to find the dose which controls her symptoms, because some women have an exaggerated idea of the power of a "hormone." The behind-the-ear scopolamine patch has had its influence on the idea of transdermal therapy, and many women have tried just touching the oil to their wrists.

It is a good idea to apply one dose (sometimes using a twenty percent solution) in the office, and to wait 30 or 40 minutes to make sure that it was large enough to take effect. Once having felt sudden relief from this "cold cream," it is easier for the patient to understand how it should be used. (This trial dose in the office is a good idea when using oral doses, too, but for an additional reason, namely, to watch for signs of an overdose.)

Many of the solvents which hold progesterone stably in a concentrated solution are highly allergenic. Injectable progesterone in oil could be used transdermally except for this problem. If necessary, micropulverized progesterone can be dissolved in warm olive oil for patients who react to

other materials, or who have a history of skin allergies. Progesterone usually corrects such allergies, but some women have found that taking it orally in oil was preferable. The French have two standard topical progesterone preparations that have been used for many years for breast pain and facial hair.

Besides the slow and steady absorption permitted by the transdermal method, and the fact that many women with PMS are exaggeratedly sensitive to ingesting anything that tastes odd, there is a special set of problems that make the topical use of progesterone very valuable. As I mentioned above, the French advocate topical progesterone for mastalgia, but I think thyroid supplementation is the more general solution to that problem. But in the case of bursitis, arthritis, tendonitis, "fibrositis," and varicose veins, it is possible to achieve a higher local concentration with transdermal use, than can conveniently be achieved by oral administration. (Though the two can be combined usefully.) Progesterone is so insoluble in water that it can penetrate tissue to a remarkable depth, before a significant amount of it is carried away. Tissue proteins have a great affinity for oils.

A LIST OF SIGNS AND SYMPTOMS THAT RESPOND TO PROGESTERONE THERAPY

Many people found the list of signs and symptoms in the first edition of this book either useful or interesting; at least it is an emphatic way of pointing out that progesterone has so many functions it can't be considered to be just a "reproductive hormone." Since I now understand better the biological meaning of these signs, I want to emphasize more strongly the importance of normalizing nutrition, thyroid function, light exposure, and bowel action in correcting the problems behind these signs and symptoms. It is really a kind of index of physiological disorders, and it happens that progesterone is a major tool for physiological adaptation.

Abdominal bloating
Accident proneness
Acne (cyclic)
Aggressiveness
Alcoholic or drug addiction
Allergic rhinitis
Appetite disturbance
Arthritis[1]
Asthma, especially in adolescence & menopause
Bleeding gums
Breast symptoms[2]
Bruising spontaneously
Capillary fragility
Carpal tunnel syndrome
Cold hands & feet
Conjunctival or retinal hemorrhage
Constipation, colicky pain
Colitis, regional enteritis
Depression
Diabetic vascular problems
Edema
Endometriosis, cervical dysplasia
Epilepsy, vertigo
Facial hair
Facial pallor, puffiness, darkening under the eyes
Fainting
Fatigue, lethargy
Fibroids
Fluctuations in weight
Formication (crawling sensation on the skin)
Gall bladder symptoms
Glaucoma (high eye pressure)
Goiter
Headache, eye pain, flashes of light, photophobia

Heart murmur
High blood pressure
Hypoglycemia
Hysteria (many emotional symptoms)
Infertility
Inflammatory and "fibrous" disease
Inner ear dizziness
Insomnia
Irritability
Low blood pressure
Lethargy and clumsiness
Menopause
Mittelschmerz[3]
Migraine
Nymphomania, loss of libido
Optic neuritis
Panic, weepiness, night-worry
Palpitations or paroxysmal tachycardia
Paraesthesias
Pituitary abnormalities
Porphyria
Sciatica
Skin disorders: facial pigmentation, erythema, urticaria
Stroke symptoms
Sweat glands: fewer functional
Toxemia of pregnancy.
Urinary frequency, etc.
Varicose veins, tired leg
Vascular abnormalities: flushing, capillary fragility, clotting, kidney underfunction, varicosities.

1. Antibodies to joint material are found after even a mechanical or thermal injury to the joint; twisting cartilage makes it antigenic; autoimmune disease is probably nothing very special, and estrogen is now known to be responsible for many forms of it, including osteoarthritis. "Rheumatism" is an early sign of stress damage to joints. See H. Selye's book on arthritis and scleroderma.
2. See Annales d'Endocrinologie 37, p. 309; Cancer 33, p. 1506; Ann. N. Y. Acad. Sci., 1977. Progesterone deficiency predisposes to cancer.
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AN EFFICIENT ORAL THERAPY

As early as 1912, Armour & Co. sold desiccated corpus luteum for use in cases of ovarian failure, and said that it prevented "nervous symptoms accompanying" menstrual abnormalities.[1] It was also used to treat obesity and other physical conditions sometimes associated with "ovarian deficiency."

In early reports on the use of synthetic progestins, they were praised as being active when taken orally, unlike natural progesterone, which was said to be "destroyed in the stomach." Although I have looked carefully, I have never found the study which demonstrated that progesterone was inactive when taken orally. I am convinced that the idea was invented by the promoters of the patented new compounds.

When fats are eaten, they are almost 100% absorbed by the small intestine. They break up in the intestine into microscopic droplets, called chylomicrons, and reach the general circulation in that form. If progesterone is perfectly dissolved in oil, it is absorbed in that way, and is not immediately exposed to enzymes in the wall of the intestine or in the liver. People often speak of "avoiding the liver on the first pass," but in fact chylomicrons pass through the liver many times before they are destroyed; after an hour, 10% of the chylomicrons are still circulating.

While dissolved progesterone circulates in the chylomicrons, it will be distributed to the various tissues. Unlike other steroid hormones, progesterone tends to become concentrated inside cells. Its concentration in red blood cells is twice as high as its concentration in serum,[2]

and the brain contains a still higher concentration. These intracellular reservoirs of progesterone prolong the elevated blood levels, so that the observed hormone level after a single oral dose is much more stable than are the triglyceride levels after a fatty meal. The perfect absorption, and the prolonged action make the oil-dissolved oral progesterone much more efficient and economical than injected or suppository forms.

Since progesterone tends to promote its own synthesis, it shouldn't be necessary to keep using it, unless the ovaries have been removed, or the thyroid or cholesterol level is very low, or aging has damaged their ability to convert cholesterol to progesterone. While an excess of carotene can inhibit progesterone synthesis, a carrot salad (grated carrots, vinegar, coconut oil, and salt) can often help to normalize progesterone, apparently by protecting against intestinal absorption of bacterial endotoxin.

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PROGESTERONE IN ORTHOMOLECULAR MEDICINE

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