Ray Peat's Newsletter

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Progesterone, thyroid, cancer

In the first half of the twentieth century, Otto Warburg and Albert Szent-Gyorgyi proposed that proliferation is the natural "primordial" tendency of all cells, including those in complex multicellular organisms, in which many cells remain in a quiescent, non-proliferating state for years. Their orientation was similar to that of Johanes Muller, who in 1840 argued that cancer might originate at the level of tissues, rather than in the nature of the individual cells making up the tissue.

Both Warburg and Szent-Gyorgyi showed that oxidative metabolism is crucial in maintaining the relative quiescence that makes it possible for multicellular organisms to exist and to preserve their organization. In these organisms, the individual cells are embedded in a glue-like matrix, in the case of animals, or in a woody scaffolding, in the case of plants; the oxygen and nutrients needed by the cells diffuse through the matrix, so its condition is crucial for the cells' functions. The extracellular matrix, and the materials that pass through it, constitute the "field" within which cells develop and function.

Early researchers understood that the connective tissue matrix changes progressively in aging, which is evident in the fact that the meat of old animals is tougher than that of young animals. Leo Loeb, studying the effects of estrogen on the uterus, showed that it increased the formation of collagen, causing cells to be separated from their blood supply by a thickened barrier of water and collagen.

Estrogen, by altering the cell matrix, alters the developmental field itself. Simply by creating a thickened barrier, it makes it difficult for cells to maintain their proper place in the organism, and some of them, in the energy-deprived state, revert to the primordial proliferative state.

Thyroid hormone, the regulator of oxidative metabolism, is the basic hormone making possible the respiration which generates and sustains the multicellular state.

The simple idea of antagonism between hormones, for example between catabolic and anabolic steroids, or between progesterone and estrogen, is firmly based on experiments, but there is an attitude in medical endocrinology, based on the names of the substances, that insists on a "synergy" between estrogen ("the hormone of estrus, creating a readiness to copulate") and progesterone ("the hormone of pregnancy"). Sequential, coordinated action isn't the same as synergy. Hunger can lead to satiety, but no one denies that these are contrasting conditions. Hundreds of biological actions created by estrogen are reversed by progesterone, and vice versa.

Shock, capillary leakage, excessive clotting of the blood, epilepsy, goiter, hyperactivity, and countless other biological problems are created by an excess of estrogen, and normalized by progesterone. The problem of cancerization by estrogen, and its opposition by progesterone, was clearly defined by Alejandro Lipschutz more than fifty years ago, but a series of deliberate actions by the drug industry, and its "regulatory agencies," has prevented a rational and coherent approach to the use of hormones in preventing and curing cancer.

For over fifty years, estrogen has been widely promoted for the prevention and treatment of various cancers, and throughout the 20th century agents of the drug industry claimed that it was not carcinogenic, and prevented the US government from classifying it as such. During the same period, and for many of the same commercial reasons, natural progesterone has occasionally been claimed either to cause cancer, or to be ineffective in its treatment. While billions of dollars were spent in "cancer research," the useful basic knowledge about the prevention and cure of cancer was ignored. Not just ignored, but suppressed: Medical journals of all sorts have simply declined to publish favorable research on

progesterone, and medical conferences on female endocrinology that claim to be open to all views are not open to favorable reports on progesterone.

Some researchers have observed that only about one percent of medical research is scientifically sound, but that view ignores the fact that the "valid one percent" is certainly going to be misinterpreted, unless the reader understands that the medical journals are intensely subjective and biased in what they choose to publish, and that they exclude the research that would provide the essential contexts for evaluating the things that ***are*** published. To find an adequate context in which to interpret current research, we have to go back at least fifty years, to a time when the science journals were relatively independent.

The idea of "genetic determination," which I have written about many times, has been useful to the drug industry. If moderate amounts of estrogen didn't cause mutations of certain genes that were thought to distinguish normal cells from cancer cells, then how could it be carcinogenic? And if cancer cells are "genetically committed," then only lethal cytotoxic methods could be considered as therapies.

The history of estrogen and progesterone research offers an alternative view of cancer, and of physiology itself. In the 1940s, Hans Selye demonstrated that progesterone produced very deep anesthesia, and that its actions were essentially instanteous. Estrogen's characteristic actions, too (such as the uptake of water by tissues, and nervous excitation) were so rapid that it was clear that the effects were produced without the activation of special "genes." But these quick actions were generally ignored, because their existence wasn't compatible with the doctrine of genetic determination.

Estrogen acts at many different levels, modifying the state of water, of proteins and fats, of the immune, circulatory, and nervous systems. It isn't just a "carcinogen," or just a "female hormone." Many substances, processes, or conditions (cholera toxin, x-rays, oxygen deprivation) imitate many of estrogen's effects.

Energy generates order, and maintains it. Destruction of order degrades the ability of cells to produce energy.

Progesterone (and related substances), too, act on many levels of organization at the same time. The interactions of proteins and water are changed immediately, with circulatory and nervous and bioelectrical responses coinciding with changes of cells' functions, including changes in the proteins of the "receptor systems." The functional changes that can be seen in the first minutes of progesterone's actions lead to metabolic changes and then to more basic structural changes.

Stabilization and activation of mitochondria by progesterone, and a shift away from glycolysis (Joe and Ramirez, 2001: GAPDH inhibition), are exactly the opposite of estrogen's toxic effects on the mitochondria (by increasing NO, for example), and activation of glycolysis.

On the molecular level, progesterone and estrogen have different structural effects, that account for their globally opposite regulatory effects. Their systematically different effects on energy production lead to global differences in the regulation of cytokines, neurotransmitters, hormones, and cellular organelles, which contribute to macroscopic shifts in the distribution of substances throughout the organism, including water, fats, and the materials such as collagen and glycoproteins that make up the extracellular matrix.

If progesterone is to be named "the hormone of gestation," then estrogen might be called "the hormone of miscarriage."

The characteristic metabolic end-product of progesterone-dominated metabolism is carbon dioxide. During gestation, the fetus is exposed to large amounts of progesterone and carbon dioxide. The very high concentration of progesterone during gestation keeps tissues from retaining excess estrogen, even when estrogen is present in the blood stream. The very high concentration of carbon dioxide has many protective effects,

Every tumor is a biologically unique substance, but it is biologically compatible with its host. This is analogous to the tissue compatibility of twins which share a single placenta, even though they may be genetically different fraternal twins.

including protection against the formation of lactic acid.

The characteristic metabolic end-product of estrogen-dominated metabolism is lactic acid. Increasing lactic acid displaces carbon dioxide.

Carbon dioxide combines spontaneously with amine groups, as in the lysine residues of proteins, and this influences the interactions of the proteins with other substances, for example, inhibiting glycation of proteins; protein glycation occurs during stress and aging, and degrades the functions of proteins and cells and systems. These changes are believed to contribute to the hardening of connective tissues with aging.

The fibrosis of aging is associated with a generalized state of inflammation, producing catabolism and atrophy of most systems, with isolated regions escaping the general cachexia, and regenerating their cells and tissues in disorganized ways, producing many abnormalities that could be diagnosed as "precancerous," a few of which develop into tumors.

A.V. Everitt's book on the pituitary and aging mentions some studies that relate to progesterone and aging. Uterine collagen aging, which increases under the influence of estrogen, is lowest in the old rodents that have been bred the most often, and this is probably partly the result of progesterone's action on collagenase and fibroblasts, as well as its ability to displace estrogen from the tissues. Leo Loeb showed that excess estrogen and aging both produced similar increases in collagen. Alejandro Lipschutz found that chronic estrogen treatment produced fibrosis of practically all tissues, and that cancer later developed in those fibrotic tissues. Then he tested various steroids, and found that progesterone had the strongest antifibromatogenic action, and that pregnenolone was next in effectiveness. (Brief intermittent exposures to estrogen didn't produce the harmful effects, and now it's known that progesterone decreases the tissues' retention of estrogen.) Lipschutz' 1950 book on steroid hormones and tumors summarizes his work.

Contemporaries of Loeb and Lipschutz, Joseph Needham, C.H. Waddington and J.W. Orr, argued that cancer evolves through a series of developments in the tissues, rather than in single cells.

A few years later, Hans Selye showed that the partial isolation of tissue itself (for example, growing inside a small glass tube implanted in a rat) caused a tremendous acceleration of the aging process in the isolated cells and matrix. An impermeable sheet of plastic implanted in an animal tends to cause a cancer to develop, if it is folded to form a concavity. The thickened connective tissue matrix that develops with aging, irritation, and stress creates innumerable areas in which cells are similarly cut off from full contact with their normal environment.

Estrogen treatment at menopause produces alkalosis and hyperventilation. Alkalosis stimulates peroxidation and various other harmful stress-products. Prenatally, if estrogen excess doesn't kill the fetus, it retards its brain growth, because many of its metabolic actions are powerfully antigestational--actions that are used medically in the contraceptive pills and abortion pills.

All cancer cells produce lactate even in the presence of oxygen, and this increases their intracellular alkalinity, promoting swelling, calcium uptake, and proliferation. Continued exposure to lactic acid increases collagen formation and fibrosis.

I think of high altitude as analogous to the protected gestational state. (Both progesterone and carbon dioxide are increased in people adapted to high altitude.) Respiratory acidosis, meaning the retention of carbon dioxide, is very protective, and is an outstanding feature of life in the uterus. Even at the time that an embryo is implanting in the uterus, adequate carbon dioxide is crucial. Many of the mysteries of embryology and developmental biology have been explained by the presence of a high level of carbon dioxide during gestation. For example, an injury to the fetus heals without scarring, that is, with complete regeneration instead of the formation of a sort of collagenous plug. Over the last fifty years, several people have discovered that simply enclosing a wound (for example an amputated finger tip) in an air-tight compartment allows remarkably complete regeneration, even in adults, who

supposedly have lost the power of regeneration. (Exposure of tissues to air causes them to lose carbon dioxide.)

High altitude sickness is now treated with acetazolamide (which causes carbon dioxide retention, and respiratory acidosis), or with direct inhalation of carbon dioxide. Sleep apnea, which has been treated for many years with progesterone, is now being treated with acetazolamide, in recognition that it is caused by alkalosis. Both progesterone and acetazolamide increase the carbon dioxide content of the tissues, by decreasing sensitivity to carbon dioxide, yet they both stimulate respiration by increasing sensitivity to oxygen deprivation. (Wagenaar, et al., 2000.) Drugs similar to acetazolamide, sulfonamides that inhibit carbonic anhydrase, have recently been discovered to stop the growth of a wide variety of tumors.

Carbon dioxide, progesterone, and the carbonic anhydrase inhibitors stabilize and protect cells in very general ways. For example, they all inhibit epileptic seizures. All of them are involved in regulating calcium, preventing bone loss and hypercalcemia. In cancer, hypercalcemia is very common, and it is important to be able to correct it, because uncontrolled calcium is profoundly dangerous. (In "Homeostasis" and other newsletters I have written about the regulation of calcium.)

Increased intracellular calcium is excitatory, and interferes with mitochondrial energy production. Prolonged oxygen deprivation increases intracellular calcium (Smith, et al., 2001). When a cancer cell interacts with other cells, it can disturb their calcium regulation, and this can cause the cell to break its contacts with other cells (Tsuji, et al., 2002), and increased intracellular calcium can cause a cell to reorganize its intracellular structure, and to be transformed into spontaneously proliferating cells (Furst, et al., 2002). The intracellular architecture which is depolymerized by calcium excitation forms a link between the extracellular matrix and the regulation of genes in the nucleus. Generally, things (estrogen, prolactin, alkalinity, swelling, cadmium, iron) that increase intracellular calcium increase cellular proliferation. Drugs that decrease intracellular calcium are increasingly being seen to stop the proliferation of cancer cells.

Increased intracellular calcium also increases the formation of collagen, and drugs that decrease intracellular calcium decrease collagen secretion.

If cancer consists of a spontaneous process of healing and regeneration that goes wrong because of changes in its environment, because it has lost contact with its "formative field," then the only reasonable approach to the prevention and treatment of cancer is to restore that formative field. The conditions of gestation, for mammals, constitute a formative field in the highest degree that we know.

During gestation, after organs have differentiated, nerve cells extend their fibers from the brain to innervate muscles and other tissues. The special conditions of life in the uterus support this process, but something similar can happen during adult life, when damaged nerves regenerate. A major difference between injury to the fetus, and injury to an adult, is that the wound regenerates perfectly without a scar in the fetus, but in the adult, regeneration is often impaired, and a connective tissue scar replaces normally functioning tissue.

The intestinal nerves of stressed animals have been found to fragment; before the axons actually break, they form beads. (Beaded nerves are often seen in fresh tissue specimens that aren't treated by dehydration and embedding.) The surface tension of an axon has to be very low, for it to remain stable with such an extreme ratio of surface to volume: the diameter of an axon is similar to that of a bacterium. Ordinary water, with its high surface tension, breaks up into drops rather than forming a filament. If something increases the surface tension of a nerve, it tends to round up; the glial cells and Schwann cells that surround the axons of fast-acting nerves provide pregnenolone and progesterone to the axon, and the extreme lipophilicity of progesterone lowers the surface tension of cytoplasm. Progesterone powerfully improves nerve cell regeneration. During stress, cells run out of oxygen and produce lactic acid instead of carbon dioxide, and the lipophilic and acidic gas is replaced by the hydrophilic lactate.

Carbon dioxide protects nerves and muscles against excessive excitation. It inhibits lactic acid formation, and lipid peroxidation (measured in the blood) can be completely suppressed by a pCO2 of about 90 mm, which isn't high enough to produce acidosis.

Hospital respirators are normally set to hyperventilate patients, and the use of supplemental oxygen tends to make hyperventilation worse, making breathing and circulation more difficult. Carbogen, 95% oxygen with 5% carbon dioxide, is available, but is seldom used. Hyperbaric oxygen is both safer and more effective when carbon dioxide is added, but the amount of carbon dioxide needed varies with the pressure. More people would recover from brain and spinal cord injuries if physicians understood nerve and respiratory physiology.

One of the most commonly recognized features of estrogen excess is leakiness of the capillaries. Simple hyperventilation is enough to cause capillaries to leak, and this involves many related events, including decreased carbon dioxide, and increased release of serotonin. Edema, fibrosis, and inflammation (resulting from capillary leakage) contribute to a change in cellular energy production, and along with the actions of serotonin and other regulatory substances released during the alkalosis of stress, cells are stimulated to multiply.

The excitation of cells produced by a deficiency of carbon dioxide increases their need for energy. If their energy production is suppressed (as by estrogen, serotonin, and edema), they will either adapt or die.

In the isolation of a degenerating extracellular matrix, with a defective energy supply, some cells will react as though they are going to repair a wound or regenerate tissue, proliferating and degrading the damaged matrix, but instead of encountering healthy tissue, they sometimes encounter only more damaged tissue, and other cells in the simplified, proliferating state. Without finding the stable field of a healthy organism, they will continue to adapt and develop, but with reference to a field that has no function. Eventually, that kind of disoriented adaptation can produce a malignant tumor.

A 1951 Symposium on Steroids in Experimental and Clinical Practice (held in Cuernavaca), edited by Abraham White, has a chapter by Roy Hertz, et al, "Observations on the effect of progesterone on carcinoma of the cervix," that follows up on the antitumorigenic effects of progesterone discovered by Lipschutz, and the chapter includes some very interesting photographs of cervical tumors before and after treatment, and they reported that "In eleven of the 17 treated patients visible and palpable evidence of regressive alteration of the tumor mass could be demonstrated. This consisted of (a) distinct reduction in size of the visible portion of the cancer as well as reduction of the palpable extent of the mass, (b) reduction in vascularity and friability of the visible lesion with a clearly demonstrable epithelization of previously raw surfaces and (c) markedly increased pliability of the previously rigid and infiltrated parametria." *[That is, the bloody messes started healing, and the woody lumps began to feel like normal tissue.]* Despite the amazingly favorable results, they conclude "We do not consider the regressive changes observed to be sufficient to indicate the use of progesteone as a therapeutic agent in carcinoma of the cervix." This conclusion is especially interesting, considering that two pages later, Escher, et al., say that the highly ambiguous effects of estrogens on breast cancer "are of value to advanced-cancer groups." I think it's likely that the institutional sponsorship of the symposium influenced those conclusions.

Hertz, et al., gave the women 250 mg of progesterone in 5 ml of vegetable oil i.m., usually daily, for ten to 170 days. They didn't mention any side effects of sedation or anesthesia. Hans Selye found that large doses of progesterone caused profound anesthesia in rats, ***but this effect has never been reported in humans, because the pharmaceutical forms of progesterone don't permit adequate doses.*** Using progesterone dissolved in tocopherol (at 10% or 20% concentration), it takes only 100 mg to semi-anesthetize some people, and very profound anesthesia can be produced by larger doses. (In this form, a very large dose can kill a rat, though it stimulates the respiratory center at lower anesthetic doses.)

Progesterone is barely soluble in ordinary vegetable oils, and publications rarely mention that the formulations which contain 250 mg/ml also contain the "bacteriostat," benzyl alcohol, which is the actual solvent, but which is so soluble in water that the progesterone crystallizes immediately after intramuscular injection. (I have previously written about the history of medical progesterone, and the fraudulent claims and doctrines that have shaped its use.)

Although my observations show that progesterone is much more effective in treating many kinds of cancer than most of the published literature indicates, journal editors "know" otherwise. When I applied for the patent on the formulation of progesterone in vitamin E, the patent examiner told me that I must remove any mention of cancer if I wanted my application to be approved. The "evil mutant cell" theory of cancer, and the official description of progesterone as a "gestational hormone" or progestin, combine to create an attitude that doesn't want to think very long about progesterone's general regulatory functions in the organism.

Synthetic "progestins" have some of the properties of progesterone, and many studies have shown that they can be curative when used against several kinds of cancer. But the prevailing cancer culture has led to their use in combination with cytotoxic chemicals, and/or radiation, rather than with the factors that would really synergize with their "progestational" actions: The factors that would correct the formative, organismic field.

Since part of progesterone's therapeutic action is its ability to raise the concentration of carbon dioxide in the tissues, other techniques that increase carbon dioxide should be used at the same time. Thyroid's action is crucial for the production of carbon dioxide, and for the avoidance of lactic acidosis, adrenalin excess, and other processes that lower carbon dioxide concentration. (And, of course, thyroid is essential for the synthesis of progesterone, and for restraining the synthesis of estrogen, and accelerating its elimination from the body.)

Progesterone, thyroid, and carbon dioxide all protect against the cancer-promoting actions of calcium, and they do this by increasing respiratory energy, which favors intracellular magnesium over calcium. Adequate magnesium in the diet is extremely important. It is counterproductive to eat a calcium-deficient diet, since that tends to increase the intracellular calcium at the expense of calcium taken from the bones.

The immense power of the pharmaceutical industry, and its controlled government agencies, creates a situation in which the work of people like Lipschutz and Needham is written out of the culture. With the loss of a meaningful context, individuals with an authoritarian inclination will believe that science consists of comparing the latest therapeutic products or technologies with the earlier products or technologies. Some of the newer products and technologies will be sold as "alternative medicine," by a different branch of industry. But if the newer alternatives still conform to the view of cancer and life that was created to sell the old products, they can never make a real difference.

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Medicina (B Aires) 1985;45(2):110-6. **[Fibrosis and cirrhosis in the rabbit induced by diethylstilbestrol and its inhibition with progesterone].** [Article in Spanish] Lanari A, de Kremer GH.

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Anticancer Res 1999 Nov-Dec;19(6A):4877-86. **Cell damage, aging and transformation: a multilevel analysis of carcinogenesis.** Rubin H. **"One of the most surprising relations is that inhibition of cell growth in a transformation-competent population by long term confluence or acutely lowered serum concentration is a strong enhancer of neoplastic change.** The transformation is preceded and accompanied by heritable damage to the entire cell population as expressed among progeny cells in a heterogeneous reduction in growth rate at low density as well as delayed reproductive death in some of the cells. The picture bears resemblance to the relation in vivo between local atrophy in the stomach and prostate and cancer in those organs, as well as the relation between tissue damage and cancer in relatively quiescent organs such as pancreas, urinary bladder, etc." "The most common genetic changes found in tumors are large chromosomal deletions." "The results in cell culture help to focus attention on proximal mechanisms of malignant cell behavior in the organism." **"The order that controls heterogeneity is weakened with age and contributes to the origin and progression of disordered growth."**

Gastroenterology 1984 Oct;87(4):777-87. **Acetaldehyde and lactate stimulate collagen synthesis of cultured baboon liver myofibroblasts.** Savolainen ER, Leo MA, Timpl R, Lieber CS.

J Endocrinol 1998 Sep;158(3):401-7. **Progesterone inhibits glucocorticoid-dependent aromatase induction in human adipose fibroblasts.** Schmidt M, Renner C, Loffler G **"Progesterone must be considered a potential physiological inhibitor of glucocorticoid-dependent aromatase induction in adipose tissue. It is proposed that it is a suppressor of aromatase induction in adipose tissue in premenopausal women."**

Hepatology 1984 Mar-Apr;4(2):295-9. **Frequency of hyperprolinemia in alcoholic liver cirrhosis: relationship to blood lactate.** Shaw S, Worner TM, Lieber CS.

Acta Pathol Jpn 1984 Jul;34(4):797-811. **Progeria with cardiac hypertrophy and review of 12 autopsy cases in the literature.** Shozawa T, Sageshima M, Okada E. "Histologic findings suggest that increasing of collagen in the connective tissue may play an important role in progeria. Further study of metabolic disturbance in the connective tissue of progeria is necessary."

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Gynecol Endocrinol 1999 Jun;13 Suppl 4:3-9. **Progestins and cancer.** Sitruk-Ware R, Plu-Bureau G. **"Progestins exert different effects according to the steroid from which they are derived, e.g. pregnanes derived from progesterone, estranes or gonanes derived from testosterone.** Some estrane derivatives are able to stimulate breast cell multiplication in vitro through an estrogen receptor-mediated pathway. Most pregnanes do not exert such an effect. Also, some pregnane derivatives stimulate apoptosis, leading to cell death. However, it is well established that high doses of progestins have been successfully used in the treatment of advanced breast cancer as second-line endocrine therapy. Finally, striking differences have been observed in progestin use in Europe and in the USA. **In France, where the rate of progestin use per head is higher than in the USA, the rate of breast cancer has not increased as sharply as observed in North America.** Although cancer genesis is multifactorial, it may be concluded that progestins do protect endometrial tissue against the proliferative action of estrogen and if they do not protect breast tissue, at least they do not stimulate its proliferation. Also, they are useful agents as a second-line therapy for breast cancer, when used at high doses."

Int J Biochem Cell Biol 1997 Nov;29(11):1273-8. **Magnesium deficiency enhances oxidative stress and collagen synthesis in vivo in the aorta of rats.** Shivakumar K, Kumar BP. "Magnesium deficiency has been shown to produce vascular lesions in experimental animals, but the underlying mechanisms of vascular injury are not clear. It has been reported that in rodents, magnesium deficiency enhances circulating levels of factors that promote free radical generation and are mitogenic." **"These findings suggest that magnesium deficiency may trigger a wound healing response, involving oxidative injury and growth stimulation, in the vascular system."**

Smithers, D.W.: A Clinical Prospect of the Cancer Problem. Livingstone, Edinburgh, London, 1960. [A cancer cell isn't a distinct structural entity.]

Nature 1971 Jan 1;229(5279):58-9. **Glycoproteins from connective tissue of twins.** Srinivasan SR, Radhakrishnamurthy B, Pargaonkar PS, Berenson GS.

Br Med J 1967 August 5;3:338-41. **Progestin therapy of breast cancer: comparison of agents.** Stoll BA.

Bioorg Med Chem 2001 Mar;9(3):703-14. **Carbonic anhydrase inhibitors: sulfonamides as antitumor agents?** Supuran CT, Briganti F, Tilli S, Chegwidden WR, Scozzafava A. "Three of the derivatives belonging to this new class of CA inhibitors were also tested as inhibitors of tumor cell growth in vitro. These sulfonamides showed potent inhibition of growth against several leukemia, non-small cell lung, ovarian, melanoma, colon, CNS, renal, prostate and breast cancer cell lines."

J Enzyme Inhib 2000;15(6):597-610. **Carbonic anhydrase inhibitors: aromatic sulfonamides and disulfonamides act as efficient tumor growth inhibitors.** Supuran CT, Scozzafava A. "Aromatic/heterocyclic sulfonamides generally act as strong inhibitors of the zinc enzyme carbonic anhydrase (CA, EC 4.2.1.1). Here we report the unexpected finding that potent aromatic sulfonamide inhibitors of CA, possessing inhibition constants in the range of 10(-8)-10(-9) M (against all the isozymes), also act as efficient in vitro tumor cell growth inhibitors, with GI50 (molarity of inhibitor producing a 50% inhibition of tumor cell growth) values of 10 nM-35 microM against several leukemia, non-small cell lung cancer, ovarian, melanoma, colon, CNS, renal, prostate and breast cancer cell lines."

Eur J Med Chem 2000 Sep;35(9):867-74. **Carbonic anhydrase inhibitors--Part 94. 1,3,4-thiadiazole-2-sulfonamidederivatives as antitumor agents?** Supuran CT, Scozzafava A. "Potent sulfonamide inhibitors of the zinc enzyme carbonic anhydrase . . . were shown to act as efficient in vitro tumour cell growth inhibitors with GI(50) (molarity of inhibitor producing a 50% inhibition of tumour cell growth) values typically in the range of 0.1-30 microM against **several leukaemia, non-small cell lung cancer, ovarian, melanoma, colon, CNS, renal, prostate and breast cancer cell lines."**

Respir Physiol 2000 Jan;119(1):19-29. **Medroxyprogesterone acetate with acetazolamide stimulates breathing in cats.** Wagenaar M, Teppema LJ, Berkenbosch A, Olievier CN, Folgering HT. "Both medroxyprogesterone acetate (MPA) and acetazolamide (ACET) increase ventilation. Combined administration of these agents could result in an additional improvement of blood gases, for example in patients with chronic obstructive pulmonary diseases." "We performed dynamic end-tidal CO2 forcing and analysed the data with a two-compartment model comprising a fast peripheral and slow central compartment, **characterized by CO2 sensitivities (Sp and Sc, respectively) and a single offset (the apnoeic threshold B). MPA reduced Sp from 0.22 +/- 0.09 (mean +/- S.D.) to 0.13 +/- 0.06 L min(-1) kPa(-1) (P < 0.01) and Sc from 1.01 +/- 0.38 to 0.88 +/- 0.32 L min(-1) kPa(-1) (P < 0.01). B decreased** from 4.02 +/- 0.27 to 3.64 +/- 0.42 kPa (P < 0.01)." "Because both treatments reduced ventilatory CO2 sensitivity, we conclude that a stimulating effect on ventilation is due to a decrease in the apnoeic threshold. Combined administration of MPA and ACET may lead to larger increases in ventilation than treatment with either drugs alone."

Am J Obstet Gynecol 1996 Jan;174(1 Pt 1):62-5. **Lipid peroxidation in cord blood at birth.** Wang W, Pang CC, Rogers MS, Chang AM. "There was a significant association between lipoperoxides and cord blood pH and base excess. A significant difference existed in the levels of umbilical artery lipoperoxides between nonacidemic and acidemic fetus, as defined by an umbilical arterial pH < 7.20."

Circ Res 1992 Oct;71(4):831-9. **Decreased collagen gene expression and absence of fibrosis in thyroid hormone-induced myocardial hypertrophy. Response of cardiac fibroblasts to thyroid hormone in vitro.** Yao J, Eghbali M. "In this study we examined the effects of thyroid hormone on collagen gene expression in thyroid hormone-induced myocardial hypertrophy and the response of cardiac fibroblasts to thyroid hormone in culture." "Collagen synthesis as shown by immunofluorescent staining of intracellular collagen in cultured fibroblasts and in frozen sections of myocardium was also diminished."

Cardiovasc Res 1992 Jun;26(6):603-7. **Decreased collagen mRNA and regression of cardiac fibrosis in the ventricular myocardium of the tight skin mouse following thyroid hormone treatment.** Yao J, Eghbali M. "The aim was to study the effect of thyroid hormone on collagen gene expression in the myocardium of the tight skin mouse (TSK), a genetic model of myocardial fibrosis." "Effects of thyroid hormone on ventricular gene expression in TSK mice result in a diminished collagen mRNA and collagen content and the disappearance of cardiac fibrosis. Thyroid hormone may selectively prevent the induction of cardiac fibrosis and play an important role in regression of cardiac fibrosis via endocrine pathways."

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