Ray Peat's Newsletter

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Sketch of some of the broader concepts needed in aging theory:

Estrogen increases with aging, and the characteristic changes of aging---including menopause, glucose intolerance/insulin resistance, autoimmunity and inflammatory dysregulation, respiratory decline, susceptibility to cancer, connective tissue hardening and slowed cellular responses---are produced by prolonged exposure to estrogen.

Radiation, cholera toxin, and a variety of stressors synergize with or imitate estrogen.

Estrogen is just one of the intrinsic excitatory substances, which are produced by stress, and which participate in self-stimulating loops.

Energy depletion, free-radical generation, and gene mutations are produced by estrogen and by the nitric oxide (NO) promoted by estrogen.

Estrogen and nitric oxide activate the pituitary, in just one of many vicious circles of self-stimulation.

Carbon dioxide produced in the high energy state provides direct protection of protein structure against random chemical changes. These protective effects occur within cells, between cells, and in the extracellular "ground substance" or matrix, in which cells are embedded. Thyroid and progesterone support CO2's protective effects.

Ammonia is one of the factors promoted by estrogen and other stressors, in competition with carbon dioxide.

Ammonia is pro-inflammatory. With NO (nitric oxide), TNF (tumor necrosis factor), glutamate, and calcium, it activates cells while interfering with their energy. *In vitro*, ammonia and lactate clearly poison cells (contributing to the myth of "programmed aging.")

The "little mouse," and the experiments of Denckla and Everitt, show that a simple growth hormone deficiency or lack of pituitary function can double the life span. Intervention in the many other self-stimulating excitatory pathways can produce additional retardation of the aging process, acting at many levels, from the extracellular matrix to the brain.

Estrogen, Aging, Radiation, Migraine & Energy

The Manhattan Project demonstrated that, by spending a couple of billion dollars, a very impressive explosion could be created by exploiting the unsurprising fact that, in the presence of a sufficient mass of suitable material, spontaneous radioactivity becomes self-stimulating. Part of the taxpayers' money was spent on convincing the public that the bomb was a natural outcome of the fundamentally humanistic scientific enterprise which would give everyone free electricity and a generally glorious life.

Now that we have genetically modified foods, and gamma-irradiated meats and vegetables, maybe it's time to evaluate the process that has led us to these technologies. By seeing how we arrived at our present scientific-technological state, I think many seemingly unrelated scientific and medical issues will take on new meaning, and I think this historical context will justify some reorientations in therapy.

Albert Einstein's name is often associated with the Manhattan Project, but years earlier he departed from the statistical world-view, the assumption of metaphysical randomness, that has characterized "quantum physics," as well as nuclear physics. During the years in which metaphysical randomness took over official physics, that world-view was also being applied to genetics. Eugenics and Racial Hygiene reached their peak almost simultaneously with the realization of the Atomic Bomb (or Tomic Bomb, as F. Soddy more correctly called it). Precisely the same mathematical formulas were used to describe nuclear fission and genetic mutation.

Young physicists from the Manhattan Project, with government financing, smoothly made a transition into genetics, becoming, almost

mysteriously, leaders in the field of "molecular biology." Government subsidies for the nuclear power industry were becoming government subsidies for the industrialization of biology.

The prestige of their background as Manhattan Project physicists made it unnecessary for them to learn anything about biology. As their institutes of molecular biology took over biology departments in the 1960s, they were able to control what was being taught to both undergraduate and graduate biology students.

The physics and physical chemistry that were really relevant to biology, that had been developed before the government/industry consortium took over, were effectively suppressed. If old science journals and monographs didn't just disappear, they were put into "storage," where they couldn't be browsed. At UCLA, for example, you have to place an order for a specific journal, and then wait days for someone to search for the book. Computerized data-bases simply ignored the older work, even though the volume of research published throughout the world in 1930 or 1950 would be similar to the amount currently published in a week or month.

The head of Oregon's Institute of Molecular Biology argued that science develops by its own logic, and can't be blamed for the anti-humanistic ways in which it is used. Since, as a Manhattan Project physicist, he didn't have any knowledge of biology or of other branches of physical science, he couldn't be aware of the powerful ways in which science was distorted by industrial and military intervention. Science, as an ideal, of course can't be blamed for the anti-scientific absurdities that have been sold to the public in the name of science.

First, a philosophy of atomistic reductionism told people that they must give up ideas of teleology, anthropomorphism, purpose, direction, consciousness, and holism, as archaic metaphysical and unscientific concepts. Then, in this cultural vacuum, it was possible to impose the metaphysic of control and of technological improvement, an accountant's metaphysics of the bottom line, which always looks for the quickest return and the most discrete result. The doctrine of genetic determinism was intrinsic to the Eugenics movement: The proper authorities could improve the race by killing the inferior specimens, because it is in the (random) nature of the world that things would degenerate if the fit weren't preserved and the unfit destroyed. The mathematical treatment of random events has no place for the complexities of context, and so is perfect for a system in which the only issue is the power to control for an immediate benefit. Ecology and physiology were marginalized by their very complexity.

These doctrines of random mutation, and of "hygienically" killing the deviant cells, took over cancer biology, with governmental financing.

There was no shortage of evidence that contradicted the idea that cancer arises as a single mutant cell, but few people are now aware of that evidence. Harry Rubin is one of the few people remaining who understand the evidence, and build on it.

The definition of a gene has been revised many times. Originally, a gene was something that produced "a trait," and then it was said to be the "functional unit of heredity." Currently, it is often stated as "the section of DNA that contains the information for making a functonal biological product, which may be a protein or an RNA molecule." But, informally, the traditional view is often passed on, leading many people to think that each protein has "its gene."

The dogmatic view (once taught by molecular geneticists) that "one gene produces one protein" has falsified everything in biology: In reality, the environmentally responsive changes in the composition of proteins means that there are a multitude of different "growth hormones," "prolactins," "interleukins," "hormone receptors," etc. Stress and aging cause cumulative deviations through this process of chemical differentiation.

Rather than seeing cancer (or aging or various degenerative diseases) as a special problem in developmental biology, governed by complex interactions of cells with their environment, **the doctrine of the deviant mutant cell has become an excuse for gross biological ignorance.**

Chronic irritation used to be emphasized as a cause of cancer, but all of the irritating factors were reduced to mutagenic factors, and this made it possible to devalue the tissue changes produced by chronic injury, which preceded and accompanied the development of cancer.

Tissue fibrosis, which was associated with both inflammation and atrophy of injured tissues, became separated from the study of cancer, because it was a complex physiological process, and not a distinct genetic event.

But changes in the connective tissue matrix were always crucially involved in the process of cancerization, and these changes overlapped with the changes that could be seen in many other biological processes.

Ionizing radiation produces inflammation, edema, over-production of collagen, and finally atrophy and fibrosis, with hardening of the collagen and slowing of repair processes. In the atrophic tissue, cancer sometimes develops. Many other harmful agents produce very similar sequences of tissue changes--heat, suffocation, malnutrition, chemical poisoning, and estrogen excess, for example.

The role of the balanced, or imbalanced, tissue environment in carcinogenesis can be seen very clearly in an experiment in which small sheets of plastic were implanted in animals. Near some of the sheets, nests of cancer cells would develop, but they always developed in a concavity that had been formed by the folding of the plastic sheet, almost isolating some cells from their normal environment. This experiment was reminiscent of the experiments of Hans Selye's, in which he found that the tissue which had grown into small subcutaneously implanted glass tubes aged much more rapidly than the rest of the animal's tissues.

The changes of aging are so similar to those of radiation damage that some people have believed that aging was caused by environmental radiation, or at least that radiation accelerates normal aging. The first isn't true, the second is probably approximately true. Anything that produces inflammation, increasing collagen production and collagen hardening, and that slows tissue renewal, is accelerating changes that seem characteristic of aging. But the idea that radiation produces aging by creating mutations has been very clearly refuted. Molecular biologists generally lost interest in the age-accelerating effects of raditation when they saw it wasn't acting through genetic mutations.

Ultraviolet damage to the skin causes changes in the extracellular connective substance that are very similar to aging, but that can be distinguished from the normal age changes by slight differences in the chemistry of the cross-links that make the tissue more rigid. For practical purposes, though, the similarities are more important than the differences.

The "collagen theory of aging" was the idea that the changes which occur in the extracellular matrix (of which collagen is only one component) lead to progressive changes in cellular metabolism, shutting off their access to the blood stream, and that these changes in the matrix are the essential cause of aging. The differences in thickness and flexibility between tanned cowhide and calf-skin, the toughness of meat from old animals, and the rigidity of ligaments in old joints make it obvious that connective tissue changes are characteristic of aging.

Some people who advocate the collagen theory of aging believe that the cross-links that accumulate with age are mainly produced by free radicals (which may be derived from peroxidized lipids, heavy metals, radiation, or ascorbic acid, for example), but others emphasize the role of glucose in forming the links, since diabetes accelerates the hardening of collagen.

In scar tissue, calluses, keloids, and oil granulomas or allergic granulomas, tissue injury or stress has produced structural changes. Tissue stress affects the structure of connective tissues very generally. Tendons and bones are guided and altered in their development by pressure and tension. Histologists have said that they can distinguish structural differences in the bones of wild animals and tame animals of the same species, apparently resulting from the differences in their way of life.

Cellular and extracellular responses are interactive, so that stressed cells produce defective extracellular matrix, which can contribute to the stress of the cells. Changes induced by stress in

some cases interfere with the proper differentiation of cells regulated by their extracellular matrix.

In early studies of estrogen-treated animals, estrogen was found to cause tremendous increases in the deposition of collagen. In the 1960s, detailed studies on the hardening of tendons with aging were done. **It was discovered that estrogen treatment accelerated the stiffening of tendons that normally occurs with aging,** and that progesterone reversed the estrogen effect.

On the level of the whole organism, stress causes overactivity of the pituitary, **and removal of the pituitary extends life, and retards the hardening of the extracellular connective material (Everitt, et al., 1983). The collagen theory of aging necessarily involves the endocrine system.**

When I was measuring the oxygen consumption of uterine tissue from animals of different ages, I found that tissue from some of the oldest animals had what appeared to be "negative oxygen consumption," that is, some gas was being produced at a higher rate than oxygen was being produced, increasing the volume or pressure of the air in the chamber, instead of decreasing it. Since I knew that fatigued nerve and muscle emit some ammonia, I arranged my experiment so that both carbon dioxide and ammonia would be absorbed from the air, and found that these tissues were actually consuming oxygen at a much higher rate than tissues from young animals. While the uterus of a young animal is flexible and bright pink, the uterus from a typical old animal was stiff and purple or blue, indicating an oxygen deficiency. Apparently, their high rate of oxygen consumption was creating a relatively hypoxic condition in the aged uterus. (The rest of my research had to do with identifying the nature of this oxygen consumption; estrogen stimulates the "NADH-oxidase" enzyme function, which---like age-pigment itself---can create a short-circuit between oxygen and the NADH energy source. This serves the purpose of allowing glycolysis to continue in the absence of normal mitochondrial functioning, and probably interferes with normal mitochondrial production of ATP, CO_2, etc., by competing for the oxygen supply.)

Estrogen is known to decrease liver glycogen storage, while progesterone increases it. If a tissue is stimulated to metabolize at a high rate, especially without an adequate supply of glucose, it will consume protein as fuel, with the production of ammonia. Apparently, what I saw in my experiments with the old uteri was a consequence of combining a high level of stimulation with a low level of glucose and oxygen. In nerves, this would be called excitotoxicity.

Although there are several ways in which estrogen can increase the formation of ammonia, just producing hypoxia is sufficient to cause a large increase in ammonia production. **Any exaggerated stimulation, stress, or energy deficit tends to increase the level of ammonia in tissue.** Because of the association of ammonia with energy depletion, many people argue that the ammonia released from nerve and muscle comes primarily from the breakdown of ATP, leading to the deamination of adenosine. But by 1970 there was already clear evidence for other important sources of ammonia. The use of amino acids for fuel, which happens during stress, releases ammonia. **Eating isolated amino acids, exercising intensely, or having an excess of cortisol, causes tissue proteins to be broken down, with the release of ammonia.** Although the free amino acid, glutamate, can be combined with ammonia to remove it safely from cells, ammonia can also be combined with the glutamic acid (or aspartic acid) groups in tissue proteins. **This binding of ammonia to an acid is called amidation.**

When I have written about the importance of carbon dioxide, I mentioned that it binds to amino groups (often lysine) in proteins, protecting those groups from combination with sugars (glycosylation) or the products of lipid peroxidation. Peptide hormones and antibodies function very differently when they have been glycosylated. The lysine groups, that are so important for carbon dioxide's protective effects, are important sites for the cross-linking reactions in collagen, and one form of cross-linking involves the connection of a glutamine group in one protein with the lysine group in another.

Amidation and deamidation occur fairly massively during fatigue and rest in brain proteins, and in many other systems. The activities of proteins are changed as a consequence, but there has been very little research into this important area, because the dogma that "one gene produces one protein" has created the sense that there is something unwholesome about these protein-modifying complexities. Nevertheless, **it is clear that inflammation, connective tissue aging, keratinization, and antigenic changes of tissues and proteins (relevant to autoimmunity and "connective tissue diseases" as well as normal development) are influenced by amidation.**

Estrogen causes epithelial cells to cornify or keratinize (condensing, and being converted mainly into the "horny" material, keratin) earlier than they would otherwise. This process of final differentiation normally occurs as the cells of the skin or mucous membrane grow outward, away from the blood vessels that supply them with nutrients and oxygen. Simply growing away from their supporting blood vessels creates a stress of deprivation. Vitamin A is one of the factors that opposes estrogen and prevents premature keratinization of epithelial cells.

The same enzymes that keratinize cells under the influence of estrogen, and that participate in the solidification of blood clots and the contraction of connetive tissue in healing wounds, can also cross-link collagen molecules.

One of the molecules forming the crosslink bond is glutamine, which exists normally in proteins, but which can also be formed by the addition of ammonia to the acidic side-chain of glutamic acid. The other amino acid that reacts to form the cross-link bond is lysine, which can be protected against chemical reactions by combining with carbon dioxide, This protective effect of carbon dioxide is probably as widely distributed as is lysine in protein, though even when a lysine group isn't exposed, all proteins have an amino group at one end that can interact with carbon dioxide or other substance. **Hormones and their "receptors," enzymes, and structural proteins all exist in multiple forms. The genetic dogma that "one gene corresponds to one protein" has been extremely misleading, and has allowed most researchers to ignore the processes that dominate physiological adaptation.**

Oxygen deprivation is enough to stimulate collagen synthesis (Chvapil; 1968, 1969, 1975), and is probably one of the common factors in tissue degeneration. **Estrogen excess tends to reduce the availability of oxygen in tissues, and oxygen deprivation in many cases imitates estrogenic stimulation.** .The ammonia produced in stressed tissues contributes to changes in collagen and the extracellular matrix, and has both local and systemic effects.

Ammonia, like estrogen, promotes the excitotoxic processes, activating the production of nitric oxide (NO), and stimulating the glutamate receptors, sometimes causing seizures, and if prolonged, causing stupor or coma. But it always activates the pituitary, and in other tissues, the production of free radicals causes molecular tissue damage. The stressors produced by estrogen, for example NO and growth hormone, activate the enzyme aromatase, which synthesizes estrogen, in just one of the many vicious circles. Growth hormone tends to increase ammonia levels.

Estrogen is just one of the intrinsic excitatory substances, which are produced by stress, and which participate in self-stimulating loops. Ammonia and nitric oxide are two of the most pervasive endogenous excitants and toxins. "NO [nitric oxide] is emerging as an important endogenously-derived neurotoxin" (Dawson and Dawson, 1995).

Ammonia, like nitric oxide, inhibits respiration, and can increase the Crabtree effect (with aerobic glycolysis stimulated by increased glucose, inhibiting respiration). This suggests an important role for it in cancer in general, and especially in liver cancer. In the uncontrolled glycolysis of cancer, ammonia can be used to form amino acids from the lactate and pyruvate produced by glycolysis, supporting growth of the tumor at the expense of the normal tissues that are producing ammonia by protein degradation.

Ammonia can produce both convulsive seizures and stupor or coma, and it alters brain

cells, shifting the balance toward that seen in Alzheimer's disease.

Ammonia contributes to the hypertrophy of damaged kidneys, and the same mechanism, decreased protein breakdown in the presence of too much ammonia, probably contributes to the increased volume of extracellular matrix that occurs in so many diseases of stress, aging, and hyperestrogenism.

Ammonia has also been found to be increased during migraine attacks. I suspect that progesterone's sometimes dramatic effect on migraine involves ammonia and energy metabolism. Ammonia disturbs carbon dioxide's regulation of brain circulation, and when ammonia is "detoxified" into glutamine (though glutamine is still toxic in excess) ATP is consumed, leading to dysregulation of vascular smooth muscle. Progesterone's ability to stop the local excitation of nerve cells spares ATP. It seems likely that nitric oxide, the production of which is inhibited by progesterone, is also involved in the vasodilation and energy depletion.

Almost any sort of liver disease increases the systemic ammonia level. Estrogen can cause a large variety of liver diseases, including fatty liver and cholestasis; ammonia, which is toxic in itself, also links into another potentially toxic system, the porphyrin synthetic system.

Porphyria (acute intermittent porphyria, hepatic porphyria) is a disease that can cause nerve damage, hypertension, and connective tissue damage. It typically involves an excess of two precursors of heme, and sometimes a deficiency of heme (needed for respiratory enzymes), and it is often triggered by hypoglycemia, by exercise, and by estrogen or by certain poisons. Although it is usually described as a strictly genetic disease, it is highly susceptible to environmental influences, and a proper reevaluation of the evidence might show that it is more often environmental than genetic. Most of the evidence for a genetic cause consists of measurements that show low activity of certain enzymes. Since the conditions prevailing when a protein is synthesized can affect its structure and functions, the simple measurement of enzyme activity is hardly an appropriate argument.

The two substances that accumulate happen to be in a synthetic sequence, subsequent to a step in which CO2 is removed, and before a step in which NH3, ammonia, is removed. The principle of mass action indicates that a reaction will slow or stop when there is a certain concentration of the product of the reaction. High CO2 and low NH3 will prevent an accumulation of these chemicals, one of which is a potent neurotoxin. The opposite situation, low CO2 and high NH3 (ammonia), will tend to cause an accumulation of these substances. Therefore, a simple metabolic shift that predictably happens in stress and malnutrition, can explain the main type of porphyria, independently of specific genetic problems. Everyone's genetic constitution is unique, and in a metabolically complex condition such as porphyria, there will be a spectrum of susceptibility. To draw a line across the spectrum, dividing people with "genetic defects" from the normal, is a purely arbitary and illogical procedure. It is much more important to identify and eliminate "porphyriogenic" environments.

Since porphyria attacks commonly occur premenstrually or after skipping a meal, the food cravings caused by increased estrogen and lowered blood sugar, are probably reinforced in many people by dread of the terrible symptoms that can be produced by not eating enough, resulting from the increased ammonia and porphyrins or porphyrin precursors. Calorie restriction can be dangerous when porphyria is developing.

The presence of porphyrin poisoning, with its associated free radical toxins, can lead to the activation of heme oxygenase, the enzyme which produces carbon monoxide, which I have discussed elsewhere as a cause of the respiratory defect that characterizes cancer. Both ammonia and porphyria have been implicated in the production of cancer.

Acetazolamide, a drug that causes carbon dioxide to be retained in the tissues, tends to block the formation of ammonia. This is probably a confirmation of the importance of carbon dioxide as an anti-ammonia factor. High altitude also causes increased retention of carbon dioxide in the tissues, because of the Haldane-Bohr effect,

and the reduction of ammonia (production, serum concentration, and excretion) at high altitude is probably even greater than the reduction of lactate production.

Fibrotic tissue can be repaired, and the essential thing is to interrupt the processes that caused it to develop. I have written previously about the effects of vitamin E, progesterone, and DHEA on scars, keloids, scleroderma, arthritis, and liver cirrhosis, but there are many helpful therapies. Saturated fats are extremely important in the reversal of fibrosis. Recently, it has been found that just covering a keloid with a layer of silicone causes it to regress to some extent. I think the sealant allows carbon dioxide to accumulate, shifting the balance away from growth and toward shrinkage of the collagenous mass.

The particular therapy that's most helpful will depend on the particular nature of the stressor, but good nutrition is always of the greatest importance. Carnitine protects against ammonia; adenosine, niacin, and caffeine protect against various types of excitotoxicity. Vitamin A protects against premature cornification, and probably other cross-linking. Thyroid, progesterone, and glucose help to minimize exaggerated protein catabolism, and magnesium has a great variety of restorative functions.

Carnitine has been used with sodium benzoate and phenylacetate to lower ammonia, but the latter can produce some side effects. Except for treating neurotoxic ammonia, I don't recommend use of carnitine supplementation, since there is good evidence that carnitine increases oxidative damage when there is an abundance of unsaturated fat in the organism. Aspirin's similarity to benzoate and phenylacetate suggests that it might sometimes help to remove ammonia. The safest procedure is to use foods, such as fruit juices, that regulate nitrogen metabolism in varied ways.

The alpha-keto acids, which are found in many fruits, can bind ammonia, becoming ordinary amino acids. Potato juice (eliminating the starch with a carrot juicer) is a rich source of these alpha-keto acids.

Estrogen increases fairly steadily with aging in men, and its effects become more harmful as testosterone and other protective antiestrogens decline with aging. In women, the absolute estrogen level rises until near menopause, but during those years very high levels of progesterone protect most women against its harmful effects. The diseases that affect women more often than men are mainly diseases caused by a failure of progesterone and thryoid to regulate estrogen. The generally greater resistance and longevity of women can be attributed largely to progesterone dominance over estrogen. The extremely high progesterone production during pregnancy probably has long lasting protective effects, since there is clear evidence that longevity increases with the number of children borne. In animals, a large number of pregnancies produces anti-aging, and anti-estrogenic, effects that can be seen even in the elasticity of tendons.

The amount of irradiation needed to extend the shelf life of food is around 100,000 rads to 300,000 rads or even more, and even that intensity can't overcome the problem of dirty production facilities. **This amount of radiation produces a large amount of ammonia in food.** Dogs fed meat that had been irradiated were found to have severely depressed essential amino acids, and a low level of magnesium, protein, and creatinine in the blood. Vitamin A and other nutrients were depleted.

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Cytotechnology 1990 May;3(3):215-29.. **Hybridoma growth limitations: the roles of energy metabolism and ammonia production.** Newland M, Greenfield PF, Reid S. "It is shown **that growth inhibition usually occurs between 2-4 mM ammonia** although some cell lines have been shown to adapt to much higher concentrations, particularly in continuous culture. In batch cultures cell growth appears to be particularly susceptible to increased ammonia concentrations during the early stages of growth; ammonia increased the rate of cell death in the late stage of batch growth."

J Pharmacol Exp Ther 1997 Feb;280(2):846-53. **Antiinflammatory and analgesic activity of an inhibitor of neuropeptide amidation.** Ogonowski AA, May SW, Moore AB, Barrett LT, O'Bryant CL, Pollock SH.. 4-Phenyl-3-butenoic acid (PBA) has

been shown in vitro to be a turnover-dependent inactivator of peptidylglycine alpha-monooxygenase (PAM), the rate-limiting enzyme involved in the formation of amidated neuropeptides from their glycine-extended precursors. In the studies reported herein, we have shown that PBA produces a dose-dependent (50-500 mg/kg s.c.) inhibition of serum PAM activity in normal rats without affecting peptidylamidoglycolate lyase activity. Because amidated neuropeptides such as substance P and **calcitonin gene-related peptide are involved in acute inflammation, we evaluated the effects of PBA on carrageenan-induced inflammation in rats. The acute administration of PBA (s.c. or i.p.) produced a dose-related inhibition of edema with maximum inhibition (67%) observed at 2 hr postphlogistic agent. In addition, the continuous administration of PBA to animals over a 7-day period using osmotic pumps not only inhibited hind paw swelling induced by carrageenan but also inhibited serum PAM activity** and reduced tissue levels of substance P in hind paws. These results demonstrate for the first time a correlation between the antiinflammatory activity produced by an inhibitor of peptide amidation with its ability to inhibit serum PAM activity and lower endogenous tissue levels of substance P. Moreover, these results confirm our contention that PAM is an excellent pharmacological target for controlling the acute inflammatory response. We also demonstrate the ability of PBA to inhibit phenyl-p-quinone and acetylcholine-induced writhing in mice without affecting the spinally mediated tail immersion assay in rats. Because this analgesic effect was extremely rapid (within 15 min), PBA may be producing this effect by a mechanism other than peptide amidation.

Vopr Med Khim 1987 Jul-Aug;33(4):52-5. **[Amidation of blood proteins during hyperglycemia in experimental diabetes mellitus].** [Article in Russian] Pushkina NV, Tsybul'skii IE, Lukash AI.

J Nutr 1992 Mar;122(3 Suppl):850-4. **Metabolism of nitrogenous compounds by ruminant liver.** Reynolds CK. **"Growth hormone decreases liver urea release and increases liver glutamate release."**

Growth hormone stimulates drug-induced porphyrin formation in liver cells maintained in a serum-free medium. Sassa S; Golde DW; Li CH. J Biol Chem, 1981 Sep 10, 256:17, 8882-4.

Exp Cell Res 1977 Jun;107(1):207-17. **Inhibitor of protein degradation formed during incubation of isolated rat hepatocytes in a cell culture medium. Its identification as ammonia.** Seglen, P.O.

Urol Res 1999 Oct;27(5):376-81. **Ammonium-chloride-induced prostatic hypertrophy in vitro: urinary ammonia as a potential risk factor for benign prostatic hyperplasia.** Won JH, Parekattil SJ, Davidson SD, Luddy JS, Choudhury MS, Mallouh C, Tazaki H, Konno S.

Ukr Biokhim Zh 1995 May-Jun;67(3):59-69. [Department of the Biochemistry of Muscles]. [Article in Ukrainian] Kurs'kyi MD **"After the muscle work up to tiredness adenine nucleotide depletion is not limited by its dephosphorylation, but goes up to formation of inosine acid and ammonia. Deamidation is shown to be in myofibrillar fraction and in sarcoplasmic reticulum of the skeletal muscle. Deamidation activity is not registered in myocardium myofibrillar fraction but it is registered in sarcoplasmic reticulum."** "These data permit creating the methods for obtaining substance "adenosine phosphate" for treatment of cardiac pathologies. **Glutaminase was found to be active in the muscles. This activity depended on the organism functioning. The ammonia usage by the muscle cells goes with glutamine synthesis and consumption of energy of ATP, e.g. protein amidation.** The later is of all-biological significance and is used in the fields of medicine actualls concerned with the following fact: the velocity of hydrolysis of amidated protein is different for such pathology as epilepsia, tuberculosis, poisoning with manganese oxides. The methods for diagnostics of the above pathological states were developed on this basis. It is proved that **glutamine nitrogen can be also used in the reaction of transamination, particularly during synthesis of purines, inosine acid and it is stored in a form of glutaminic acid.** Changes in carbohydrate and phosphorus metabolism, in nitrogen and energetic exchanges and mitochondria overfilling with calcium were determined under E-avitaminosis dystrophy."

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