Estrogen, memory and heredity: Imprinting and the stress response

From the original article in 2009. Author: Ray Peat.

Stresses, including estrogen excess, activate the Heat Shock Proteins (HSP), the stress-proteins, a primitive defense system.

Heat Shock Proteins and "hormone receptors" are closely related and interdependent.

Stress (at least partly via HSP) activates viral expression, ordinary gene expression, and destabilizes the genome, activating the "endonucleases," enzymes which break up DNA chains.

Stress increases genetic variability.

DNA chains can be chemically modified (e.g., methylated) in a way that limits enzymes' accesss, probably as protection, and to regulate gene expression.

Genes, and subsequent growth and development, are modified by the prenatal hormonal environment, that of the newborn, and even that of the parents before conception.

Genomic imprinting makes maternal genes behave differently from paternal genes.

Hormonal imprinting early in life sets the pattern of expression of genes.

"Crossing-over" intermixes the genes on the chromosomes as cells multiply.

Stresses and regulatory substances can change the patterns of gene expression that define cell types.

"Stem cells" are those capable of renewing tissues, and may be "pluripotent," able to become glial cells and neurons in the brain, or, in the bone marrow, to become red blood cells or white blood cells, depending on regulatory influences.

"Cloning" animals from body cells strongly suggests that any cell is potentially totipotent, able to differentiate into any other type of cell.

We are "imprinted" by our mothers' hormonal and nutritional conditions, but we can intervene to correct these "inherited" conditions, by maintaining optimal hormonal and nutritional balances.

Recent work in several areas of biology is showing that heredity is not rigidly deterministic, in the way implied by traditional genetics, and it is opening the way for the development of therapies for incurable, chronic, or congenital problems, *in natural and holistic ways that don't involve the mechanistic interventions of "gene therapy" or "genetic engineering."* For example, nontoxic treatments for cancer that were demonstrated decades ago, were discarded because they didn't seem consistent with "genetics." Many problems that are classified as congenital or genetic, turn out to be physiological, and correctable. Even the brain and the heart, which until recently were considered to be incapable of regenerative repair, are now seen to be capable of great anatomical flexibility.

There are still great authoritarian forces opposed to recognizing, and supporting, the organism's full potential. **The most useful therapies will remain in obscurity until many people see that those therapies have a firmer scientific foundation than orthodox (antiquated) medical genetics has.**

Over 100 years ago, Samuel Butler had an argument with Charles Darwin, and concluded that Darwin was philosophically muddled, and dishonest. Butler was annoyed that Darwin had belittled the work of his predecessors, including his grandfather, Erasmus Darwin. Butler was defending the idea of biological intelligence, the incorporation of experience into physiology and heredity.

My parents had an old copy of one of Darwin's books, and I was impressed by the fact that in his introduction, Darwin was careful to point out that *his ideas were already being misrepresented, and that he did not hold "natural selection" to be the only mechanism of evolution,* but that several factors were important, including sexual selection and the inheritance of acquired traits. I suppose those remarks might have been motivated partly by knowing that Butler didn't approve of the way he was behaving, but they didn't seem to have much influence on the way history has characterized Darwin's work. All of my biology professors would have been happier if Darwin had never made those remarks. I suspect that Darwin's problem was that *any theory of evolution* was under such heavy attack that he couldn't devote much time to the relatively minor issue of how evolution works.

After Darwin's death, the study of heredity made some strange concessions to the culture of anti-evolutionism. As people began thinking about "particles that carry heredity," the "genes," ideas from the anti-evolutionist culture formed much of the context for understanding these "particles."

Darwin had suggested that the mature organism reconstitutes itself in the germ cells, by sending gemmules or pangens (buds or sprouts or derivatives) from its various parts, so that the parent's traits would be incorporated into the reproductive cells. This was called pangenesis, meaning that the whole organism was the source for the new offspring. This theory opened the possibility for newly acquired traits to be passed on. It grew out of the experience of animal breeders and horticulturists, who were dedicated to improving their breeds and strains, *by selecting the best individuals grown under the best conditions*. It was known that the miniature ponies, **Shetlands for example, would grow larger each generation when bred under favorable conditions of domestication, rather than under the harsh conditions of their native**

island. It apparently never occurred to most plant and animal breeders that they might be able to *improve* a breed by subjecting it to harmful conditions.

Around the end of the 19th century, August Weismann began a systematic attack on the ideas of Darwin. As part of his campaign, he invented the doctrine that the reproductive cells are absolutely isolated from the rest of the organism, and that they are immortal. The rest of the organism is built up by the *deletion* of genetic information. This doctrine was very convenient for those who maintained that all organisms had been created in a single moment, and that the *appearance* of evolution resulted from the extinction of some species, but not the new appearance of some species. Some people, reasoning from Weismannism, suggested that evolution might have resulted without any change in the immortal genetic material, except deletion, in a manner analogous to Weismann's theory of the developing individual. Bacteria, in that view, would contain all the genes needed to make a tree or a person, and the more complex forms would have evolved through the differential loss of that primeval genetic information.

The changes produced by *subtraction* were compatible with the notion of fallen man in a corrupt world, while the *addition* of heritable traits through experience would connote a sharing in the process of creation. The hereditary particles making up Weismann's "immortal isolated germ line" connoted a single original creation.

As mutations in the genes came to be seen as a reality, experiments with X-rays suggested to some that all mutations were harmful, and this attitude blended into the stream of doctrine which insisted that no *improvement* could be inherited. Although many experiments showed what seemed to be meaningfully *directed* mutations, the doctrine held its ground, as its advocates taught that mutations were always random. (The doctrine of random change, like the idea that entropy only increases, excluded acts of creation from the fallen material world.) If a new trait appeared under new conditions, it was said to be *only because an old trait was being revealed by the induced loss* of another trait.

I think anyone who reads the "landmark publications" in genetics will see that genetics had very little to do with scientific method, as commonly conceived, and that it had all the traits of a cult. Analysis of the language of genetics reveals that terms have more often been used to cover up empty speculation than to clarify situations of fact.

Parallel to the way Darwin infuriated Samuel Butler by misrepresenting the origins of his theory, the neodarwinists who debate the creationists over school textbooks are ignoring the ways in which the culture of antievolutionism shaped their own view of genetics.

The discovery of enzymes that produce DNA modeled on RNA, "reverse transcriptases," began undermining traditional genetics, because it showed that new information can enter our genome.

The discovery that bacteria can pass "genes" from one individual to another, conferring antibiotic resistance upon previously sensitive strains, was a major nuisance to people working in infectious disease, since it complicates the treating of disease, but it indicated that "evolution," or genetic change, was capable of happening in non-random ways.

Early in the study of viral genetics, many people realized that "organisms" which can't reproduce without their relatively complex hosts, presented a problem for evolutionary theory. If the virus requires a cell in order to exist, it is hardly a separate organism. A few people suggested that viruses were, or were based on, functional normal parts of higher organisms. Some researchers have suggested that virus-like particles serve to carry information from one part of an organism to other parts of that organism. Mobile genetic elements are now well recognized, operating within cells, and it is common laboratory practice to use viral particles to transfer genetic material from one cell to another.

Cellular systems which cut and splice nucleic acids, creating sequences of information which don't exist in the inherited chromosomes, are now accepted parts of cell biology. Hormonal and environmental influences on the stability of messenger RNA, and on mobile genetic elements, and on genomic stability in general, are recognized. ***The center of gravity in the study of the nucleic acids has now shifted from heredity to development.***

Almost nothing remains of Weismannism, which was the foundation of neodarwinism. The "isolation of the germline" doctrine persists in a few places, such as explaining why "the ovary runs out of eggs," despite some examples of egg-cell renewal.

But when the identity of "germline cells" is found to depend on signals from the environment, the last vestige of Weismannian germ-line doctrine disappears. The only meaning of "germline" is that some cells are destined to be germ cells, and the meaning disappears when such cells differentiate to form body parts. (see Donovan, 1998, Labosky, et al., 1994.)

The difference between primordial germ cells and embryonic cells is a matter of "imprinting," the process in which a hormone or "growth factor" or other "signal" directs a cell down a certain course of differentiation. "Imprinting" is where genetics and physiology, phylogeny and ontoneny, come together, and the new facts that are being discovered are removing the last vestige of scientific content from Weismannism/neodarwinism.

The argument between Peter Duesberg and the virus establishment, in which Duesberg argues that acquired immunodeficiency is produced by a variety of causes, including drug use, and the establishment argues that the HIV retrovirus is the only cause, becomes a little clearer when we consider it in the context of the larger debate between the genetic determinists and the Darwinian adaptationists. I will talk about that in more detail in a newsletter on immunodeficiency.

The issues of cancer, aging, and "hormone receptors," are also illuminated by seeing the organism as capable of adaptive modification of its genes.

These newer molecular approaches to the study of biology are vindicating some of the practical observations of plant and animal breeders, and terms such as *telegony, heterosis,* and *xenia* might come into common use again, along with *genomic imprinting*.

Here, I want to give examples of "hormonal imprinting" amd "genetic imprinting," and to show how the idea of the "retrovirus" or "mobile genetic elements" relates to practical health issues and therapies. The developing egg cell is constructed and modified in many ways during its growth. The nurse cells which surround it in the ovarian follicle inject massive quantities of material, especially RNA, into the expanding egg cell. Regulatory substances and energy production modify enzyme activities and structural proteins, which will influence the way it develops after fertilization. During the entire lifetime of the individual person, the developing egg cells are open to influences from the organism as a whole. Because of the Weismannian scientific culture, it's important to start with a few of the clearest interaction between the environment and the reproductive cell, but many other types of interaction are starting to be explored.

It has been suggested that environmental stress is responsible for viral epidemics, by activating viruses in their animal hosts, and causing them to spread to humans. Whether that's true or not, it is well recognized that stress causes increased susceptibility to the development of viral infections. It also causes increased genetic variability, which is logical in the evolutionary sense, that a species should become more variable when its environmental niche has changed. The mobile genetic elements that were first recognized by Barbara McClintock are now considered to be the most important means by which stress increases genetic variability.

In bacteria (J. Cairns**;** Salyers & Shoemaker, 1996), genetic changes are known to occur in response to specific substances, which lead to adaptation to that substance. The mobile elements which are responsible for the defensive adaptive response to antibiotics are similar to viruses. **In these instances, the genetic dogma which has been taught very recently in the universities couldn't have been more clearly disproved. So far, the tendency in the United States is to concentrate on the details because of their technological potential (for genetic engineering of lucrative products) and to ignore the larger biological meaning of this interaction of stress with genetics.**

Resistance to antibiotics is transmitted to other bacteria by "injecting," during conjugation of a resistant bacterium with a sensitive one, a small virus-like granule containing the DNA required for detoxifying the antibiotic, along with some adjoining genes. The antibiotic itself, producing stress, stimulates the formation of this genetic package. (Whole university courses used to be devoted to showing why such things couldn't happen.)

The enzymes which cut out sections of DNA are the "restrictases," which are famous for their use in identifying samples of DNA. These "endonucleases" are activated by stress. In "excitotoxicity," which kills nerve cells through a combination of intense activation with deficient energy stores (i.e., stress), these enzymes are activated.

In apoptosis, or "programmed cell death," these enzymes are activated, along with enzymes which repair the broken genes, and the resulting energy drain from an impossible repair job causes the cell's sudden dissolution. Between excitotoxicity and apoptosis, there are intermediate states, in which the dissolution is retarded or reversed.

When the stress is more generalized, so that the cells survive, the more sensitive sections of DNA are rearranged within the cell. Some of them may escape as infective particles.

Barbara McClintock wrote about the effects of stress causing genetic rearrangement, and traced the movements of the mobile genetic elements. At the same time, without knowing about her work, Leonell Strong was working with mice, exploring the role of "genetic instability" in causing cancer, and identifying estrogen and "milk particle," or "milk factor," a virus-like particle that interacted with estrogen, as causes of breast cancer.

With only the elements of *stress,* the *endonucleases,* and the *mobile packets of genes,* adaptively increased variability, and the spreading of genes among a population can be explained. However, there is a subtler level at which the adaptations acquired by an indiviual can be passed on to offspring. This is "imprinting."

"Genetic imprinting" is being studied mainly in terms of the covering of regions of DNA with methyl groups. This is thought to have evolved as a way to keep the endonucleases from attacking the DNA. Sections of DNA that have been methylated can be passed on to offspring in that form, and they can be traced as a pattern of gene activity or inactivity. The maternal genes function in a manner identifiably different from the paternal genes. Having passed through the mother's body, the genes have been modified.

"Hormonal imprinting" refers to the great changes in sensitivity to hormones (and related substances) that persist after exposure to that substance early in life. When the mother's hormones are imbalanced during pregnancy or nursing, the baby is "imprinted" with an altered sensitivity to hormones. Leonell Strong showed that these effects could be exaggerated generation after generation. But--strangely, considering that he was a student of T. H. Morgan, who is considered to be the founder of classical genetics-- **Strong found that a single treatment, or a series of treatments, with an extract of liver, or with certain nucleosides (the units for constructing DNA), could reverse the course of generations of breeding, and eliminate the susceptibility to cancer.**

In modern terms, he was probably working with a combination of genetic imprinting and hormonal imprinting. His "milk factor" very probably was one of the "endogenous retroviruses," or mobile genetic elements. (However, Gaal, et al., 1998, found that imprinting factors can be transmitted in the milk.)

Movable genetic elements appear to regulate normal developmental processes (Long, et al., 1998) and the introduction of new particles can "improve fitness." This is an aspect of the HIV controversy that has been completely ignored, as far as I can tell. Peter Duesberg argues that the presence of antibodies to the HIV indicates that the immune system is active, and that there is no evidence showing the virus to be harmful. My suggestion would be that the virus is probably present quietly

in many people who have no antibodies to it, and that environmental toxins and other stressors cause it to be adaptively expressed, creating the possibility for an antibody response. The "viral particle" itself might be biologically useful, though this wouldn't exclude the possibility that an abnormal immunological response to it could have harmful repercussions.

The importance of the retroviruses in the human genome hasn't been widely appreciated. ("almost 10% . . . homology with the retroviruses," Deb, et al, 1998.)

Environmental pollution with estrogens and immunosuppressive substances, when it persists throughout the developmental period, and across generations, will be dangerous at levels much below those that show an immediate hormonal or immunosuppressive effect. Tests that determine the "mutagenicity" or "carcinogenicity" of a substance are performed within a context of a theoretical genetics which is demonstrably false**;** until the complexities of imprinting and transgenerational effects are taken into account, it would be wrong to accept the claim that there are "safe levels," or "thresholds of harmful effects."

When babies are imprinted by the mother's diuretics, by milk substitutes, and by industrial effluents, the worst effects are likely to be seen decades later, or even generations later.

There is a simple image that I think makes it possible to grasp as a whole the unity of things which have been described as existing on different "levels," the genetic, the metabolic, and the ecological. This is the image of an interaction between water and large molecules, such as proteins and nucleic acids, with the system--the way the large molecule is folded, and the way the water molecules are ordered--having more than one arrangement, or physical state, each state differing slightly in the amount of potential energy it contains. Then, the differences between respiratory energy (producing carbon dioxide and consuming electron-equivalents), and relatively anaerobic conditions, determine the probability that the system will return to its higher energy state after it has been perturbed.

A brief perturbation amounts to simple perception and response, reflecting the basic "irritability" of life, to use Lamarck's term. But with more intense disturbances, the structures are altered at deeper levels, and structures will be restored with different degrees of completeness, and the organism will have adapted, according to its resources, either toward increased "fitness" and sensitivity, or toward decreased sensitivity.

On the level of an individual, the movement away from fitness and sensitivity would resemble the development of aging and degenerative disease**;** on the level of a species, it would amount to "reverse evolution," a mammal would become more reptilian, a primate would become more rodent-like.

Protective interventions, and therapies, will consist of things which protect the structures (preserving sensitivity, while blocking excessive stimulation), and which increase the energy resources. A great variety of physiological indicators show that substances such as progesterone, thyroid and carbon dioxide are acting "universally" as protectants, in ways that make sense only with some perspective such as this, of the systematic changes in the physical state of the living substance.

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Genetics 1991 Aug;128(4):695-701 **Adaptive reversion of a frameshift mutation in Escherichia coli.** Cairns J, Foster PL Department

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Genetika 1997 Aug;33(8):1083-93 **[Stress induction of retrotransposon transposition in Drosophila: reality of the phenomenon, characteristic features, possible role in rapid evolution].** Vasil'eva LA, Ratner VA, Bubenshchikova EV "This stress response involved mobilization of retrotransposons." **"In all these cases, stress induction of retrotransposon transpositions was mediated by molecular mechanisms of the heat shock system-the general system of cell resistance to external and physiological stress factors. From the viewpoint of evolution, stress induction of transpositions is a powerful factor generating new genetic variation in populations under stressful environmental conditions.** Passing through a "bottleneck," a population can rapidly and significantly alter its population norm and become the founder of new, normal forms."

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Genetika 1991 Mar;27(3):404-10 **[Maintenance of the copy number of retrotransposon MDG3 in the Drosophila melanogaster genome].** Glushkova IV, Beliaeva ESp, Gvozdev VA The genomes of laboratory stocks and natural population of Drosophila melanogaster contain 8-12 copies of retrotransposon MDG3 detected by in situ hybridization. Construction of genotypes with decreased MDG3 copy number using X-chromosome and chromosome 3 free of MDG3 copies **results in appearance of hybrid genomes carrying up to 7-10 copies, instead of 2-4 copies expected.** New MDG3 copies are detected in different genome regions, including the 42B hot spot of their location. The chromosomes, where new clusters of MDG3 were observed, carry conserved "parental pattern" of MDG1 arrangement. **The data obtained suggest the existence of genomic mechanism for maintenance of retrotransposon copy number on a definite level.**

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Genetika 1996 Jul;32(7):902-13 **[Analysis of motifs of functional MDG2 sites in assuring its possible molecular functions].** Ratner VA, Amikishiev VG "Enhancers of mobile genetic elements are assumed to determine modification of adjacent genes and polygenes. **Excisions and transpositions of mobile elements seem to be induced by external stress factors or physiological factors through a heat-shock system."**

Genomics 1998 Dec 15;54(3):542-55 **A long terminal repeat of the human endogenous retrovirus ERV-9 is located in the 5' boundary area of the human beta-globin locus control region.** Long Q, Bengra C, Li C, Kutlar F, Tuan D. "Transcription of the human beta-like **globin genes in erythroid cells** is regulated by the far-upstream locus control region (LCR). In an attempt to define the 5' border of the LCR, we have cloned and sequenced 5 kb of new upstream DNA. We found an LTR **retrotransposon belonging to the ERV-9 family of human endogenous retroviruses** in the apparent 5' boundary area of the LCR." "This LTR is conserved in human and gorilla, indicating its evolutionary stability in the genomes of the higher primates. In both recombinant constructs and the endogenous human genome, the LTR enhancer and promoter activate the transcription of cis-linked DNA preferentially in erythroid cells. **Our findings suggest the possibility that this LTR retrotransposon may serve a relevant host function in regulating the transcription of the beta-globin** LCR." Copyright 1998 Academic Press.

Genetika 1995 Dec;31(12):1605-13 **[Heterologous induction of the retrotransposon Ty1: reverse transcriptase plays a key role in initiating the retrotransposition cycle].** Reznik NL, Kidgotko OV, Zolotova LI, Shuppe NG A new method was developed to study the mechanism of initiation of the retrotransposition cycle: retrotransposons of Drosophila melanogaster, gypsy, copia, and 17.6 were expressed in yeast under the control of potent yeast promoters. **Expression of retrotransposons induced formation of viruslike particles (VLPs) associated with full-length Ty1 RNA and DNA sequences.** This phenomenon was termed heterologous induction. **When the gene for reverse transcriptase of human immunodeficiency virus (HIV) was expressed in yeast, the same results were obtained. These data allowed us to assume the excess of active reverse transcriptase to play the central role in induction of transposition.** Possible mechanisms of induction of Ty1 transposition by homologous and heterologous elements are discussed.

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J Hypertens 1998 Jun;16(6):823-8 **Female Wistar-Kyoto and SHR/y rats have the same genotype but different patterns of expression of renin and angiotensinogen genes.** Milsted A, Marcelo MC, Turner ME, Ely DL "Female SHR/y rats have the parental Wistar-Kyoto rat autosomes and X chromosomes and have no chromosomes of spontaneously hypertensive rat origin; thus they are genetically equivalent to female Wistar-Kyoto rats." "The combination of removing estrogen early in development and supplementing the ovariectomized females with testosterone revealed strain differences in response of blood pressure." "Differences in regulation of renin-angiotensin system genes between strains may result from epigenetic mechanisms such as **genome imprinting** of these genes or of another gene that functions as a common regulator of renin and angiotensinogen."

Gen Pharmacol 1998 May;30(5):685-7 **Imprinting of thymic glucocorticoid receptor and uterine estrogen receptor by a synthetic steroid hormone at different times after birth.** Csaba G, Inczefi-Gonda A. 1. "Single allylestrenol treatment (hormonal imprinting) of 3-day old rats reduced the density of thymus glucocorticoid receptors and increased the density of uterus estrogen receptors at adult age." "4. The experiments demonstrate that hormonal imprinting can be provoked by allylestrenol not only pre- or neonatally, as was done in previous experiments, but also a few days later. The imprintability was lost between the 4th and 8th day of life."

Gen Pharmacol 1998 May;30(5):647-9 **Fetal digoxin treatment enhances the binding capacity of thymic glucocorticoid receptors in adult female rats.** Csaba G, Inczefi-Gonda A. 1. Hormonal imprinting is provoked in the perinatal critical period in the presence of the appropriate hormone or molecules similar to it. As a consequence of hormonal imprinting, the developing receptor finishes its maturation normally (in the presence of the adequate hormone) or abnormally (under the effect of foreign molecules that are able to bind to the receptor). 2. Digoxin--which has a steroid character--caused faulty imprinting by treatments at the 15th, 17th and 20th days of pregnancy. In the adult (3-month-old) animals, the density of thymic glucocorticoid receptors was significantly elevated, whereas the density of uterine estrogen receptors was not, without any change in receptor affinity. 3. The experiments call attention to the steroid receptor imprinting effect of fetal digoxin treatment that must be considered in regard to this treatment at this period and later in regard steroid treatments.

Hum Exp Toxicol 1998 Feb;17(2):88-92 **Transgenerational effect of a single neonatal benzpyrene treatment on the glucocorticoid receptor of the rat thymus.** Csaba G, Inczefi-Gonda A. Hormonal imprinting is provoked perinatally by the appropriate **hormone on its receptor,** causing a life-long adjustment of the connection between the two participants. Faulty imprinting is caused by the presence of molecules similar to the hormone in this critical period, which results in a persistent alteration of the receptor. In the present experiment the transgenerational imprinting effect of a steroid-like environmental pollutant, benzpyrene, on the receptor binding capacity of filial thymic dexamethasone and uterine estrogen receptors was studied. The receptor density (Bmax) of the thymic glucocorticoid receptors of the males was reduced **up to the third (F2) generation.** In females this reduction was observed only in the F1 generation of treated animals. There was no change in receptor affinity (Kd). Uterine estrogen receptors were not subjected to transgenerational imprinting. The experiments demonstrate (1) the possibility of the **transgenerational transmission** of imprinting effect, (2) the differences of steroid receptors in different organs, and (3) the differences of male's and female's reactions from this aspect. The results call attention to the dangers of perinatal aromatic hydrocarbon exposition to the progeny generations.

Genetika 1994 Apr;30(4):437-44 [Tv1--a new family of Drosophila virilis retrotransposons]. Andrianov BV, Shuppe NG. **"The method is based on the hypothesis about the universal character of retrotransposition through reverse transcription."**

Genetika 1990 Mar;26(3):399-411 **[Transpositional bursts and chromosome rearrangements in unstable lines of Drosophila].** Gerasimova TI, Ladvishchenko AB, Mogila VA, Georgieva SG, Kiselev SL, Maksymiv DV "The phenomenon of transpositional bursts--massive simultaneous transpositions of mobile elements belonging to different structural classes and accompanied by multiple mutagenesis were earlier described. Although the mechanisms of this phenomenon are still unclear, it is obvious now that **it embraces total genome and includes not only transpositions of different mobile elements but also recombination processes--homologous recombination** for LTR's and gene conversion."

Eksp Onkol 1986;8(2):29-32 **[Nature of the endogenous retrovirus-like particles of the rat liver].** Korokhov NP, Pyrinova GB, Kurtsman MIa, Tomsons VP, Salganik RI.