Ray Peat's Newsletter

We maintain that biological regularities do not resemble mathmatical laws. Trofim Lysenko

Cumulative damage, degeneration, & aging--possibilities of reversal

Coacervation ==The separation of a mixture of oppositely charged long molecules into different liquid phases, with different solubilities and other properties; adding other substances or changing conditions such as pressure and temperature, may cause changes in the properties of each phase, including disappearance of a phase, or the appearance of new phases. Coacervates have many properties resembling living material, such as coherence and "tunability" or steerability or self-regulation of various properties. The essential role of mRNA in this process in living organisms gives a new perspective on the current issues of vaccine safety.

LeChatelier's principle == when a system experiences a disturbance (such as concentration, temperature, or pressure changes), it will respond to restore a new equilibrium state. A complex system, such as a coacervate, a cell, or tissue, or organ, or organism, follows the principle with often unexpected adaptive changes, including altered cell structure, energy production, temperature control, and growth rate. This responsiveness to environmental conditions offers an opportunity to therapeutically "tune" a damaged system.

Membraneless organelles == Until a few years ago, the many identifiable things in cells were thought to be either precipitated solids, or membrane-bound compartments. When most of them were found to lack boundary membranes, a process of liquid-liquid phase separation was recognized as their cause. The interaction of different types of RNA with proteins was found to be the normal basis for the coacervation. These "bodies" that perform the cells' work tend to come into existence as needed.

Phase transition == Traditionally, there were said to be three phases of matter, gas, liquid and solid. Since the 1930s, non-dogmatic research has considered the living state to be a special state of matter, in which many variations, corresponding to degrees of vitality, occur.

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After considering in the last newsletter how subnormal body temperature and low oxidative metabolism can accelerate inflammatory and degenerative processes, it occurred to me that it would be good to consider what happens when the body temperature is increased by external heat, beyond the level at which the organism functions optimally. Partly, I'm thinking about the damage that can be done by the increasing popularity of sauna treatments, and various kinds of "hyperthermic therapy for cancer," usually disregarding the actual internal temperature of the tissues as well as the general state of the organism (including levels of serum glucose and free fatty acids). But the most important thing is what temperature means to a living organism.

For at least 70 years, biology education and publication in the US and Western Europe have

been dominated by the idea that biochemical reactions occur mainly in the cytoplasm of cells, which consists of a watery solution of enzymes and small molecules, enclosed by a membrane that, using pumps, controls the movement of substances into and out of cells. Random diffusion governs the movements of the dissolved molecules. For them, biochemistry began when you extracted the juice from cells, to study its reactions in a test-tube. They believed that the principles were so obvious that it wasn't necessary to test their validity, and that people who did test them were doing "pathological science."

In the new paradigm with its view of life as a matter of meaningful and sensitive interactions between the living states and their environments, the effects of temperature are vastly more important and interesting than in the world of randomness.

A few years ago, the drug industry revived interest in coacervates, using the principle to "micro-encapsulate" their drugs. That made phase separation a matter of economic importance, and that has taken the vitality out of the basic "arguments" of the membrane-committed people against those like Gilbert Ling who showed that life is a special physical state of matter, with variations corresponding to cells' energy and structure.

Now, the old paradigm of random interactions has been replaced by a less abstract view of life as a matter of meaningful and sensitive interactions between the living states and their environments. In this paradigm, the effects of temperature are vastly more important and more interesting than in the world of randomness.

Many of the new observations related to seeing cells as self-organizing coacervate systems are reminiscent of Gilbert Ling's observations. For example, ATP increases the solubility of proteins (Patel, et al., 2017), and when energy is depleted, some proteins come out of solution, forming membrane-less organelles, filaments, and granules. Prions, the agents of transmission of mad cow disease, are formed in a process of phase separation, that can be started by infection with a prion particle, especially in an energy depleted condition. In such an unstable situation, the introduction of extraneous filamentous material—such as vaccine or viral RNA, or polyethylene glycol (PEG), or carrageenan—could have a "seeding" effect similar to that of prions.

50 years ago, the randomizing, denaturing effects of heat on protein systems (such as cooking an egg), seemed sufficient to explain the destructive effects of heat on living tissue, but in the late 1970s a series of major discoveries led to a surge of interest in the reactions of cells and organisms to excessive heat.

Gideon Goldstein had been studying thymus gland extracts for years when he found that a certain small protein in his extracts could be found in every cell type of every living thing, so he called it Ubiquitous Immunopoietic Polypeptide, because it caused precursor cells to differentiate into B and T cells. Later called ubiquitin, it was found to guide protein breakdown and turnover. Another type of nearly ubiquitous protein is called chaperones; they guide the folding of newly synthesized proteins, and can also govern the movement and degradation of proteins, and are involved in embryonic development and epigenetic adaptations. It was finally discovered that a variety of proteins that are produced massively during heat stress, called heat shock proteins (HSP), are also chaperone proteins, and are as ubiquitous as ubiquitin.

HSPs are involved in the differentiation of both eggs and sperm cells (Sarge and Cullen, 1997), as well as in the development of the fertilized egg through the epigenetic processes of embryonic development. Fertility requires the maintenance of the testes and ovaries at a temperature significantly lower than the body's core temperature, allowing cellular order to exist with a minimum of energy expense. This provides an interesting perspective on the meaning of the heat stress that can massively increase the formation of the HSP, resulting in a shift away from efficient oxidative metabolism toward glycolysis (Wang, et al., 1985). The developmental chaperone effects and the energy effects seem to be inseparable—"Taken together, these data are

indicative of the fact that multifunctional Hsp70 protein expression is related to the extent of energy expenditure that cannot be distinguished from the chaperoning effects on protein metabolism in previous studies" (Wang, et al., 2012). This shift of energy supply has been recognized as a factor in breast cancer metabolism and growth (Zhao, et al, 2009), and other age-related processes.

Increasing temperature increases the rate of energy use, while lower temperature lowers the rate of energy use. When energy availability matches energy needs, there is no heat stress. The HSP chaperone function can slow the degradation of proteins under stress; if the HSPs were to be named in the present, they could be called "energy deprivation stabilizing proteins."

Although the increased HSP can save the cells' or organism's life, it degrades oxidative energy production and metabolic efficiency. When environmental conditions are too bad for active adaptation, many organisms are able to reduce their needs drastically; HSP, by reducing oxidative metabolism and suppressing energy-expensive processes, have an important role in producing this torpor. HSP are involved in the induction of dormancy or torpor in organisms ranging from the cellular slime mold Dictyostelium, to mammals.

In the early stages of forming an individual, starting with the parents' biological well-being, and continuing through the embryological developments into adulthood, the quality of tissue energy supplies, cellular energy balances, and the resulting orderliness of the tissue substance, govern the nature of the outcome. Long before the existence of HSP/chaperones was suspected, progesterone was known to be an essential protector of cell structure and energy production, while estrogen's destabilizing, disordering interference with oxidative energy function was known. With the discovery of the HSP, it was important to understand how these two systems, based on steroids and proteins, interact.

For more than 20 years, there was intense interest in the interactions of the HSP and the steroid hormone receptors. The interest was focussed mostly on the activation of estrogen by HSP, and on estrogen's stimulation of HSP synthesis. A few years ago, it became clear that progesterone inhibits HSP formation, and that HSP suppresses the effects of progesterone as well as its synthesis. These relations were already implicit in the existing knowledge that estrogen is excitatory, analogous to excessively increasing temperature, and that it shifts energy production toward glycolysis, and shifts cell functions toward dedifferentiation and cancer metabolism, while progesterone has opposing effects**:** It reduces excitation, decreasing the need for energy, while shifting energy production away from inefficient glycolysis; it can restore normal differentiation while reversing features of cancer, including HSP70 (Blumenthal, et al., 2003). This self-stimulating relationship between estrogen and the HSP would tend to support dead-ends of low energy disorganization. Things that block HSP and estrogen would tend to restore progesterone production, with improved energy and structure.

When energy availability matches energy needs, there is no heat stress. Heat shock proteins (HSP) can slow the degradation of proteins under stress but they do this by degrading oxidative energy production and metabolic efficiency.

These interactions help to understand the benefits and dangers of a warm bath or a sauna. At bedtime, a mild warm bath can compensate for low internal heat production, increasing the metabolic rate and helping to increase glycogen stores and increase progesterone level, making deep restorative sleep possible. But if the bath is too warm or too prolonged, or if estrogen's influence is too great, the increased metabolic rate can intensify the inefficient metabolism further depleting energy stores, and leading to higher stress hormones. Having extra carbohydrate before and during the warm bath improves its therapeutic function, and decreases the risk of heat shock.

Sidney Fox's famous spontaneously formed, self-replicating proteinoid microspheres, with some properties resembling coacervates, are able to continue their life-like replication only when the experimenter keeps adding necessary

components to their environment. In an inadequate environment, their activity stops. Self-organizing systems are maintained by the flow of energy and substance from the environment. In natural cells and organisms, with aging, the life process slows and then ends, as the protective adaptations to stress no longer find in the environment the necessary resources to continue. This is because of cumulative changes in the structure and composition of their cells and tissues, that have resulted from adapting to stress with small energetic retreats—decreasing oxidative energy production and consumption.

When these adaptations involve increases in the quantity of HSP, there is a corresponding reduction in the quantity of functional, energy-consuming proteins in the cells. The loss of muscle mass with aging, sarcopenia, is a clear example of this process (Bautmans, et al., 2008; Haak, et al., 2009). Autoimmunity is often directly involved in sarcopenia, and the HSP overload is an important factor in the (often estrogen-related) autoimmune diseases, including asthma and arthritis.

Estrogen is excitatory, and shifts energy production toward glycolysis, and shifts cell functions toward dedifferentiation and cancer metabolism, while progesterone reverses all those effects. Estrogen stimulates HSP synthesis which suppresses the effects of progesterone as well as its synthesis.

Nitric oxide, increased under the influence of estrogen, is a strong inducer of HSP (Xu, et al., 1997; Miragem and Homem de Bittencourt, 2017). Independently, estrogen and nitric oxide are known to promote fibrosis and cancer, and now the basic role of HSP in fibrosis (Bonniaud, et al., 2017) and cancer is being recognized, and the drug companies are creating a variety of HSP inhibitors.

The accumulation of collagen with age, creating an increasing barrier between cells and the environment, has been seen as one of the general factors in aging. HSP acting inside cells is producing similar cumulative effects of stress, while also contributing to building the collagen barriers.

Nitric oxide, increased under the influence of estrogen, is a strong inducer of HSP. Independently, estrogen and nitric oxide are known to promote fibrosis and cancer and now the basic role of HSP in fibrosis and cancer is being recognized. Anti-HSP drugs might be helpful, but it's reasonable to try to prevent problems, rather than treating them as they approach an irreversible state.

One of the heat shock proteins, HSP32, is also known as heme oxygenase, and synthesizes carbon monoxide from heme. In the brain, its activity increases with age and various brain diseases (Hirose, et al., 2003). In rats, HSP content of the brain increases steadily with aging, along with decreased mitochondrial oxidative metabolism, and increased glutathione (Calabrese, et al., 2004).

The new anti-HSP drugs are likely to be helpful, but it's reasonable to try to prevent problems, rather than treating them as they approach an irreversible state. Keeping energy efficiency high, while reducing wasteful excitations, has a long history in health optimization. Avoiding excessive polyunsaturated fats and phosphate in the diet, and regularly getting the essential nutrients needed to maintain thyroid and progesterone production, is simple. Choosing foods that contain substances that protect against the many known pro-inflammatory, age-accelerating processes is relatively simple—citrus fruits, for example, contain a great variety of substances related to nobiletin, naringin, fisetin, and quercetin, that inhibit the formation of HSP (Hosokawa, et al., 1990; Morino, et al.,1997; Kim, et al., 2015). Reducing the amount of methionine in animals' diet can greatly extend their lifespan; this effect might be related to the

fact that methionine induces the formation of HSP. Serotonin, derived from tryptophan, also activates HSP, so restriction of methionine and tryptophan in the diet, either by protein restriction or by substituting gelatin for "complete" proteins seems likely to protect against the age-related increase of HSP in essential tissues.

Keeping energy efficiency high, while reducing wasteful excitations has a long history in health optimization.

In the gene-centered view of life, there was no ability to explain transgenerational inheritance, the fact that things that happened to your grandparents and parents can influence the nature of your metabolism and the quality of your life. The understanding of the coherence of life, and its coacervate-like qualities, in which environmental influences can affect the way the organism uses its genes in a continuous process of development, makes it clear that time is very relevant to the organism—its present structure and properties reflect its previous states, and project its future tendencies and possibilities, its trajectory in life. The HSP, as an important component of the living substance, is a factor in the transgenerational epigenetic processes (Norouzitallab, et al., 2014). In general, the changes that compensate for stress damage protect the organism, in the sense of ensuring survival, by desensitizing the organism to stimuli that could otherwise lead to increased energy expenditure. At the beginning of life, the HSP seem to function as they do at older ages, as a sort of ballast or inertia, preserving life at the expense of normal functions. Reduced energy production in compensation for stress at the beginning of life determines the quality of gestation and the life trajectory of the developmental process, limiting brain size, ability to produce and to use energy, and longevity.

In this view of the self-organizing nature of life, the experiments (for example, Ahmad and Zamenhof, 1987; Zamenhof, 1976; Zamenhof and Klimuszko, 1977) in which providing more glucose than normal to developing embryos allowed them to develop larger, more intelligent brains than had existed until that time, suggest that the present situation for vertebrate animals in the natural world is frustrating a developmental potential and intention, directing developmental potential into the dead end of defending against stresses, and away from the intrinsic neotenous or pedogenic path, in which the childish features of metabolic intensity, playfulness, flexibility, and imaginativeness are preserved beyond early childhood, avoiding indefinitely the degenerative processes of decreasing energy and increasing disorder.

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