Ray Peat's Newsletter

Hayflickers, Dolly & dandruff: The "telomeric clock" is not a valid theory of aging.

The roles of nutrition, estrogen, and progesterone in stress-related energy problems: A meaningful pattern for all organisms.

I. Introduction

Besides the commercially promoted idea that melatonin has something to do with a "biological clock," there are two main doctrines among biologists about the nature of the clock that they suppose exists. One group argues that a group of brain cells called the suprachiasmatic nucleus has a regular rate of firing that is "determined by genes" and that controls biological rhythms. Unfortunately for that theory, the firing rate of those cells turns out to be variable under different conditions of metabolism and temperature (Ruby and Heller, 1996).

"Estrogen's identity as a shock-hormone gives an insight into the context-dependent aging of cells and carcinogenesis. The pro-respiratory progesterone is involved as estrogen's antagonist at the deepest molecular levels."

Another general kind of clock is proposed to be "determined by the genes," or genetically "programmed," and in this case the clock is supposed to determine how long an animal can live.

Neither of these groups has even tried to dispose of the facts that have accumulated over several decades suggesting that there is no independent biological clock at all, but rather an ability of cells and organisms to perceive rhythmic environmental conditions. Frank A. Brown, Jr. (Univ. of Indiana) and Alexandre Rothen (Rockefeller Univ.) devised many experiments that clearly demonstrated that biochemical, metabolic and physiological rhythms are responsive to cues other than light and darkness. The geomagnetic field is one type of cue that has demonstrable biological effects.

The doctrine of a genetic clock causing aging denies the role of environmental factors in the aging process. Cigarette companies argued that "we *don't know* the cause of cancer, so go ahead and smoke." The genetic clock people claim to *know* the cause of aging, and that it is not environmental factors.

"The stem cell is defined as that cell in a tissue which, under normal circumstances, maintainsits own population, undiminished in function and size, and furnishes daughters to provide new functional cells of that tissue.The daughters may, or may not, have to undergo further differentiation and/or maturation in order to achieve their functional stage. The fundamental characteristic of a stem cell, therefore, is self-renewal. Evidence is presented which implicates the microenvironment as a major component of the stem cell system, without which stem cells cannot be maintained. Furthermore, it is suggested that stem cell properties do not reside in one specific cell type in the population but, when necessary, cells other than those normally playing the stem cell role, can have stem cell function imposed upon them by the appropriate microenvironment. The stem cell "niche" hypothesis is presented to explain the dependence of stem cells upon their microenvironment. The postulate is offered that there are no cells which are intrinsically stem cells but that a range of cells in a tissue possess stem cell potential to a greater or lesser extent." "The stem cell system," R. Schofield, Biomed Pharmacother, 1983, 37:8, 375-80.

can live much longer than the animal they came from, and that the age of the donor doesn't determine the survival of the transplant.

Studies of the rate of cell division in the lining of the intestine and of the bone marrow cells that continuously produce red blood cells throughout the life-span also have shown gross violations of the "Hayflick limit." Dandruff, the result of the steady division of cells in the epidermis, and the growth of nails and hair, are easily visible demonstrations that Hayflick's observations were just the result of the special conditions he created in his cell culture bottles.

The gradual accumulation of support for the principles Carrel outlined includes evidence that cell-to-cell interactions (R. Auerbach, 1972), adequacy of glucose supply, oxygen and carbon dioxide, appropriate pH, osmolarity, hormones, extracellular matrix (Gospodarowicz), hormones, and many regulatory substances including proteins and fats, **can fundamentally change the ability of cells to divide in culture vessels.**

For example, Gospodarowicz, et al. (1983) found that growing cells on "extracellular matrix," and with some natural substances from serum, rather than on plastic, made the difference between an *in vitro* longevity of 15 or 24 divisions, and "at least 88" cell divisions.

If the "intrinsic cell aging" people want to talk in terms of "programming," then we would have to say that cells are constantly open to "reprogramming," which is to say that they are perceptive and responsive to their environment.

Hayflick's method began with tissue that could be kept, either at room temperature or at 5 degrees, "for at least 5 days" (and "up to 3 weeks") "without apparent loss of viability." Although lactic acid production is a sign of stress, it seems that Hayflick took it as an indication of life: "Once the cultures have become confluent cell sheets, the cells are very active metabolically, as shown by the fact that the GM [growth medium] becomes acid faster than in cultures of heteroploid cell lines inoculated with the same number of cells." "Although mitotic activity eventually ceases in the culture, acid production continues; and as dictated by drops in the pH, cultures can be fed for a few months until all acid production ceases and the culture is observed to have completely degenerated." Among the ridiculously antiphysiological conditions used in Haflick's experiments was the addition of high concentrations of penicillin and streptomycin, or aureomycin, to the growth medium. (See Pershadang, et al., 1982.) He refers to Carrel's techniques as "primitive," and says "In any event, Carrel's experiment has never been confirmed." (Carrel's experiment continued for 35 years, so it will be a while before anyone repeats it.) **Carrel's "primitive" method involved frequent addition of chick embryo extract** rather than Hayflick's commercial solutions of salts, buffers, and antibiotics, with the addition of very small amounts of calf or horse serum. Using fluids from the same species, from an embryo rather than from an adult, and avoiding harmful additives, might be more properly called a sophisticated technique, rather than primitive incompetence. (Smith, et al., 1985, showed that DNA "repair capacity was always found to be greatest in medium supplemented with autologous plasma.")

The essence of the telomeric clock doctrine is that the telomere shortens with aging, making cell division impossible, and causing the organism to suffer the symptoms of aging, while the "immortal germ cells and cancer cells" have active telomerase that allows them to maintain long telomeres. Besides the "inappropriate" telomere length that has been seen in some individuals of different ages, there are so many exceptions to the rule that it is inaccurate to speak of a rule.

Mice, with a very short life-span, have active telomerase in their body tissues, while people normally don't. Telomerase isn't needed to form or maintain telomeres. Some cancers have long telomeres, some don't. Telomere length varies between organs in the same animal, and even between chromosomes in the same cell.

To say that the theory of the telomeric-mitotic clock is complete junk is not to question the importance of the telomere itself--like any part of the cell, it is complex, important, and interesting.

La cell n'est pas limitée et dépend de l'on glucose, Dioxide de C., pH, hormone, macro, micro et peu se reprogrammer par rapport à son environnement

IV. DNA, stress, and estrogen

If Hayflick and Carrel have anything in common, it is the observation that aging is closely associated with the slowing of cell division.

Carrel's observation that the rate of healing is slower in old individuals has been repeated in different systems, for example (Lambert, et al., 1979) **showing that DNA repair synthesis is retarded in cells from old people. Estrogen also slows DNA repair** (O'Brien, 1993), as well as causing increased DNA breakage.

Estrogen's identity as a shock-hormone gives an insight into the context-dependent aging of cells and carcinogenesis. The pro-respiratory progesterone is involved as estrogen's antagonist at the deepest molecular levels.

Fifty years ago, estrogen was shown to imitate all of the physiological features of the shock phase of the stress reaction, and later it was found that histamine and estrogen (and now, nitric oxide) have parallel shock-promoting actions.

More recently, cells (all kinds of cell, including bacteria) have been found to have a system of proteins, called heat shock proteins, that are produced in response to any stress or shock, and estrogen turns out to have a very close association with these stress-induced proteins. Estrogen induces the heat shock proteins, and the heat shock proteins activate or **stabilize the estrogen receptor, so that injury in general facilitates the action of estrogen on the cell.** Progesterone and its receptor have an opposite and antagonistic effect on the heat shock proteins.

In 1970, my proposal that the estrogenic state and the senescent state were very closely related seemed strange to people who had heard estrogen treatment promoted as the way to prolong youth and to stay "forever feminine," but a few years after I had finished my dissertation, Terry Parkening, who had worked in Proferssor Soderwall's lab at the same time I had, began publishing observations of elevated estrogen levels in a variety of aging animals. Estrogen is now known to increase with athletic stress, trauma, sickness, endotoxin poisoning, etc., and to be an essential factor in prostate cancer, as well as in essentially all other cancers, so it doesn't seem to be such a big step to go from "stress hormone" to "age hormone." Estrogen is beginning to lose its false identity as the "female hormone," which was always just a promotional concept of the pharmaceutical industry. Hundreds of false claims have been made about estrogen's "youth promoting" effects, but they always turn out to be the opposite of what is claimed. For example, "estrogen increases the collagen content of skin," but in fact collagen accumulation is characteristic of aging, radiation injury, and many other types of damage. "Estrogen makes the skin plumper," but it is by causing water retention; bloating might stretch wrinkly skin until it is smooth, or even tight, but a swollen old face is, if anything, biologically older than a lean and creased face. (I have discussed many other such advertising ploys in my books, e.g., *From PMS to Menopause: Hormones in Context.*)

The types of adaptation to stress that are known to occur both *in vitro* and in normal aging of the animal, include the various defensive systems such as the heat shock proteins, which are induced by stresses that interfere with the cell's energy supply.

During the last 35 years there have been many demonstrations that cells in culture do not get an optimal amount of oxygen. (Wolffe, et al., 1984, for example.) Kondo et al. (1997) have recently shown that cells grown at the interface where the culture medium meets the air are more like normal cells: They "possess highly differentiated functions and structures compared with the cells cultured under immersion." Previously, as Warburg pointed out, it was found that the cells that grow in a sheet on the bottom of the vessel were much more oxygen-deprived than the cells which are immersed, but suspended, and receive oxygen and nutrients from all sides.

Suffocation and x-ray injury produce an estrogen-like response in animals. The oxygen deprivation in tissue culture, which Warburg showed created the characteristic cancer metabolism, produces the pro-estrogenic heat shock proteins, as well as other stress substances. The antagonism of progesterone to the actions of this heat stress system gives us

Stress ↑ Heme oxygenase (Protéine) level ↑ Carbon monoxide et leur ↑ métabo du cancer
métabo du cancer = glycolyse aérobie avec acide-Lactique : Pas normal car O2 est là

further insight into how to redirect cells away from the stress pathway.

During oxidative stress, a variety of stress proteins are produced, besides the heat shock system. Heme oxygenase, which produces carbon monoxide, is one of these stress proteins, and I have previously discussed how this stress-induced production of carbon monoxide could stabilize the cells' dedifferentiated tumor-producing state, since carbon monoxide produces what Warburg has characterized as the "cancer metabolism," aerobic glycolysis, in which cells produce lactic acid even in the presence of oxygen. In Hayflick's original article (Hayflick and Moorhead, 1961), the production of lactic acid by the cells doesn't seem to be of interest to the authors. I have also introduced the idea that the stress-proteins could have far reaching effects through an effect on the structure of water.

But apart from those points, it is now well established that the heat shock proteins stabilize and reinforce the effects of estrogen. Estrogen tends to shift cells away from differentiated functioning and toward simple cell division, a sort of dedifferentiation. This cell division is important for reproduction, and it is also part of a basic process of tissue regeneration. **During stress or injury, as well as in normal growth, cells have to make the basic decision of whether to grow or to die in the non-inflammatory process called apoptosis, or to differentiate and contribute to the functional systems of the organism.** The heat shock/estrogen system protects cells against "altruistic cell death," but ordinarily the organism rescues the cells from that dedifferentiated state by providing energy, oxygen, and signals to restore them to an appropriate functional state.

The stress pathway at first stimulates cell division, directing cells to differentiate down a pathway that is useful in tissue repair, but this stress-response is not useful in the culture dish, and the absence of the rest of the organism means that nothing will come from their growth decision, other than persisting under the damaging, stressful conditions.

In Hayflick's cell culture, the cells were clearly under sufficient stress to activate their estrogenic cell division process, but in the absence of either adequate energy or appropriate signals, they were on a dead-end path. The specific substances in the culture medium could be investigated if we needed to know the detailed cellular physiology of that dead-end path, but giving serious scientific consideration to Hayflick's doctrine is itself a dead-end path.

The editors of *Experimental Cell Research*, who devoted 36 pages to the 1961 article, and 22 pages to the 1965 article, bear a portion of responsibility for publishing ridiculous, illogical, unfounded, and simply false statements; it would be hard to identify any standard of quality that was followed in accepting those articles for publication. The mass media can't be blamed too much in this case, because the scientific media themselves have been manipulated.

To talk about "reversing aging" by adding telomerase to cells reminds me of the advertisements for an apparatus that allowed you to recline with your head lower than your feet, except that when you age upside down, by lying around on that device, there is a silly grain of truth in the claim that you have "reversed" the aging process.

The fact that cells are always open to "reprogramming," which simply means responding appropriately to their environment, is an important thing to keep in mind. Alexis Carrel's experiments are still the best demonstration that biological aging is essentially a response to something in the cells' environment. Carrel's emphasis on fats as an important aspect of aging is massively supported by research in nutrition, organ transplantation, and tissue culture.

It is now clear that estrogen is intimately related to the universal stress-reaction system, the heat shock proteins. Progesterone, the most direct and general antagonist to estrogen, is now seen to be involved in this fundamental system--it opposes the actions of the stress proteins, and the stress proteins mediate the factors which cause a progesterone deficiency.

Progesterone, thyroid, saturated fats, and light are primary antistress factors which have already been shown to protect against some of the effects of aging (such as autoimmune

Les H.S.P testo et estro shift la différenciation cell vers dédifférenciation

reactions), and against the stresses which contribute to aging, and in many cases to reverse age-associated changes that have already occurred (such as regenerating the thymus). To fully reverse aging we need to know all of the factors that cause it; Dolly is proof that adult cells are not, in themselves, "old," and is confirmation that Carrel was on the right track.

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whether a glial stress response is implicated in estrogen-induced granulation. **Our findings indicate that estrogen elicits a heat shock response and subsequent granulation in astrocytes residing in estradiol receptor-rich brain regions including the arcuate nucleus and the wall surrounding the third ventricle but not in estradiol receptor-deficient regions such as the striatum and corpus callosum. The heat shock proteins induced by estrogen, namely, the 27, 72, and 90 kDa stress proteins, are upregulated in astrocytes in response to oxidative challenge supporting our hypothesis that estrogen mediates senescent changes in the rodent hypothalamus through oxidative mechanisms."**

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