SAMPLE

Ray Peat's Newsletter

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Regeneration and the Anti-adaptogens

I don't think aging is necessary, and I think I have begun to see the organism in a context that can explain the cause of aging in a relatively simple way.

In outline, this is how I see it:

1. Every cell and tissue is capable of renewal;

2. the (Hayflick) doctrine of absolutely limited cellular renewal capacity has been disproved in many ways;

3. the great variety of degenerative diseases which can be promoted by a few factors--radiation, oxygen deprivation, polyunsaturated fats, and estrogen--can serve as a guide to the nature of our basic control systems;

4. the factors which disrupt our natural regulatory systems contain clues to possible restorative methods.

Every important issue in life is an opportunity for powerful self-interest to intervene and take control. In transportation, corporations interested in selling gasoline and cars destroyed the cities' elegant systems of electric trolleys, in energy the nuclear and petroleum interests fought the development of solar and wind power, and the timber industry lobbies against innovation in house construction. The issue of aging and death is one that has been consciously dealt with throughout human existence, and it has accumulated a most complex system of mental commitments. This investment of emotion and belief affects every aspect of theory and practice in biology and medicine. We have to keep asking "is this researcher ignoring some facts that might seem to conflict with his ideology?"

Definitions:

Hayflick limit: Leonard Hayflick found that certain animal or human cells which can be grown in a dish would die out after 50 divisions, and he announced that this limited ability to divide sets the maximum limit of the lifespan. He has said that this is governed by the principle that entropy tends to increase. Another group found that the same kind of cell continued to divide nicely after 110 divisions, and didn't begin to die out until they began to use the serum from a different calf. The cells of the skin and bowel divide thousands of times in a normal lifetime, and transplanted pieces of skin or mammary gland remained healthy through the lifetimes of ten animals in series.

Telomere: A structure on the ends of chromosomes that gets shorter with each division in some cells. The enzyme telomerase reconstitutes the telomeres in "immortal cells," such as germ cells and cancer cells. In aging, most aspects of cell function are weakened, but this particular enzyme operates in a location close enough to "the genes" that some people think it is behind the "Hayflick limit." But many other repair systems also slow down with aging; nothing gives this structure special explanatory power.

Previously, I have talked about the doctrine that our cells are divided into the immortal cells of "the germ line," and the mortal "somatic" cells of all the rest of the body. This doctrine says "people

are mortal, so their cells must be intrinsically mortal, but they can have descendants ad infinitum, so their germ cells must be different from all the rest of their cells, and immortal." Alexis Carrel was famous for demonstrating that heart cells could be immortal in the right environment, but his work is now ignored or dismissed. "Only cancer cells and the germ line are immortal," the present doctrine says; ("and maybe embryonic cells"). It seems that the immortalization of our mortal somatic cells is acceptable, as long as these cells have the function of killing us.

I think some of Carrel's ideas about the nature of living organization and of aging are worth quoting. (Man the Unknown, 1935.)

"Isolated cells have the singular power of reproducing...the edifices characterizing each organ. If a few red corpuscles, impelled by gravity, flow from a drop of blood placed in liquid plasma and form a tiny stream, banks are soon built up. Then, these banks cover themselves with filaments of fibrin, and the stream becomes a pipe, through which the red cells glide just as in a blood vessel. Next, leucocytes come, adhere to the surface of the pipe, and surround it with their undulating membrane. The blood stream now assumes the appearance of a capillary vessel enveloped in a layer of contractile cells. Thus, isolated red and white corpuscles manage to construct a segment of circulatory apparatus, although there is neither heart, circulation, nor tissues to be irrigated." "The spontaneous tendency toward formation of the organs by their constitutive cells, like the social aptitude of the insects, is a primary datum of observation." (Page 107.)

"The simplest system, where the phenomenon of sensescence is observed, consists of a group of tissue cells cultivated in a small volume of nutritive medium. In such a system, the medium is progressively modified by the products of nutrition and, in its turn, modifies the cells. Then appear senescence and death. The rhythm of physiological time depends on the relations between the tissues and their medium. It varies according to the volume, the metabolic activity, the nature of the cell colony, and the quantity and the chemical composition of the fluid and gaseous media. The technique used in the preparation of a culture accounts for the rhythm of life of such culture. For example, a fragment of heart fed with a single drop of plasma in the confined atmosphere of a hollow slide, and another one immersed in a flask containing a large volume of nutritive fluids and gases, have quite different fates. The rate of accumulation of the waste products in the medium, and the nature of these products, determine the characteristics of the duration of the tissues. When the composition of the medium is maintained constant, the cell colonies remain indefinitely in the same state of activity." "If, by an appropriate technique, their volume is prevented from increasing, they never grow old. Colonies obtained from a heart fragment removed in January, 1912, from a chick embryo, are growing as actively today as twenty-three years ago. In fact, they are immortal." (Page 173.)

Heart cells are recognizable even in isolation, because they beat. It would be impossible to mistake them for another type of cell.

Years later, Hans Selye was observing the reaction to a small glass tube inserted under a rat's skin. He noticed that the tube was soon enclosed by a capsule of fibrous tissue, and that the cells gradually grew in a strand from the ends down the channel of the tube. These cells were isolated from the fluids that normally surround cells, and Selye found that after a short time they took on the appearance of cells from a very old animal, while the cells of the surrounding capsule remained normal. Selye drained the fluid at intervals, allowing it to be replaced by fresh fluid, and found that at the end of the rat's life-span, the cells of this filament showed no signs of aging.

Carrel's work with tissue-culture led him to believe that changes in the organism's fluids were a major part of the aging process. Extracts from animal embryos have been used medically for treating old people, because of their confirmed effect on cell function. "Blood plasma alone displays, throughout the entire life-time, progressive modifications characterizing the senescence of the body as a whole. We know that it contains the secretions of all tissues and organs. Plasma and tissues being a closed system, any alteration in the tissues reacts on the plasma, and vice versa. During the course of life, this system undergoes

continuous changes. Some of these changes may be detected both by chemical analysis and by physiological reactions. The plasma or the serum of an aging animal has been found to increase its restraining effect on the growth of cell colonies. The ratio of the area of a colony living in serum, to that of an identical colony living in a saline solution and acting as a control, is called the growth index. The older the animal to which the serum belongs, the smaller is this index." "During the first days of life, blood serum does not inhibit the growth of cell colonies any more than does the control solution. At this moment the value of this index approaches unity. As the animal becomes older, its serum restrains cell multiplication more effectively. And the index decreases. During the last years of life, it is generally equal to zero." {Page 168.)

In 1921, a researcher (A. J. Lotka) looking for a job at the Rockefeller Institute visited Carrel's laboratory. "I saw a young lady making chicken hash in the most heartless but thoroughly scientific manner. I saw a little piece of chicken heart foolishly throbbing after all occasion for throbs had long ceased. I saw a thirteen year old dog rejuventated by the infusion of younger blood. It was hardly converted into a giddy young thing, but they told me there was still marked improvement even after twelve months." (S. E. Kingsland, *Modeling Nature*, Univ. of Chicago Press, 1995.)

Carrel discussed Lecomte du Nouy's equations for describing the regenerative activity of the body at a given age. (A 21 year-old person heals twice as quickly as a 40 year-old person.) The rate of healing and the growth index of plasma, according to Carrel, **"...correspond to successive states in the chemical composition of the humors. The proteins of blood serum become more abundant and their characters are modified. It is chiefly the fats which give to serum the property of acting upon certain cell types and of diminishing the rapidity of their multiplication. These fats increase in quantity and change in nature during life."** (Page 174.)

Here, I want to review some of the effects of fats that I have talked about elsewhere. Polezhaev's work in regeneration has suggested that the fatty residue left from degenerating cells stimulates the formation of new cells. Linoleic acid, like phorbol esters and estrogen, activates protein kinase C, and the cell growth system.

In looking at a tissue slide that was used to diagnose "ductal carcinoma in situ," I noticed that the structures resembled cross-sections of tubercles. In the breast ducts, fatty residues from milk secretions should be able to stimulate cell division. The fats formed by the tuberculosis bacillus stimulate the cellular reaction that produces the tubercle structure. Since a tuberculous breast grossly resembles a cancerous breast, it is important that the possible structural similarity of the two diseases, under the microscope, be considered. The bacteria can disappear from the cells in a tubercle, and the "defining" presence of giant cells in the tubercular lesion isn't invariable.)

It has been suggested that the tubercle develops and persists because the body's proteolytic enzymes are inhibited by the unsaturated fats. (Even older ideas of "fatty degeneration," going back to the very beginnings of biochemistry, were based on the fact that proteins are deposited from solution at an interface, such as that formed by a drop of oil, forming a sort of proteinaceous skin around fat droplets.) Whether the process is simply the result of inactivating proteolytic enzymes, or the result of a more specific disordering of cell control systems, it is a well established experimental fact that oils stimulate a kind of fibrous tumor, called the "oil granuloma." If the oil can't be digested and removed, the body reacts by forming a growth around it. Inside the cell, unsaturated fatty acids slow many cellular processes, including respiratory energy production and protein turnover, changes which parallel the changes occurring in aging.

About 30 years ago, Leonard Hayflick found that certain animal or human cells which can be grown in a dish would die out after about 50 divisions. He also found that cells from old individuals would stop dividing sooner when grown in tissue culture. He announced that this limited ability to divide sets the maximum limit of the lifespan. He has said that this is governed by the principle that entropy tends to increase. Another group found that the same kind of cell continued to divide nicely after 110 divisions, and didn't begin to

die out until they began to use the serum from a different calf. Their result resembled Carrel's findings, in which the fluid from younger organisms supported more vigorous growth in tissue culture, and clearly casts doubt on Hayflick's principle. But even without such contradictions of Hayflick's tissue culture results, Hayflick's claims couldn't really be taken seriously as anything but a theoretical model of what is happening to cells in an aging organism, because cells that are removed from their complex environment in the organism have been deprived of a rich and communicative framework.

The cells of the skin and bowel divide thousands of times in a normal lifetime, showing that there is a kind of arrogant silliness in the claim that "human cells have a strictly limited capacity to divide." (I call this "disproof by dandruff.")

Pieces of skin or mammary gland, removed from old rats and transplanted into young rats, remained healthy through the lifetimes of ten animals in series. When young animals have been surgically attached to old animals ("parabiosis"), the pair has lived out the life-span of the younger animal, allowing the older one to reach an abnormally advanced age. In some studies, beneficial changes have been seen in the old individual, and some harmful effects appeared in the young animal. I have described these experiments previously.

Selye's experiment, besides showing the importance of fluid renewal in cell aging, also showed one of the ways in which cells respond to structure. Cells build structures, and then they respond to them. They "know" where they are in a given structure. Cells produce materials--some of them soluble, others insoluble--that produce a characteristic local environment. In plants, the cellulose scaffolding between cells, and other extracellular matrix materials, serve as part of the information that guides the functioning of cells,[1] so that removal of the cellulose allows the cell to stop a specialized function, and begin to grow and take on new functions, even in some cases producing a complete new organism. In a wound in an animal's skin, cell division is stimulated to heal the wound. I think it is the doctrine of the germ line/somatic distinction that has prevented more vigorous research in the origin of teratomas, growths of radically different tissue types (hair, teeth, bones, fingernails, mammary tissue, e.g.) in an inappropriate location--often the ovary, but sometimes in the bladder, tongue, rectum or other location. These have been explained as "embryonic rests," or undeveloped Siamese twins, as a way to avoid the idea that somatic cells have the capacity to revert to totipotency. Their occurrence is strongly reminiscent of the situation in plants, in which an injured (isolated) somatic cell becomes "totipotent," resembling a germ cell or embryonic cell.

If cells have systems that regulate their functions, and known substances distrupt those functions, the endogenous regulatory material must have some of the properties of the disruptive material. For example, digitalis and ouabain are plant steroid-derivatives that are poisonous to animal cells--especially the heart cells--by acting at a "site" which is normally regulated by substances such as DHEA and progesterone.

For plants, cholesterol is a hormone, while it is only a precursor for hormones in animals. If plants ate animals, they might eventually accumulate enough cholesterol to disrupt the processes normally regulated by their very small amounts of cholesterol.

The fact that opium from poppies, and similar substances found in other plants, have a powerful effect on animals, and can be found associated with certain sites in their cells, led to the belief that these were regulatory sites, that might normally be controlled by very small amounts of materials produced in the animals' tissues, for regulatory purposes. This led to the discovery of the endorphins, the peptide molecules that have morphine-like effects.

Valium (or the traditional valerian root extract) was found to be associated with a certain "receptor site," which is now known as the "benzodiazepine receptor." A peptide called "endozepine" is one of the natural regulators of that control system, but it is also influenced by GABA (gamma amino butyric acid), progesterone, pregnenolone, and other materials. Butyric acid itself might affect this system.

Marihuana acts on cells by acting at a site that is called the "cannabinoid receptor," because the

Recepteur Zodiazepine = valium, valerian Root, Endozepine Regulariser le syst de recepteur Zodiazepine et endiazepine est influencé par GABA, Proges

body's natural regulator acting on that site isn't yet known.

The unsaturated fatty acids, linolenic acid and linoleic acid, produced by plants, interfere with intercellular communication,[2] as well as intracellular regulatory sites. (PKC, osmotic balance[3], respiration.) The body's natural regulatory materials are probably similar in structure, but produced in controlled amounts and locations.

The Mead acids are unsaturated fatty acids produced in small quantities by the body when the diet doesn't contain an overwhelming amount of the plant-derived fatty acids. Wherever the plant fats act, we can expect to find a process that is regulated by the Mead acids, though not necessarily in the same way or with the same result. Even if the materials had the same effect on the control system, the increasing accumulation of an active material will tend to make control impossible, acting as a constant signal to activate the system. (Therefore, even an exaggerated accumulation of the natural transmitter substance would be disruptive if it were released in an uncontrolled way. The regulatory substance ideally would not be stored in excess, or it would be released in a controlled way. The Mead acids seem to meet these criteria.) [The position of the certain type of fatty acid on glycerol, for example, is regulated by specific enzymes.]

A naturally occurring combination of a fatty acid with ethanolamine, called anandamide, activates the "marihuana receptor" of cells. It prevents some types of cell activation. The Mead acid ethanolamide, like the arachidonic acid form, can be enzymatically formed in various human tissues, such as the hippocampus, but the two substances have slightly different effects. Marihuana's anticonvulsant properties might be more effectively represented by the Mead acid derivative. The anti-excitatory effect might also be effective in preventing the loss of cells in the hippocampus, hypothalamus, and other brain regions, which (building on Olney's work 25 years ago) is increasingly understood to result from excitotoxicity.

The architecture of tissues interacts with the cytoskeleton and the nuclear scaffolding to define the possibilities and opportunities that are available to the cell and to the organism.

The organization of life is maintained by the energy it uses, and the use of energy requires a specific organization. There are processes in cells that regulate the interactions of growth, division and other functions, but these processes are responsive to the cells' environment--they aren't just "emitted by" or "unrolled from" the cells' repertoire of abilities.

The cell's structure has sensitive "leverage" points that serve for purposes of "perception" or "signalling." When organization fails, it is just reasonable to consider whether extraneous conditions or "signals" have intervened. If it were in life's nature to become disorganized, it is hard to imagine that it would persist and thrive.

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