Stem cells, cell culture, and culture: Issues in regeneration

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Cell renewal is a factor in all aspects of health and disease, not just in aging and the degenerative diseases. Many people are doing valid research relating to cell renewal and regeneration, but its usefulness is seriously limited by cultural and commercial constraints. By recovering some of our suppressed traditional culture, I think regenerative therapies can be developed quickly, by identifying and eliminating as far as possible the main factors that interfere with tissue renewal.

Science grew up in the highly authoritarian cultures of western Europe, and even as it contributed to cultural change, it kept an authoritarian mystique. Any culture functions as a system of definitions of reality and the limits of possibility, and to a great extent the "laws of nature" are decreed so that they will harmonize with the recognized laws of society.

The practical success of Newton's "laws" of motion when they were applied to ballistics and "rocket science" has led many people to value calculation, based on those laws, over evidence. In biology, the idea that an organism is "the information it contains in its DNA blueprint" is an extention of this. The organism is turned into something like a deductive expression of the law of DNA. This attitude has been disastrous.

The old feudal idea of a divine and stable social organization was applied by some people to their idea of biological organization, in which each cell (ruled by its nucleus) had its ordained place in the organism, with the brain and the "master gland," the pituitary, ruling the subordinate organs, tissues, and cells. "Anatomy" was taught from dead specimens, microscope slides, and illustrations in books. Most biologists' thoughts about cells in organisms reflect the static imagery of their instruction. (*"The histological image of these tissues actually reflects an instantaneous picture of cells in a continuous flux."* Zajicek, 1981.)

When a person has playful and observant interactions with natural things, both regularities and irregularities will be noticed, and in trying to understand those events, the richness of the experience will suggest an expansive range of possibilities. Perception and experimentation lead to understandings that are independent of culture and tradition.

But the mystique of science easily imposes itself, and distracts our attention from direct interactions with things. As we learn to operate lab instruments, we are taught the kinds of results that can be expected, and the concepts that will explain and predict the results of our operations. Science, as we learn about it in schools and the mass media, is mostly a set of catechisms.

Our theories about organisms inform our experiments with cells or tissues that have been isolated from those organisms. The conditions for growing cells in dishes are thought of as "physiological," in relation to the solution's "physiological osmolarity," "physiological pH," nutrients, oxygenation, temperature, pressure, etc. But these concepts of what is physiological derive from the monolithic ideology of the doctrinaire, and often fraudulent, mainstream of biological science.

The catechismic nature of science has led people to expect some "break-throughs" to occur in certain areas, and as authoritarian science has grown into "big science" managed by corporations and governments, those break-throughs are generally expected to be produced by the newest and most expensive developments of "high technology."

But looking closely at the real events and processes in the sciences in the last couple of centuries, it turns out that useful advances have been produced mainly by breaking away from authoritarian doctrines, to return to common sense and relatively simple direct observations.

Although people were cloning animals in the 1960s, it was still widely taught that it was impossible. The students of the professors who taught that it was impossible are now saying that it requires high technology and new research.

For the last 100 years the most authoritative view in biology has been that there are no stem cells in adults, that brains, hearts, pancreases and oocytes are absolutely incapable of regeneration. But now, people seem to be finding stem cells wherever they look, but there is a mystique of high technology involved in finding and using them.

Whether it's deliberate or not, the emphasis on stem cell technology has the function of directing attention away from traditional knowledge, the way allopathic medicine has de-emphasized the intrinsic ability of people to recover from disease.

This resembles the way that the Mendel-Morgan gene doctrine was used to suppress the knowledge gained from centuries of experience of plant and animal breeders, and to belittle the discoveries of Luther Burbank, Paul Kammerer, Trofim Lysenko, and Barbara McClintock. The same type of biochemical process that caused the hereditary changes those researchers studied are involved in the differentiation and dedifferentiation of stem cells that regulate healing and regeneration.

In the 1940s, even children discussed the biological discoveries of the 1920s and 1930s, the work in regeneration and adaptation, parthenogenesis, and immortalization. The ideas of J. Loeb, T. Boveri, A. Gurwitsch, J. Needham, C.M. Child, A. Carrel, et al., had become part of the general culture.

But that real biology was killed by a consortium of industry and government that began a little before the second world war. In 1940, the government was supporting research in chemical and biological warfare, and with the Manhattan Project the role of government became so large that all of the major research universities were affected. Shortly after the war, many researchers from the Manhattan Project were redeployed into "molecular genetics," where the engineering attitude was applied to organisms.

The simplistic genetic dogmas were compatible with the reductionist engineering approach to the organism. The role of the government assured that the universities would subscribe to the basic scientific agenda. The atmosphere of that time was described by Carl Lindegren as "The Cold War in Biology" (1966).

The disappearance of the field concept in developmental biology was one of the strangest events in the history of science. It didn't just fade away, it was "disappeared," in a massive undertaking of social engineering. In its absence, stem cells will seem to be a profitable technological marvel, rather than a universal life function, with a central role in everything we are and everything we do and can become.

Many people have tried to explain aging as a loss of cells, resulting from an intrinsic inability of any cell other than a germ cell to multiply more than a certain number of times. More than 40 years ago Leonard Hayflick popularized this doctrine in its most extreme form, saying that no cell can divide more than 50 times unless it is converted into a cancer cell. He and his followers claimed that they had explained why organisms must age and die. At the moment the ovum is fertilized, the clock starts ticking for the essentially mortal somatic cells.

In 1970, it was being seriously proposed that memory was produced by the death of brain cells, in a manner analogous to the holes punched in cards to enter data into computers. The cultural dogma made it impossible to consider that learning could be associated with the birth of new cells in the adult brain.

With the announcement in 1997 of the cloning of the sheep Dolly from a somatic cell taken from a 6 year old sheep, there was renewed interest in the idea made famous by Alexis Carrel that all cells are potentially immortal, and in the possibility of preserving the vitality of human cells. Within a few months, Hayflick began reminding the public that "In the early 1960's we overthrew this dogma after finding that normal cells do have a finite replicative capacity." ("During the first half of this century it was believed that because cultured normal cells were immortal, aging must be caused by extra-cellular events.") The way Hayflick "overthrew" more than 35 years of work at the Rockefeller Institute was by growing one type of cell, a lung fibroblast, in culture dishes, and finding that the cultures deteriorated quickly.

To draw global conclusions about an organism's development and aging from the degenerative processes seen in a single type of cell, grown in isolation from all normal stimuli, would have been treated as nothing but wild speculation, except that it occurred within a culture that needed it. No aspect of Hayflick's cell culture system could properly be called physiological.

Other researchers, simply by changing a single factor, caused great increases in the longevity of the cultured cells. Simply using a lower, more natural oxygen concentration, the cells were able to undergo 20 more divisions. Just by adding niacin, 30 more divisions; vitamin E, 70 more divisions. Excess oxygen is a poison requiring constant adaptation.

Hayflick also published the observation that, while the cells kept in dishes at approximately body temperature deteriorated, cells kept frozen in liquid nitrogen didn't deteriorate, and he concluded that "time" wasn't the cause of aging. When I read his comments about the frozen cells, I wondered how anyone of normal intelligence could make such stupid statements. Since then, facts that came out because of the Freedom of Information Act, cause me to believe that a financial motive guided his thoughts about his cultured fibroblasts.

Hayflick and his followers have been attacking the idea of anti-aging medicine as quackery. But he is closely involved with the Geron corporation, which proposes that genetic alterations relating to telomeres may be able to cure cancer and prevent aging. Their claims were reported by CNN as "Scientists discover cellular 'fountain of youth'."

The "wear and tear" doctrine of aging that derived from the ideology of the gene was reinforced and renewed by Hayflick's cell culture observations, and it continued to rule the universities and popular culture.

But detailed investigation of skin cell growth showed that cells in the lower layer of the skin divide at least 10,000 times in a normal lifetime, and similar processes occur in the lining of the intestine. The endometrium and other highly renewable tissues just as obviously violated Hayflick's limit. Transplantation experiments showed that pieces of mammary tissue or skin tissue could survive through ten normal lifetimes of experimental animals without suffering the effects of aging.

Even the liver and adrenal gland are now known to be continuously renewed by "cell streaming," though at a slower rate than the skin, conjunctiva, and intestine. Neurogenesis in the brain is now not only widely accepted, it is even proposed as a mechanism to explain the therapeutic effects of antidepressants (Santarelli, et al., 2003).

August Weismann's most influential doctrine said that "somatic cells are mortal, only the germline cells are immortal," but he based the doctrine on his mistaken belief that only the "germline" cells contained all the genes of the organism. In 1885, to "refute" Darwin's belief that acquired traits could be inherited, he promulgated an absolute "barrier" between "germline" and "soma," and invented facts to show that hereditary information can flow only from the germline to the somatic cells, and not the other direction. Shortly after DNA became popular in the 1950s as "the genetic material," Weismann's barrier was restated as the Central Dogma of molecular genetics, that information flows only from DNA to RNA to protein, and never the other direction.

It was only in 2003, after the reality of cloning was widely recognized, that a few experimenters began to investigate the origin of "germline" cells in the ovary, and to discover that they derive from somatic cells (Johnson, et al., 2004). With this discovery, the ancient knowledge that a twig (*klon*, in Greek) cut from a tree could grow into a whole tree, bearing fruit and viable seeds, was readmitted to general biology, and the Weismann barrier was seen to be an illusion.

Millions of people have "explained" female reproductive aging as the consequence of the ovary "running out of eggs." Innumerable publications purported to show the exact ways in which that process occurs, following the Weismann doctrine. But now that it is clear that adult ovaries can give birth to new oocytes, a new explanation for female reproductive aging is needed. It is likely that the same factors that cause female reproductive aging also cause aging of other systems and organs

and tissues, and that those factors are extrinsic to the cells themselves, as Alexis Carrel and others demonstrated long ago. This is a way of saying that all cells are potential stem cells. The "niche" in which new cells are born in the streaming organism, and the processes by which damaged cells are removed, are physiological issues that can be illuminated by the idea of a morphogenetic field.

When the post-war genetic engineers took over biological research, the idea of a biophysical field was totally abandoned, but after about 15 years, it became necessary to think of problems beyond those existing within a single bacterium, namely, the problem of how an ovum becomes and embryo. Francis Crick, of DNA fame, who was educated as a physicist, revived (without a meaningful historical context) the idea of a diffusion gradient as a simple integrating factor that wouldn't be too offensive to the reductionists. But for events far beyond the scale of the egg's internal structure, for example to explain how a nerve axon can travel a very long distance to innervate exactly the right kind of cell, the diffusion of molecules loses its simplicity and plausibility. (Early in the history of experimental embryology, it was observed that electrical fields affect the direction of growth of nerve fibers.)

C. M. Child saw a gradient of metabolic activity as an essential component of the morphogenetic field. This kind of gradient doesn't deny the existence of diffusion gradients, or other physical components of a field. Electrical and osmotic (and electro-osmotic) events are generated by metabolism, and affect other factors, including pH, oxidation and reduction, cell motility and cell shape, ionic selectivity and other types of cellular selectivity and specificity. Gradients of DNA methylation exist, and affect the expression of inherited information.

Methylation decreases the expression of particular genes, and during the differention of cells in the development of an embryo, genes are methylated and demethylated as the cell adapts to produce the proteins that are involved in the structure and function of a particular tissue. Methylation (which increases a molecule's affinity for fats) is a widespread process in cells, and for example regulates cellular excitability. It is affected by diet and a variety of stresses.

DNA methylation patterns are normally fairly stable, and can help to account for the transgenerational transmission of acquired adaptations, and for neonatal imprinting that can last a lifetime. But with injury, stress, and aging, the methylation patterns of differentiated tissues can be changed, contributing to the development of tumors, or to the loss of cellular functions. Even learning can change the methylation of specific genes. During *in vitro* culture, the enzymes of gene methylation are known to be increased, relative to their normal activity (Wang, et al., 2005).

The phenomenon of "gene" methylation in response to environmental and metabolic conditions may eventually lead to the extinction of the doctrine that "cells are controlled by their genes."

During successful adaptation to stress, cells make adjustments to their metabolic systems (for example with a holistic change of the degree of phosphorylation, which increases molecules' affinity for water), and their metabolic processes can contribute to changes in their state of differentiation. Some changes may lead to successful adaptation (for example by producing biogenic stimulators that stimulate cell functioning and regeneration), others to failed adaptation. Even the decomposition of cells can release substances that contribute to the adaptation of surrounding cells, for example when sphingosines stimulate the production of stem cells.

DNA methylation is just one relatively stable event that occurs in relation to a metabolic field. Modifications of histones (regulatory proteins in chromosomes, which are acetylated as well as methylated) and structural-contractile filaments also contribute to the differentiation of cells, but the pattern of DNA methylation seems to guide the methylation of histones and the structure of the chromosomes (Nan, et al., 1998).

Steroids and phospholipids, neurotransmitters and endorphins, ATP, GTP, other phosphates, retinoids, NO and CO_2--many materials and processes participate in the coherence of the living state, the living substance. Carbon dioxide, for example, by binding to lysine amino groups in the histones, will influence their methylation. Carbon dioxide is likely to affect other amino groups in the chromosomes.

The number and arrangement of mitochondria is an important factor in producing and maintaining the metabolic gradients. Things that decrease mitochondrial energy production--nitric oxide, histamine, cytokines, cortisol--increase DNA methylation. Decreased gene expression is associated with reduced respiratory energy. It seems reasonable to guess that increased gene expression would demand increased availability of energy.

As an ovum differentiates into an organism, cells become progressively more specialized, inhibiting the expression of many genes. Less energy is needed by stably functioning cells, than by actively adapting cells. A.I. Zotin described the process of maturing and differentiating as a decrease of entropy, an increase of order accompanying a decreased energy expenditure. The entropic egg develops into a less entropic embryo with a great expenditure of energy.

The partially differentiated stem cell doesn't go through all the stages of development, but it does expend energy intensely as it matures.

The restoration of energy is one requirement for the activation of regeneration. When a hormone such as noradrenaline or insulin causes a stem cell to differentiate in vitro, it causes new mitochondria to form. This is somewhat analogous to the insertion of mitochondria into the ripening oocyte, by the nurse cells that surround it. The conditionally decreased entropy of maturation is reversed, and when sufficient respiratory energy is available, the renewed and refreshed cell will be able to renew an appropriate degree of differentiation.

When simple organisms, such as bacteria, fungi, or protozoa are stressed, for example by the absence of nutrients or the presence of toxins, they slow their metabolism, and suppress the expression of genes, increasing the methylation of DNA, to form resistant and quiescent spores. Our differentiated state doesn't go to the metabolic extreme seen in sporulation, but it's useful to look at maturity and aging in this context, because it suggests that the wrong kind of stress decreases the ability of

the organism to adapt, by processes resembling those in the spore-forming organisms.

Charles Vacanti, who has grown cartilage from cells taken from 100 year old human cartilage, believes our tissues contain "spore cells," very small cells with slow metabolism and extreme resistance to heat, cold, and starvation.

If the slowed metabolism of aging, like that of sporulating cells, is produced by a certain kind of stress that lowers cellular energy and functions, it might be useful to think of the other stages of the stress reaction in relation to the production of stem cells. Selye divided stress into a first stage of shock, followed by a prolonged adaptation, which could sometimes end in exhaustion. If the maturity of differentiated functioning is equivalent to the adaptation phase, and cellular decline and disintegration is the exhaustion phase, then the shock-like reaction would correspond to the birth of new stem cells.

Selye described estrogen's effects as equivalent to the shock-phase of stress. Estrogen's basic action is to make oxygen unavailable, lowering the oxygen tension of the tissues, locally and temporarily. Like nitric oxide, which is produced by estrogenic stimulation, estrogen interferes with energy production, so if its stimulation is prolonged, cells are damaged or killed, rather than being stimulated to regenerate.

Extrinsic factors elicit renewal, the way stress can elicit adaptation. While aging cells can't use the oxygen that is present, a scarcity of oxygen can serve as a stimulus to maximize the respiratory systems. Brief oxygen deprivation excites a cell, causes it to swell, and to begin to divide.

Oxygen deprivation, as in the normally hypoxic bone marrow, stimulates the formation of stem cells, as well as the biogenesis of mitochondria. As the newly formed cells, with abundant mitochondria, get adequate oxygen, they begin differentiation.

Form, based on cellular differentiation, follows function--a vein transplanted into an artery develops anatomically into an artery, a colon attached directly to the anus becomes a new rectum with its appropriate innervation, a broken bone restructures to form a normal bone. If the bladder is forced to function more than normal, by artificially keeping it filled, its thin wall of smooth muscle develops into a thick wall of striated muscle that rhythmically contracts, like the heart. If a tadpole is given a vegetarian diet, the absorptive surface of its digestive system will develop to be twice the size of those that are fed meat. Pressure, stretching, and pulsation are among the signals that guide cells' differentiation.

Very early in the study of embryology it was noticed that the presence of one tissue sometimes induced the differentiation of another kind, and also that there were factors in embryonic tissues that would stimulate cell division generally, and others that could inhibit the growth of a particular tissue type. Diffusable substances and light were among the factors identified as growth regulators.

Extracts of particular tissues were found to suppress the multiplication of cells in that type of tissue, in adult animals as well as in embryos. In the 1960s, the tissue-specific inhibitors were called chalones.

The brain's development is governed by the presence in the organism of the body part to which it corresponds, such as the eyes or legs. The number of cells in a particular part of the nervous system is governed by the quantity of nervous input, sensory or motor, that it receives. An enriched environment causes a bigger brain to grow. Sensory nerve stimulation of a particular region of the brain causes nerve cells to migrate to that area (a process called neurobiotaxis; deBeers, 1927), but nerve stimulation also causes mitochondria to accumulate in stimulated areas. Nerve activity has a trophic, sustaining influence on other organs, as well as on the brain. Nerve stimulation, like mechanical pressure or stretching, is an important signal for cellular differentiation.

When stem cells or progenitor cells are called on to replace cells in an organ, they are said to be "recruited" by that organ, or to "home" to that organ, if they are coming from elsewhere. Traditionally, the bone marrow has been considered to be the source of circulating stem cells, but it now appears that a variety of other less differentiated cells can be recruited when needed. Cells from the blood can repair the endothelium of blood vessels, and endothelial cells can become mesenchymal cells, in the heart, for example.

The standard doctrine about cancer is that a tumor derives from a single mutant cell, but it has been known for a long time that different types of cell, such as phagocytes and mast cells, usually reside in tumors, and it is now becoming clear that tumors recruit cells, including apparently normal cells, from other parts of the same organ. For example, a brain tumor of glial cells, a glioma, recruits glial cells from surrounding areas of the brain, in a process that's analogous to the embryological movement of nerve cells to a center of excitation. Each tumor, in a sense, seems to be a center of excitation, and its fate seems to depend on the nature of the cells that respond to its signals.

To accommodate some of the newer facts about tumors, the cancer establishment has begun speaking of "the cancer stem cell" as the real villain, the origin of the tumor, while the bulk of the tumor is seen to be made up of defective cells that have a short life-span. But if we recognize that tumors are recruiting cells from beyond their boundaries, this process would account for the growth and survival of a tumor even while most of its cells are inert and dying, without invoking the invisible cancer stem cell. And this view, that it is the field which is defective rather than the cell, is consistent with the evidence which has been accumulating for 35 years that tumor cells, given the right environment, can differentiate into healthy cells. (Hendrix, et al., 2007)

Simply stretching an organ (Woo, et al., 2007) is stimulus enough to cause it to recruit cells from the bloodstream, and will probably stimulate multiplication in its local resident cells, too. Every "cancer field" probably begins as a healing process, and generally the healing and regeneration are at least partially successful.

When an organ--the brain, heart, liver, or a blood vessel--is inflamed or suffering from an insufficient blood supply, stem cells introduced into the blood will migrate specifically to that organ.

Organ specific materials (chalones) are known to circulate in the blood, inhibiting cell division in cells typical to that organ, but it also seems that organ specific materials are secreted by a damaged organ, that help to prepare stem cells for their migration into that organ. When undifferentiated cells are cultured with serum from a person with liver failure, they begin to differentiate into liver cells.

It is still common to speak of each organ as having a "clonal origin" in the differentiating embryo, as a simple expansion of a certain embryonic anlage. The implication of this way of thinking is that differentiation is *determination* in an irreversible sense. This is another case of medical ideas being based on images of fixed histological material. Normal cells, including nerve and muscle cells, can change type, with connective tissue cells becoming nerve cells, nerve cells becoming muscle and fiber cells, fat, fiber, and muscle cells redifferentiating, for example.

Cell movements in solid tissues aren't limited to the short distances between capillaries and the tissues nourished by those capillaries, rather, cells can migrate much greater distances, without entering the bloodstream. The speed of a single cell moving by ameboid motion can be measured by watching cells on a glass slide as they move toward food, or by watching cells of the slime mold Dictyostelium when they are aggregating, or by watching the pigment cells in and around moles or melanomas, under the influence of hormones. At body temperature, a single cell can crawl about an inch per day. Waves or spots of brown pigment can be seen migrating through the skin away from a mole, preceding the disintegration of the mole under the influence of progesterone or DHEA. Under ordinary conditions, pigment cells can sometimes be seen migrating into depigmented areas of skin, during the recovery of an area affected by vitiligo. These organized movements of masses of cells happen to be easy to see, but there is evidence that other types of cell can reconstruct tissues by their ameboid movements, when circumstances are right. Tumors or tissue abnormalities can appear or disappear with a suddenness that seems impossible to people who have studied only fixed tissue preparations.

Stimulation is anabolic, building tissue, when the organism is adapting to the stimulation. Unused structures in cells and tissues are always being recycled by metabolic processes. When tissues are injured and become unable to function, some of their substances stimulate the growth of replacement cells.

Some types of injury or irritation can activate regenerative processes. A dermatology journal described the case of an old man who had been bald for many years who fell head-first into his fireplace. As his burned scalp healed, new hair grew. In the U.S., experimenters (Ito, et al., 2007) have found that injuring the skin of mice stimulates the formation of stem cells that are able to become hair follicle cells, supporting the regeneration of cells that had been absent. A brief exposure to estrogen, and other stress related signals (nitric oxide, endorphin, prostaglandins) can initiate stem cell proliferation.

I n the years after the first world war, Vladimir Filatov, who developed techniques of reconstructive surgery, including corneal transplants, found that cold storage of tissues (for example, corneas from cadavers) caused them to function better than fresh tissues, and he found that these stressed tissues would often spread a healing influence out into the surrounding tissues. Extracts of stressed tissues produced similar effects.

L.V. Polezhaev began studying the regenerative capacities of mammals in the late 1940s, and his work showed that processes similar to embryonic induction are involved in the organism's responses to damaged tissues. For example, when a piece of killed muscle tissue is enclosed in a capsule ("diffusion chamber") that permits molecules, but no cells, to diffuse through it, and implanted subcutaneously, it had no inductive effect on surrounding cells. But when the pores of the capsule allowed cells to enter, skeletal muscle formed where the dead tissue had been, and tissue resembling heart muscle formed outside the capsule. Phagocytosis had been essential for the induction to occur.

Macrophages are ordinarily thought of as "antigen-presenting cells" that help to activate the specific immune responses. But apparently phagocytosis is involved in the replacement of damaged tissues, by recruiting or inducing the differentiation of replacement cells. The phagocytosis function isn't limited to the blood cells commonly called phagocytes; even nerve cells can ingest particles and fragments of damaged tissues.

Many factors regulate the process of phagocytosis. Stress and lipid peroxidation decrease phagocytosis (Izgüt-Uysal, et al., 2004), and also damage mitochondria and inhibit cell renewal.

Unsaturated fatty acids inhibit phagocytosis (Guimaraes, et al., 1991, 1992; Costa Rosa, et al., 1996; Virella, et al., 1989; Akamatsu, et al., 1990), and suppress mitochondrial function (Gomes, et al., 2006). Dietary restriction activates phagocytosis (Moriguchi, et al., 1989), suggesting that normal diets contain suppressive materials.

Subnormal temperatures cause a shift from phagocytosis to inflammation. Light, especially the red light which penetrates easily into tissues, activates the formation of new cells as well as their differentiation. It affects energy production, increasing the formation of mitochondria, and the activity of the DNA methyltransferase enzymes. Red light accelerates wound healing, and improves the quality of the scar, reducing the amount of fibrosis. The daily cycling between darkness and light is probably an important factor in regulating the birth and differentiation of cells.

Darkness suppresses mitochondrial function, and light activates it. Prolonged darkness increases cortisol, and cortisol (which makes cells more susceptible to excitotoxic death) inhibits stem cell proliferation (Li, et al., 2006; Liu, et al., 2003). Neurogenesis is suppressed by stress, and increased by spontaneous activity, and has a circadian rhythm. Aging and depression both involve a diminished ability to rhythmically lower the production of cortisol. Cell renewal requires a rhythmic decrease in the exposure to cortisol..

In the spring, with increased day length, the brains of song-birds grow, with an increased proliferation of cells in the part of the brain involved in singing. The production of progesterone increases in most animals in the spring, and it is the main hormone responsible for the birds' brain growth.

Progesterone and its metabolites protect brain cells against injury, and improve the brain's ability to recover after traumatic

injury (Brinton and Wang, 2006). In the 1960s, Marion Diamond's group showed that environmental enrichment, or progesterone, caused brains to grow larger, and that these changes were passed on to descendants in a cumulative, increasing way. This suggests that the factors that promote neurogenesis also cause changes in the apparatus of reproduction and inheritance, that support the development of the brain--probably including the methylation system, which is involved in regulating genes, and also mood and behavior.

Women's monthly cycles, in which a brief estrogen dominance is followed by sustained exposure to progesterone, are probably an important factor in the renewal of the cells of the brain and other organs, as well as those of the reproductive organs. The daily rhythms of hormones and metabolism are known to be involved in the regulation of cell renewal.

Environmental enrichment, learning, high altitude, and thyroid hormone promote the formation of new mitochondria, and stimulate stem cell proliferation. At least in some laboratories, 20% oxygen, approximately the amount as in the atmosphere, suppresses the proliferation of stem cells (He, et al., 2007). This was the unphysiologically high concentration of oxygen used in Hayflick's cell cultures. At high altitudes, where tissues are exposed to less oxygen, and more carbon dioxide, there is a lower incidence of all the degenerative diseases, including cancer, heart disease, and dementia. Improved cellular energy production and more active renewal of cells would probably account for those differences.

For Crick, the idea of a diffusion gradient to explain embryonic development was simply an extension of his reductionist orientation, in which diffusing molecules induced or inhibited bacterial genes, and in which genes controlled cells. For people with that orientation, the adaptive mutations described by Carl Lindegren, and later by John Cairns, or even the stress-induced variability described by Lysenko, Strong, and McClintock, were heretical. Polezhaev's demonstration that cells could do something that molecular diffusion didn't do, threatened to take biology away from the reductionists. If the organism's adaptation to the environment involves changing its own genes, Crick's paradigm fails.

Crick's Central Dogma, derived from the ideology that produced Weismann's Barrier, has been invoked by generations of professors who wanted to deny the possibility of adaptive tissue renewal and regeneration. Without the dogma, new ideas about aging and disease will be needed. If somatic cells can adjust their genes, and if they can also differentiate into new eggs and sperms, new ideas about inheritance of acquired traits will be needed.

The replacement of injured cells means that mutations need not accumulate. Cell renewal with elimination of mutant cells has been observed in sun-damaged skin simply by stopping the damage, and mitochondria with damaged DNA can be replaced by healthy mitochondria simply by doing the right kind of exercise.

The regulation of cell renewal probably involves all of the processes of life, but there are a few simple, interacting factors that suppress renewal. The accumulation of polyunsaturated fats, interacting with a high concentration of oxygen, damages mitochondria, and causes a chronic excessive exposure to cortisol. With mitochondrial damage, cells are unable to produce the progesterone needed to oppose cortisol and to protect cells.

Choosing the right foods, the right atmosphere, the right mental and physical activities, and finding the optimal rhythms of light, darkness, and activity, can begin to alter the streaming renewal of cells in all the organs. Designing a more perfect environment is going to be much simpler than the schemes of the genetic engineers.

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