Henry Ford Hospital Medical Journal

Volume 11 | Number 4 Article 4

12-1963

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Henry Ford Hosp. Med. Bull.
Vol. 11, December, 1963

CELL GENERATION SYSTEMS: A NEW CONCEPT IN MEDICINE*

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Introduction

Lamellar bone is a tissue and organ whose state of health is utterly dependent on the function of a cell generation system, a fact impressed on one by studying it. The objective of this article is to describe cell generation systems and to introduce the idea as a new and potentially useful concept with which one may evaluate physiology and disease. The concept provides a simple, logical and largely factual basis for organizing and patterning a considerable mass of otherwise disjointed knowledge. As far as is known, the synthesis that follows is original, although little of the factual material drawn on is.

We shall proceed by defining what a cell generation system is, then outline some properties of known systems, and finally discuss the possible application of this knowledge to a number of specific problems.

DEFINITION OF A CELL GENERATION SYSTEM

The heart of cell generation systems is the *stem cell,* which generates new cells by cell division. Of the two daughter cells of each division, one is another stem cell with the same functional abilities and limitations as its parent. The other daughter differs from the parent by having specialized biochemical abilities.

Stem cell function is dual: to generate the two types of new cells, and to perpetuate the existence of the stem cell line.

The function of the specialized cells is to provide those biochemical abilities needed in the metabolism of the tissue, organ and organism. An excellent summary in nontechnical language is given by Baserga and Kisielski. It covers much of this material, but without making all of the deductions and syntheses found here.[4]

*Based on work done in the Henry Ford Hospital Orthopaedic Research Laboratory, and aided by grants 293, Henry Ford Hospital, and AM-04186, National Institutes of Health. A Publication of the Orthopaedic Research Laboratory, Department of Orthopaedic Surgery, C. L. Mitchell, M.D. Chairman.

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GENERAL PROPERTIES OF CELL GENERATION SYSTEMS*

While evidence of the existence of cell generation systems has been in the literature for a long time, it converged to a separate idea only after the techniques of autoradiography and tritium labelling of thymidine were combined into a powerful tool for studying histogenesis of cells by men such as Belanger and LeBlond,[5] Kember,[25] Owen[28] and Young.[38,39] The chief function of thymidine is incorporation into the DNA of cell nuclei which are making a duplicate set of chromosomes in preparation for cell division. Identifying nuclei which take up thymidine is therefore equivalent to identifying cells preparing to divide. This method made it possible to study cell generation activity with a breadth and depth previously impossible.

By abstraction (in the mathematical sense) the older and newer studies of cell histogenesis and bone cell dynamics made it clear that there are basic similarities in the cell generation systems of many tissues, many species and phyla,[7] and even across the divide between the animal and vegetable kingdoms. This means two things at least: a) There is true generality in the ideas about to be outlined; b) Studies of cell generation activity can serve as cybernetic aids in solving the puzzles of how cell division, and specialized biochemical capability, are provided for and regulated. Intriguing possibilities are opened by combining the presently outlined ideas with the work and thought of Teir,[34] of Weiss and Kavanau,[24,37] of Mayr,[27] of Szilard,[33] of Danziger and Elmergreen,[9] of Roston,[30] of Szent-Gyorgi, Hegyeli and McLaughlin,[32] and of Young.[38]

The dynamic* activity in cell generation systems has been termed in total, the *cytodynamic sequence*.[14,15] It has at least three separate parts: the phase of activation, the phase of generation and apportionment, and the metabolic sequence. Probably it will be necessary to improve on this classification as our knowledge improves.

A) THE PHASE OF ACTIVATION

Each cell generation system has a *stem cell** at its heart. This stem cell has no known specialized biochemical capabilities and so is not involved in metabolism in the classical sense in any known way. The functions of this cell are to generate new daughter cells by cell division and to perpetuate the cell line. Division of stem cells is accompanied by chromosome duplication and mitosis.

A stem cell divides when three conditions have been met. These are: a) the provision of some type of "command" from the cell's environment that instructs it to divide; b) the cell's ability to perceive or detect the command; c) the cell's ability to execute the instructions contained in the command. When these conditions have been met, the stem cell is said to be *activated.* and it begins to divide, usually

*This synthesis has been pieced together from a most polygot diet of facts. Time and better knowledge and better thinking will probably modify and amend much of what seems clear and direct at this writing.
*Dynamic means changes with reference to time.
*Apologies to hematologists, to whom this word has a related but more specific meaning.[20]

repeatedly for some average number of times, thus generating some average number of daughter cells (Figure I). These events are separately suggested by the studies such as those of Owen,[28] Ford and Young[11,39] and Burnett, Baird and Diehl.[7]

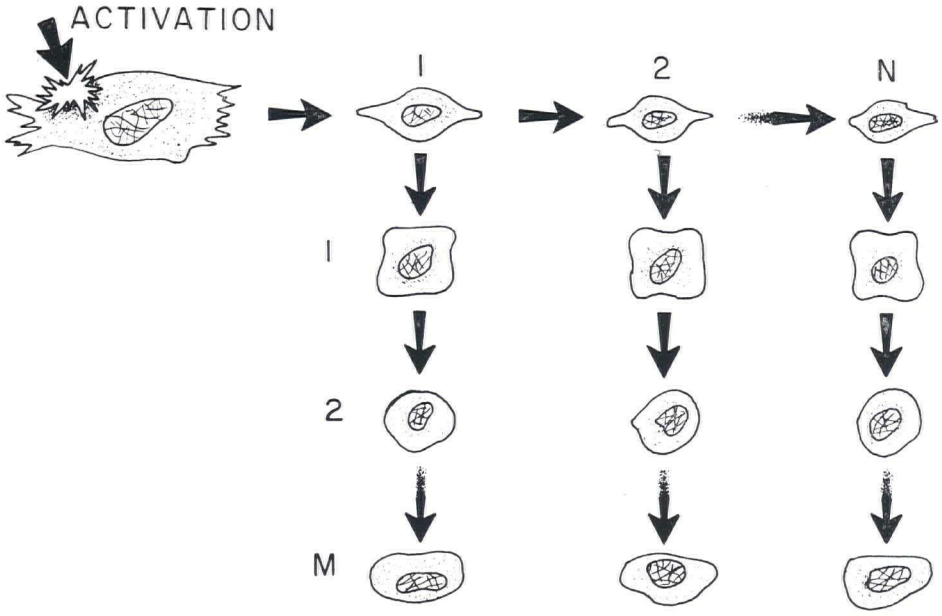

Figure 1

The resting stem cell at the upper left, when activated, begins to divide, as shown from left to right. Division continues for some unknown number of times, indicated by (1,2.....N). At the end of (N) divisions there is only one mesenchymal cell left but there are (N) metabolically specialized cells. The metabolically specialized cells undergo a series of internal transitions, shown from top to bottom and indicated by (1,2..... M). At the end of their sequence they probably die in most tissues. There are two important properties of such an arrangement of cell activity. The total metabolic capacity pattern depends on the relative sizes of the specialized cell populations.

Table I

Tissue	Stem Cell Known to Exist	Specialized Cells	Fate of Specialized Cells
Adrenal Cortex	+	+++	?
Bone	+	+++	Embedded alive and preserved
Liver	+	+?+?	?
Renal Tubule	0	+++	?
Blood Granulocytes	+	+	Die
Blood Erythrocytes	+	+	Die
Blood Lymphocytes	+	++	Die
Parathyroid Gland	?	++	?
Small Bowel Epithelium	+	++	Shed continuously
Skin	+	+++	Shed continuously
Ant. Pituitary	?	++++	?
Uterine Epithelium	+	++	Shed cyclically

There are probably different kinds of stem cells, so that those making epithelial cells cannot make bone cells, and those making adrenal cortical cells cannot make liver cells. There may even be hierarchies of stem cells within a given tissue, an example being the hematopoietic system, and aptly illustrated in Ham and Leeson's recent textbook.[20] How much of this fractionation of stem cell potentialities is a permanent cell characteristic, and how much represents a temporary concentration on one of several possible routes of specialization, remains to be seen. The nature of the command given to stem cells is also not clear at this time. It is probably a complex relationship between several agents and properties of the cell and its environment, rather than a single chemical compound. It is probably different in different stem cells.

In some tissues the stem cell is pluripotent, in that it can make different kinds of specialized cells according to the type of command that is given it. In bone for example, the stem cell (termed elsewhere the mesenchmal cell by us,[13,15] and the progenitor cell by Young[38]) can produce fibroblasts, chondroblasts, fibrous osteoblasts or osteoclasts, the particular case depending on the particular command.* An even larger choice is available to some of the stem cells of hematologic interest.[20]

B) THE PHASE OF GENERATION AND APPORTIONMENT

After activation the stem cell divides, but in a special way so that the two daughter cells differ from each other. One of the daughters is another stem cell with the same capabilities and limitations as the parent stem cell. That is, it too can divide, but it does not have metabolically useful, special biochemical abilities. The other daughter is unable to divide but does have metabolically useful, special biochemical abilities. These abilities supply the metabolic capacities of all types of tissues and organs. Some of this interpretation is directly suggested by the studies of Quastler and Sherman,[29] of Ford and Young[11,38,39] and of Hattner and the writer.[21]

This curious *apportionment of abilities* among the daughter cells illustrates an apparently basic property of adult cells:

In normal cells, reproductive ability and metabolically specialized biochemical ability are mutually exclusive. That is, a normal cell can do one or the other but not both.

This either-or law seems to break down in neoplasms, in which both daughter cells can divide and both have some specialized biochemical abilities. In neoplasms both of these abilities are diluted in comparison to normal cells.[4]

In the interest of verbal economy we will continue to use the term, *stem cell.* It is synonymous with other terms such as mesenchymal cell, progenitor cell, osteoprogenitor cell and pluripotent cell. The term, *metabolically specialized cell,* will

*Interaction between the cell's environment and its nuclear library of possible metabolic roles is involved in these various choices. There seem to be different groups of choices, and the cell's exterior and interior are not equally important in deciding on the execution of any particular group. For one, the exterior will be of prime importance, for another the interior.

identify those cells which cannot reproduce but which do have special machinery which does the biochemical work involved in metabolism. Some examples of metabolically specialized cells are: osteoclasts, lymphocytes, prickle cells, adrenal cortical cells, beta cells, chief cells, pituitary acidophils, renal tubular cells, neurons and hepatic cells.[1,3,20]

One property of the apportionment mechanism just described is that *after* any number, say (N), cell divisions by a cell line belonging to one stem cell*, there will be only one stem cell but there will be (N) metabolically specialized cells. In other words, the apportionment mechanism allows the generation of as many metabolically specialized cells as needed without loading the tissue up with dead weight in the form of a similar number of metabolically inactive stem cells. This property is illustrated in figure (1), and seems to be an important difference between normal and malignant tissues. In cancer both daughter cells can divide so that the total number of cells present after a given number of cell divisions is an exponential function. In normal cells it is a linear and direct function of the number of divisions. The apportionment mechanism suggests that integrity of the stem cell line is critically important in maintaining metabolic capability over a long life span, while an adequate supply of metabolically specialized cells is critically important in supporting life at any given moment.

C) THE METABOLIC SEQUENCE

As they age from the time of their generation, metabolically specialized cells undergo changes in their metabolic specialization. These changes occur in a definite sequence, and involve a definite number of steps or transitions from one type of specialization to another. In any given tissue both the sequence and the number of steps in it are normally invariant and characteristic of the tissue. The various steps occur at definite average times after cell generation, and this too is normally constant in a given tissue. A given step may have associated with it one or more special biochemical abilities.*

The above group of changes is called the metabolic sequence. It seems to be caused by changes in the cell nucleus which affect the number and type of enzymes in the cell cytoplasm. The nuclear changes probably are automatically executed and at least partly preprogrammed in the nucleus, and in some way are triggered off by the activating command.[14,15] The cell's environment is also involved in arranging the execution of the sequences and in inhibiting some.

It follows that the youngest specialized cells have one kind of metabolic specialization, and the oldest ones have a different kind. In some tissues there are intervening stages. Examples of such transitions are the change from osteoclast to osteoblast to osteocyte in lamellar bone remodelling,[15] and the change from the crypt to the tip of the villus in the bowel epithelium, as shown by Quastler and Sherman.[29]

*The metabolically specialized cells derived from a single, parent stem cell will be referred to as a *clone* of cells later in the text.

*The transition may merge gradually, one into the next, as they seem to do in skin and adrenal cortex, or they may be functionally discrete, as in the transition from osteoclast to osteoblast.

Most of the cells in the organs familiar to all of us are one or more populations of metabolically specialized cells, evolving through their metabolic sequences. The total time required for the sequences to evolve may vary from two days* to many years,** depending on the tissue and organism being observed.

Usually the specialized cells change their location in the tissue or organ as they evolve through their metabolic sequences. This may be caused by the need of the stem cell to remain in a fixed part of the tissue or organ if it is to continue to function properly. This property of the stem cell may be related to the anatomy of the blood supply. Examples of physical movement accompanying the metabolic sequence occur in skin where new cells start at the basal layer and end at the surface;[20] in the bowel, where new cells start in the crypts and end at the tips of the villi;[29] in the adrenal cortex, as recently shown by Ford and Young,[11] and in bone. In the adrenal cortex, the events and timing in the metabolic sequence are so constant that one can slice layers off the cortex in such a way that most of the cells forming aldosterone will be in one, those forming hydrocortisone another and those forming DOCA in a third.[35] In Table I some known cell generation systems are listed, with the number of events in the metabolic sequence outlined when this information is available.

Most if not all of the tissues we are familiar with are composed largely of populations or clones of metabolically specialized cells. The stem cells, which seem to be present in all tissues (except the adult nervous system and striated muscle? See Altman's report, which is apt to have followers of the same vein[2]) are physically such a small part of the tissue that they are hard to identify with classical histological methods. This physical inconspicuousness effectively hid their crucial dynamic role from most members of generations of physiologists and pathologists.

The fate of metabolically specialized cells after they reach the end of their metabolic sequences is unsettled for most tissues. In the bowel, skin and other epithelial surfaces it is known that the cells are shed off.[29] In bone, many end up as osteocytes where they can live an average of 25 years before spontaneously dying, according to combined information supplied by Owen and the writer.[13,28] In other tissues, the fate of these cells is not certain but it seems probable that they show some equivalent of the shedding that occurs in epithelium.

CONTROL OF METABOLISM IN A TISSUE DEPENDENT ON A CELL GENERATION SYSTEM

The classical way of controlling metabolism endogenously is to regulate the biochemical machinery of metabolically specialized cells. This view is well displayed in the literature, Bourne's and Danielli's review being a good (in all respects!) example.[6] A cell generation system offers several other unique ways of regulating or deranging the metabolism of the tissue or organ. Although derangement of one or more of the dynamic properties of cell generation systems promises to be very im-

*Epithelium, small intestine, mouse; onion root tip.
**CNS, man; some lichens.

portant in understanding disease, it must be emphasized that such derangements have usually been unrecognized previously, although not unseen.* In some diseases there are all possible types of derangements, while in others there is a single one, features which add greatly to the complexity of understanding the mechanisms of disease.

From the cell generation viewpoint, there are three big ways in which regulation or disease of metabolism may occur.** These involve changing activation frequency, arresting the metabolic sequence, and selectively inhibiting one of the steps in the metabolic sequence. From the classical viewpoint, regulation or disease can occur by governing the specialized biochemical machinery inside the cell cytoplasm. Complex combinations of these modes can occur.

A) CHANGE IN ACTIVATION FREQUENCY

This means changing the rate at which new cells are generated by arresting, slowing or speeding activation. This would lead to a deficit or surplus, respectively, of metabolically specialized cells and their specialized biochemical functions. For example, in the adrenal cortex a decrease in activation frequency can cause an Addison-like state, while an increase is known as adrenal cortical hyperplasia. Duodenal ulcers and ulcerative colitis are possible examples of profound local decreases in activation frequency in bowel epithelium, as are stasis ulcers on the legs.*

Thus the first and obvious effect on metabolism of a change in activation frequency is a corresponding change in the total metabolic work load the tissue can handle, but with preservation of reasonably normal proportions between the youngest and the oldest cell populations and their respective metabolic functions.

A second, less obvious and less predictable, effect of changing activation frequency is an alteration of the relative sizes of young and old metabolically specialized cell populations. This causes a disproportionate change in the relative work loads that can be handled by the young and the old cells, often described as a change in the metabolic pattern of the organ.

When activation frequency is slowed, there may be an accumulation of the older metabolically specialized cells, since they have not been forced to "shed" or to do whatever the equivalent of shedding is for the tissue in question. This causes the metabolic functions of the older cells to be too much in evidence compared to those of the younger cells. Likely examples of this type of derangement are some of the hypoaldosteronic states of the aged, and some of the sprue like syndromes,

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*Of all branches of medicine, hemtology has come farthest in recognizing and using these ideas.

**I *suspect* that a stem cell can receive a genetic "hit" a la Szilard, and thus obtain a defective DNA library. This defect is passed on to both daughters at cell division. The specialized cells are impaired, but functional. Many spottily distributed diseases could be examples of this mechanism, among them being vitiligo, Ehrenfried's disease and psoriasis. There are probably still other ways of "using" a cell generation system to derange metabolism.

*And the deficiency of beta cells in Langerhan's islands in diabetes mellitus may be of similar origin.

the former involving a cell generation derangement in the adrenal cortex, the latter in the epithelium of the bowel.

It is also possible that an increase in activation frequency could cause a disproportionately large increase in the younger specialized cells compared to the older ones, with an opposite change in the pattern of the metabolism of the organ.

In the above changes, there is no abnormality in any of the cells that are present. All of them have their proper enzymes, do not have unique ones, do not lack some compound or possess a unique one. These facts are self evident after a search of the literature. They are summarized in good texts such as Aegerter and Kirkpatrick's,[1] and Anderson's.[3] In other words, *disease has been produced by juggling the absolute and relative sizes of a number of different cell populations.* Each cell in each cell population appears to be normal in every way.

B) ARREST OF THE METABOLIC SEQUENCE

This means stopping the evolution of metabolically specialized cells at some point along the metabolic sequence. This prevents the development of the steps that would normally follow the point where the arrest occurs, and thus deprives the tissue of these metabolic functions. Sequence arrests seem to occur more often in disease than in normal regulation of metabolism if our knowledge of this activity in bone is a valid indication.

Examples of sequence arrests include some of the hypokeratinizing skin diseases, and the Cushingoid skeleton. The latter will be considered more fully in the Discussion.

In some diseases there is wide scale death of metabolically specialized cells. This causes illness due to lack of the metabolic functions usually supplied by the dead cells. Acute yellow atrophy of the liver and mercuric poisoning of the kidney are two examples. Recovery from such diseases probably depends on the integrity of the local stem cell population. This way of causing disease will not be considered further.

C) SELECTIVE INHIBITION OF PART OF THE METABOLIC SEQUENCE

This means that one of the steps in a metabolic sequence is inhibited, and so subtracted from the total sequence, along with the special metabolic functions provided by the missing step. There is no effect on the steps that occur after the inhibited step, which is the big difference between a sequence arrest and a selective inhibition. This kind of activity seems to occur more often in normal regulation than in disease, if the examples known in bone are a valid indication.

Selective inhibition almost certainly is involved in regulating resorption and formation during the remodelling of bones that occurs during growth. This derives from work by the writer, and by Epker.[10] Here only resorption, or only formation,

may occur at a given bone surface for long periods of time, although the natural metabolic sequence in lamellar bone is osteoclast — osteoblast — osteocyte. The missing one can be accounted for by inhibition. Interestingly, analogous inhibitory regulation of growth processes occurs in the cartilaginous skeletons of elasmobranchs, and in many types of trees.[18] The major difference in their cell generation systems is that they lack entirely any resorptive capacity.

D) TARGET METABOLIC REGULATION

This means regulation of the chemical machinery actually involved in performing a metabolic function, such as that forming gamma globulin in plasma cells. This is the classical meaning of the phrase, "regulation of cell metabolism". It may be achieved by altering membrane permeability, reactant concentration, enzyme availability, inhibitors, activators and so on. The writer has called such modes of regulation *target metabolic regulation* to indicate that the regulatory act is aimed directly at the activity that is its target.[17]

There are numerous examples of disease and regulation based on this way of governing cell metabolism. Diabetes mellitus and von Gierke's disease are but two examples. Most medical thought and research effort devoted to understanding control of metabolism has been predicated on the tacit assumption* that target metabolic regulation was the regulatory mode of major concern. A good example is endocrinological thought, well represented by Turner's excellent book.[35] While its importance cannot be denied, target metabolic regulation has probably been assigned too exclusive a role in our present thinking.

THE LOGIC OF REGULATION OF METABOLISM AND OF CELL GENERATION SYSTEMS

The word "logic" is used in its computer sense, and means the nature of the information, and of the information processing, that goes on in the interior of whatever handles the information, whether it be a computer, cell nucleus or human brain. Information means anything that can be used to control the operation of the cell's numerous biochemical systems and modes of behavior. For example, it might be swapping one amino acid for another at some point in a protein, or one base for another in a DNA or RNA chain; or it might be changing the concentration of reactants in a chemical process, or changing the permeability of a cell membrane to a class of chemical compounds or to a specific compound.

A) CELL GENERATION LOGIC

This is a logical system based on single steps or events, which mathematically speaking, are discontinuous, discrete and finite. The logical activity in question occurs primarily in the cell nucleus. Its electrical analog is the switch, which is either on or off.

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*Tacit because it was never seriously proposed that there were other, major endogenous modes of to compete with target metabolic regulation in adults.

To illustrate, consider a part of a DNA chain in a cell nucleus that has in it the information needed to make one of the cell's proteins.

Either this information, i.e., the protein's amino acid sequence is copied onto a messenger RNA chain, or it is not. There is no half way. This is an all-or-none business.

Another illustration can be taken from bone. A given stem cell of the lamellar remodelling cell generation system either is activated, or it is not, and so either generates a remodelling focus, or does not. There is no half way. When dealing with a whole skeleton (or other organ) which has hundreds of thousands of stem cells, it takes special methods, approaches and thinking to detect the basic, all-or-none nature of the underlying regulatory logic involved in the cell generation activity.

The generation and propagation of nerve impulses works the same way although it appears to be a cell membrane function. The pioneer physiologists recognized this fact when they formulated the "all-or-none" law to cover it. Digital computers also work with this type of logic.

Cell generation logical activity probably involves mostly the physical chemistry of DNA and RNA. These two substances seem to be peculiarly able to perform as parts of biological digital devices, meaning that they were made to participate in stepwise logical activities.*

Cell generation system logic is responsible for the kinds of metabolic functions provided for in a tissue, and for the sizes of the cell populations handling the metabolic specializations found in a tissue.

Classes of devices that function in a stepwise logical fashion cannot be studied or understood in terms of systems that work with different types of logic. Particularly, the stepwise systems cannot be studied through systems with continuous logical processes. This has not been clearly understood by many physiologists and biochemists but it is a crucial point in attempting to accelerate our understanding of the cellular functions of our bodies.

B) TARGET METABOLIC LOGIC

This is a logical system built around an infinitely variable ability to change, and is characterized mathematically as being continuous and finite. The electrical analog is the variable capacitor. The logical activity in question occurs primarily in the cell cytoplasm. The only real limitation on the smallness of the change possible in such a system is Planck's constant, and this is so small that it will concern few of us. Such systems are called *differential logical* systems, mainly because they can be expressed in terms of differential equations. The logical activities of cell generation systems cannot, but can be handled as *Boolean algebraic problems.*

*The nuclear histones probably are also involved in nuclear logical activity, but as yet we do not know how.

The variables in regulation of target metabolic pathways include such things as concentration, temperature, diffusion, membrane permeability, and pressure.

These variables may range over a nearly infinitely large number of numerical values between the two extremes that are still compatible with the life of the cell, although these extremes may differ little from each other as is the case for temperature, or by factors greater than one million as is the case for concentration. The literature dealing with these problems is enormous. One may gain access to it through the standard physiology texts which are almost exclusively oriented towards target metabolic regulation, both of endogenous and exogenous origin. Standard pharmacology texts are oriented towards exogenous target metabolic control.

Target metabolic logic is responsible for the efficiency with which a cell's biochemical machinery is operated, and cannot supply new kinds of metabolic functions.

C) THE HYBRID LOGIC OF REGULATION OF CELL METABOLISM

It is now evident that a whole cell is a hybrid device from the standpoint of its logical processes. The nucleus works by means of discrete steps (mostly), the biochemical machinery in the cytoplasm works by means of continuously variable degrees of change (mostly). The nucleus controls the biochemical machinery by providing the information needed to synthesize proteins, while the rest of the cell provides both the necessary conditions for the nucleus to function and the metabolic work essential to the life of the orginism.

So the nucleus and the cell are interdependent and functionally related in somewhat the same way as are the heart and the brain.

Since metabolism is conducted by whole cells it follows that metabolism in general is regulated by a hybrid logic. The logical processes in the nucleus appear to be of primary importance, those in the cytoplasm of secondary importance, from the standpoint of the chain of causality in the logical activity of the cell.*

When the metabolism of even a single cell can vary continuously, although stepwise logical activity underlies the regulation of its metabolism, one begins to see why it took so long to recognize and begin to measure the stepwise part of cellular function.

Discussion

The foregoing material will now be applied in a necessarily brief discussion of selected problems. Speculative as opposed to established interpretations or associations will be indicated as they are given.

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*A proposed example of such a causal chain:

(Unknown substance) → (Increased parathyroid stem cell activation)

(Increased chief cell generation or hyperplasia; *not* adenoma) → (Increased parathormone)

(Change calcium absorption, bowel:? reason
(Change tubular phosphate resorption: target metabolic effect
(Increased bone resorption: bone cell generation system effect)

A) THE CUSHINGOID SKELETON

This problem is selected as an example of a group in which cell generation system derangement accounts for the bulk of the known bone pathology.* Among this group are the thyrotoxic skeleton, senile osteoporosis, osteopetrosis and some types of osteomalacia.

The major features of the Cushingoid skeleton are: osteoporosis; increased brittleness; spontaneous fractures.

The *osteoporosis* seems to be mostly the result of a metabolic sequence arrest, osteoclasts being prevented from evolving to osteoblasts. This causes an excess of resorption relative to formation. This arrest is less complete within the cortex than at the endosteal surfaces. The absolute resorption rate is not increased, and may be decreased, contrary to original medical thinking on this point.[13]

The *brittleness* arises mostly from two causes. The first is a pronounced decrease in the bone remodelling rate, i.e., the rate at which the bone is being turned over and replaced by new bone. This decrease comes about by a drop in the frequency of stem cell activation to levels about 0.1 of normal. A decreased remodelling rate causes an increase in average mineralization density which increases the brittleness of the bone.[13] The second major factor in the increased brittleness is the osteoporosis already discussed.

The *spontaneous fractures* arise mostly from three causes. The first is a blunting of the ability of the stem cells to detect the microscopic bone damage that is a normal part of living.[12] This damage is usually repaired by a remodelling process soon after it occurs, and so does not reach the stage that it is grossly detectable. It is suspected that when the stem cell's ability to detect this damage is dulled, the damage does accumulate and may be enough so that normal forces on the weakened bone can complete the damage as a "spontaneous" fracture, which is never truly spontaneous. The second major cause in these fractures is the brittleness, and the third is the osteoporosis, both already discussed.

Only one aspect of the Cushingoid skeleton seems to be traceable to an effect of the corticoid hormones on target metabolic paths. This is a slight increase in degree of mineralization beyond that which could be explained by the remodelling rate change. This probably is a target metabolic effect on the osteocytes in bone.[18]

B) A NEWLY RECOGNIZED ROLE FOR HORMONE FUNCTION

The material above implied what will now be stated bluntly: many hormones have important roles in regulating cell generation systems. Some bone effects of the corticoids have already been described, and many of their effects on bowel epithelium, Paget's disease of bone, skin and the hematopoietic system appear to be additional examples of regulation of cell generation systems.

*The special experience of the Othopaedic Research Laboratory is drawn on heavily here.

Growth hormone, parathormone, thyroxine, estrogens and androgens also have known effects on cell generation systems in various tissues, including bone.[1,13,35] It takes only a moment's thought to realize that, for example, the cyclic generation and shedding of the uterine epithelium in response to a woman's ovulatory function is a cell generation system in action, and has all of the properties outlined for cell generation systems in general. Another example is the production of cartilage cells in response to growth hormone. Our thinking processes have been channeled by the meanings we attach to words, so that it is unconventional to regard such problems from the present viewpoint. This does not mean that it is unrealistic or unprofitable to do so.

Not all hormones, nor all actions of a given hormone, need affect cell generation systems. A rule of thumb permits one to detect cell generation activity, and to distinguish between effects of agents* on cell generation systems and on target metabolic pathways.

If an agent's effect appears in minutes or hours it is mediated by a target metabolic pathway. If it appears in days (less in animals) it is mediated by a cell generation system.

This rule is correct in the average case. Reflection about the fundamental differences in the two modes of regulation will show why.

Judged by this rule, insulin, glucagon, epinephrine and norepinephrine (as examples) function chiefly as regulators of target metabolic pathways.[35] On the other hand, thyroxine, growth hormone, estrogens, androgens and the luteinizing hormone (as examples) function chiefly as regulators of cell generation systems.[13,35] The corticoids and parathormone seem to be about equally involved in both modes of regulation. In time all of the hormones may prove to be so involved, although it is clear now that some of them concentrate predominantly on one or the other.

How hormones affect cell generation systems and their logical activity is not known. This will prove to be one of the important remaining problems in understanding control of cell metabolism. We suspect that one function of the hormones is to control the sensitivity of the stem cell to the activating command. This cannot be the only effect; the ability of the corticoids to cause sequence arrests has already been noted.

C) AGEING

In normal lamellar bone, a change in activation frequency between birth and age 35 occurs which has a magnitude of 100-1, as reported by Sedlin, Villanueva and the writer.[19,31,36] Gerontological analysts find this change compatible with current, orthodox thinking about ageing mechanisms, and it is the unwritten assumption underlying the excellent reports by Curtis,[8] and by Szilard,[33] as well as the numerous

*The word, agent, is intended to cover a wide range of things, such as hormones, vitamins, organic and inorganic compounds, concentration, temperature, acceleration, radiation, pressure and so on.

and comprehensive articles by Shock, access to which may be had through the AAAS Symposium volume edited by him.

There is a catch. In a careful and massive study, Klein found that there is no detectable change in the kinetics of the protein forming machinery of normal human osteoblasts over the entire span of life from birth to age 80.[26] This is incompatible with most gerontological thinking of today, because this thinking is predicated on the concept that the metabolically specialized cell declines in metabolic "efficiency" (whatever this is) with age.

In lamellar bone metabolism, it is the stem cell which shows major changes in activity with age. There is little or no change in the kinetics of the biochemical machinery that actually makes the new bone protein, and therefore in the metabolic efficiency of the osteoblasts.

The relative accuracy of the study that is quoted is good ($\pm$ 10 percent) and is a far cry from the 10,000 percent change in activation frequency referred to.

These facts suggest that a major, cellular, dynamic change, associated with ageing, occurs in the stem cell population, and is reflected in dynamic abberrations in cell generation system functions. A minor area of age-related damage could exist in the chemical machinery of the metabolically specialized cells, but would be circa 1/500 of the size of the stem-cell change, again provided our bone information is a valid indicator.

Perhaps study of the effects of ageing on cell function would be more profitable if aimed at stem cells and cell generation systems than they have been in the past when aimed at the metabolically specialized cell. Note for example that an abnormal BSP test need not mean abnormal biochemical machinery in the liver cells. It could mean that there is an abnormal population distribution or size of metabolically specialized cells in the liver, those types of cells primarily involved in the BSP test being relatively or/and absolutely fewer than normal. If so, this would point to a derangement in the liver's cell generation system.

Some provocative questions occur (they have occurred to others too, notably to that humble but fertile master of pathodynamic insight, L. Johston:[22,23]) Is senescence a matter of running out of stem cells? Could it be cured by an inexhaustible supply of stem cells? Is a stem cell defect the cause of progeria and muscular dystrophy?

D) NEOPLASIA

It cannot be a meaningless accident that in the normal cell generation systems where relevant data is available, the capacity for division goes to one daughter, and the capacity for metabolic work to the other, of a given stem cell division. Nor is it meaningless that in malignant cells this apportionment of functions is deranged so that both daughters can divide and both can function metabolically, although more slowly than normal cells do.[4] It seems that normally division and metabolic capacity are mutually exclusive. This suggests three things.

1) This quirk might be the true key to the nature of cancer, which for generations has been approached as a problem involving an abnormal compound, enzyme or regulator in tumor cells. All attempts to find such a substance have failed, and they have been massive in number and scope.

We should face the possibility that cancer is a pathological logical process in cell nuclei, a dynamic abnormality which works with normal cell constituents as its tools. If this is true, understanding and curing cancer must follow understanding the nature of the logical activity in normal and in malignant cells. The field of oncology is a noted, inveterate and omnivorous devourer of "bright" ideas. Yet we predict that the preceding words have pointed out a bonanza direction for future oncologic thought.

2) The mutually exclusive principle may be the result of a single logical sequence in the cell nucleus, involving the receipt and processing of one "bit" of information. Which of the daughter cells gets the bit and which does not is not clear. While it is fashionable to think of metabolically specialized cells as having *extra* attributes that their stem cells do not, it is logically simpler* to assume that they are instead *missing* something which the stem cell has, and because of this lack they are biochemically unbalanced, a situation which we term a metabolic cell specialization. If this slightly inverted view is correct, then the meanings we attach to words have really confused things because the very term, metabolic specialization, suggests an extra, rather than a missing, attribute.

3) The mutually exclusive property can be used as a lever with which to begin studying the nature of the logical processes in cell nuclei, both normal and malignant.

E) CONGENITAL ANOMALIES

Many types of congenital anomalies seem to be examples of abberrations in cell generation systems. Since by definition these deformities are present at birth, they were caused during intrauterine life, which is characterized by intensive generation of specialized cells from less specialized cells. In this case however, the specialized cells are involved in producing new functional tissue rather than in conducting metabolic work.

For example, failure of the abdominal wall to develop could be attributed to loss of the stem cells that should have generated the necessary myoblasts, fibroblasts, lipoblasts and so on. This suggests that we are observing a system with a hierarchy of stem cells* and that locally one of the earlier members of a hierarchy was eliminated, or was prevented from executing a sequence of differentiations analogous to the metabolic sequence arrest already discussed. This would cause the failure to generate the missing tissue.

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*In the computer programming sense.

*It may well be that the more specialized stem cells generated by less specialized ones also show a sequential and orderly execution of some predetermined program. This activity would be analogous to that involved in the metabolic sequence of specialized cells.

Or consider congenital absence of the fibula, with the associated lacks on the lateral side of the foot that often accompany this lesion. Again it appears as though an early member of a stem cell hierarchy on the lateral side of the developing limb bud was somehow eliminated. Therefore, the subsequent steps in the hierarchy of events were subtracted from the total cell activity, and this subtraction included the fibula and many adjacent tissues.

Congenital absence of the bile ducts, of fingers and similar deformities appear to be more examples of cell generation disturbance during embryological development.* **

The meaning of these remarks is that anomalies attributable to cell generation systems cannot be understood until we understand the logical activity that goes on in the cell nuclei during ontogony.

Summary

The writer introduces the concept of the cell generation system which is composed of a population of *stem cells* whose function is to generate new daughter cells, and to preserve the cell line. The two daughter cells of each stem cell division differ. One is another stem cell, capable of further division but not of specialized biochemical activity. The other is incapable of division but has specialized, metabolically essential, biochemical abilities.

These cells are called *metabolically specialized cells.* They change in metabolic specialization after they are generated. The change occurs in a definite order and number of steps in a given tissue. The steps occur at definite times after generation.

The metabolism of most tissues is dependent on the proper function of their cell generation systems. Profound changes in tissue metabolism arise from changes in various phases of cell generation activity, without the appearance of any abnormal cells, and without requiring any abnormality in the biochemical machinery in the cells. These changes occur by changing the relative and absolute sizes of the various specialized cell populations in the tissue. When aligned with existing knowledge of cell biochemistry, the cell generation idea measureably enlarges our perspective of physiology and disease. The idea should prove useful in designing future experimental work concerning the control of metabolism, ageing, neoplasia and congenital anomalies.

Acknowledgments

It is a pleasure to acknowledge the help of Miss D. Smith and Mrs. B. Hentschel in the preparation of this manuscript, and of Mr. J. Gray for the illustration.

*An odd example is mosaic disease, where some of the stem cells inherit and retain exclusively features of only one parent, and so breed functional tissue with only one parent's (the mother's) characteristics; embedded in and quite compatible with tissue which is normal.

**And in an ear of corn one often sees a row of kernels suddenly disappear, the resulting defect being filled in by the adjacent rows moving over slightly. This is due to sudden loss of the stem cell that was generating the row.

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