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MOLECULAR VERSUS SYSTEMIC THEORIES ON THE GENESIS OF AGEING*

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BIOLOGY in this decade has attained heights of accomplishment and intellectual influence unmatched since the ascendancy of Darwinism a century ago. We have all been witness to this development, and taken part in the events which shaped a diverse body of methods and results into the powerful and productive movement known as molecular biology. My intent here is to examine the impact of this movement on gerontology.

An adequate characterization of the cohesive principles of the molecular biology movement—as explicit dogma and as unverbalized beliefs and taboos—is not yet possible. This is a task that will demand the scholarship and historiographic detachment of a Joseph Needham. Even though it cannot be codified, such a body of principles does exist for molecular biology, as for every great scientific movement. Kuhn (1962) calls such a corpus of doctrine a *paradigm*, and shows by historical examples how a paradigm becomes a self-perpetuating orthodoxy, facilitating the kinds of success that reinforce it and discouraging lines of work that would reveal its weaknesses. The repressive influence of a dominant paradigm is especially unfortunate for scientific domains that are new and weak, and have at best a marginal relation to the paradigm. Such fields can suffer gross distortion. For illustrations of this, we need look no farther than the shadow that the Darwinian theory of natural selection cast over the social sciences in the nineteenth century. The entire spectrum of economic and political thought of this period, from Spencer to Marx, was permeated with facile analogies between biological evolution and human cultural processes, to the detriment of empirical analysis and theory.

Gerontology is a young discipline, and most of its growth occurred within the period of ascendancy of the molecular paradigm. The consequences are obvious, for biological gerontology is regarded by the great majority of its practitioners and expositors as a branch of molecular biology. This is shown not only by explicit affirmations, but more convincingly by the unanimity with which experiment protocols conform to the molecular paradigm.

This essay will give evidence that this is an unfortunate misalliance, which could have consequences for gerontology in this century even more disastrous than the misdirection suffered by the social sciences in the nineteenth. This is not a philosophical discourse which will assert that it is better, or, in Comfort's phrase, more edifying, to take one or

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another non-molecular view of the ageing process. It is rather an assessment of scientific strategies, of the relation of methods and results, which is supported with facts and reason, and which you may refute if you can.

The argument rests on three main points. First, the attempts to produce molecular theories of ageing without reference to any other level of biological phenomena lead to logical fallacies. Second, the molecular view leads to a persistent under-emphasis of certain systemic aspects of ageing and death, to the detriment of progress. Third, a complete and self-sufficient discipline of gerontology can be founded if and only if gerontologists can learn to put the molecular viewpoint back into a correct biological perspective, in which the systemic aspects of the organism are seen to be in some respects more basic than the molecular.

There are many molecular theories of ageing. I shall tentatively divide them into two classes, which I shall call the *somatic mutation* and the *pleiotropic*. Among several serious efforts to build somatic mutation models, that of the late Prof. Leo Szilard (1959) is outstanding. On statistical grounds he concluded that the mutations responsible for ageing cannot be point mutations, but must be losses of whole chromosomes. Such a loss he called a *fault*. There is a constant rate of occurrence of faults throughout life, and when a certain fraction, *1-f*, of the cells of the body have accumulated faults the organism dies. Since the fault rate is constant with age, and between individuals, all individuals born with the same set of faults should, according to Szilard, die at the same age. This is obviously not the case, so he postulates a distribution of faults in the population at conception, arising from mutations in the parental germ lines which are transmitted through the gametes. Hence the distribution of ages at death is, barring accidents, virtually completely determined by the distribution of faults in the population at conception.

This theory, which is cited in passing by every writer who wishes to appear knowledgeable about mathematical models, is wrong in almost every particular, yet it survives with undimmed lustre in spite of challenges by Maynard Smith (1959) and others. Its assertion that the variance of ages at death is entirely genetic is falsified by abundant data on human and animal populations showing that the heritability of longevity is less than 50 per cent. The postulate of a broad distribution of inherited chromosomal faults in the population is contradicted by the evidence that genomes with even a single deleted or duplicated chromosome give rise to phenotypic abnormalities such as sterility, hermaphroditism, mongolism, and personality disorders, such as criminal tendency. The postulation of a death process determined entirely by the number of faults leaves no place for diseases, which we know are random processes with no determinate relation to the accumulated number of mutations in the body, and some of which are characterized by a broad exponential distribution of after-survival times. If some other somatic mutation theories are not so open to criticism, it is because they are not capable of being falsified, and so are not proper scientific theories in the first place.

The outstanding pleiotropic theory is that developed by Sir Peter Medawar (1957) and independently by Williams (1957). This theory says that every individual in a species contains in his genotype, as a result of natural selection, genes with a special serial pleiotropic character, such that they have an advantageous phenotypic expression in the productive phase of life, and then change to a disadvantageous expression after the end of the reproductive span. The pleiotropic theories have serious, if not fatal, flaws. These age-dependent pleiotropic genes have not yet been shown to exist. Until they are supported by at least indirect confirming evidence, they will have, on my scale of subjective

probability, about the same credibility as extraterrestrial U.F.O.'s. These are also physically possible, and the only objection one can have to them is a pragmatic one, that they are absurdly unlikely as compared with more mundane, or even sublunar, explanations. The sad fact is that these interesting, if improbable, genes are unnecessary, for vertebrate ageing is not a two-stage phenomenon. There is much evidence that ageing, where it occurs, progresses uniformly from a beginning in early adulthood at the latest. Such a pattern can be adequately dealt with in terms of the more parsimonious hypothesis of univalent genes and a uniform rate of irreversible change, be it mutation or cell death or hysteresial transitions in DNA or collagen. Disease probabilities do indeed increase rapidly in later life, but we know that physical probabilities often vary geometrically as the physical causative factor varies arithmetically. As experimentalists, we are all grateful for the operation of this statistical law, for it is thanks to its operation that the probability of our results being due to chance decreases from 5 to 2 to 1 per cent as the t value increases from 2·0 to 2·3 to 2·6, i.e. in small equal steps.

A more fundamental argument against the pleiotropic theories is that they covertly introduce an infinite regress. Suppose that a pleiotropic gene does exist, and can recognize that the host has grown past the reproductive age. How did the host undergo this prior change? According to this theory, it must have been due to the action of an earlier pleiotropic gene. Either one runs into an infinite regress of pleiotropic genes, or one is forced to postulate a second kind of pleiotropic gene, which can measure time, and change its state, even in a perfectly uniform environment, when it has seen a fullness of years. This is truly an edifying thought, which has Biblical sanction.

Finally we come to the most serious criticism of the somatic mutation, pleiotropic, and indeed all exclusively molecular theories of ageing. Each of them advances some material change as the cause of ageing. We can all agree, I am sure, that ageing is a physical process and so must have some material cause. What these theories fail to demonstrate, or even to show awareness of, is any basis of physical necessity, of what Aristotle called efficient cause: the kind of explanation, in other words, that would enable us to understand why these age changes occur at their observed rates, so that a mouse, which at the molecular level is only trivially different from a man, is senile at 3 years instead of ninety. The rudiments of such explanations were offered sixty years ago (Rubner, 1908), but they are now virtually forgotten.

This talk is an effort to define the grounds for a true union between the molecular-cellular and the functional-systemic views of ageing. The flourishing state of experimental molecular gerontology is no impediment to this union, but the molecular theories can only be compared to shallow-rooted weeds, for they offer no sustenance to gerontology, and they choke off the growth of valuable alternative lines of thought. They must be rooted out so that a rigorous theoretical structure can develop which provides an adequate basis of physical necessity for the occurrence of the molecular transitions of manifest ageing.

My remarks thus far have been sharply critical but this is because I conclude from past experience that I must be. My situation is like that of the Tennessee horse-trader who sold a mule. The buyer came back to complain that the mule would not work. They went to his farm and the dealer picked up a lath and gave the mule a lusty whack. As he drew back for another stroke, the buyer exclaimed "See here, you have no cause to beat my mule!" The trader turned and said, in a very hurt tone, "I ain't beating your mule, I'm just gettin' his attention."

Now, if I have your attention, I shall go on to discuss some systemic aspects of longevity, ageing and death.

Is the prevalence of the molecular paradigm indeed crowding out the one hundred, or even the one or two flowers that might otherwise bloom? To answer this, we must first recognize that gerontology is solving one group of problems eminently well in consequence of its acceptance of the molecular paradigm. These are the problems which arise from efforts to answer the basic question "Why do we grow old?" The answers are in the form of the many fascinating discoveries made recently about the material basis of ageing. Let us consider another basic question, however, which may be phrased "Why do we die?" Here the situation is far less satisfactory, for the total volume of work done on thanatobiology, the biology of death, is derisory in comparison with the work done on molecular ageing. The fundamental problem for thanatobiology is to explain how the life table of a population, including its diseases, can be related in a physically and statistically valid way to the known or presumed properties of the physical ageing process in the population. If there were a vigorous and critical subdiscipline of thanatobiology, we could be spared the proliferation of naive theories of death, which say, for example, that an organism dies when a fraction, f, of its cells mutate, or when it sustains a certain number of "hits", which have no biological properties at all save the useful one of yielding a killing curve which matches the shape of the life table when the correct value of the "hit" number is chosen. These theories are non-operational, and moreover they make no use of any vital characteristic of the organism, which presumably suffers these events in a completely passive way, as if there were no such thing as physiology, and homeostatic physiology in particular.

Physiological theories of death, which seek to reconcile the sigmoid survival curve with the known processes of ageing, are few. I can cite the early work of Simms (1942), the stochastic theory which I introduced (Sacher, 1956) and which Strehler (1960) published independently, and the multiplicative disease probability model of Simms (1946) and Hardin Jones (1956). These theories more or less successfully explain how a slow, steady decrement of physiological performance can give rise to exponentially rising death rates, as described by the Gompertz equation. Through these theories we begin to understand why a human population (or a mouse population) dies out when its physiological performance falls to about half the prime value in the young adult. These reasons relate to hitherto unexploited characteristics of physiological regulations, and in particular to the fact that the regulatory processes are finite and fallible. Here, then, is evidence for life-limiting principles which are intrinsic, in that they are essential characteristics of the phenome, and which are yet systemic, in that they are only describable as performances of the organism as a whole.

Thus we do have clues to the kind of physical necessity which generates the Gompertzian life table. These clues point to directions of inquiry which could lead to a slowing of the ageing process without the need for genetic engineering, euphenics, or the other glittering possibilities that are offered to us by eminent spokesmen for molecular biology. These systemic approaches are not being pursued, but I must say that I do not think this neglect is due to the proscription of such work. There are other psychological factors operating also.

There is one further question about ageing which is being systematically neglected at present. This question may be phrased "Why do we live as long as we do?" More specifically, why does man live thirty times longer than the mouse, or three times longer

than a like-sized mammal, such as a deer or a cougar? These questions can be answered only in terms of the system properties of the Class Mammalia, or their allometry, which is a biological term for the same thing. No essential molecular differences between these species have yet been demonstrated, and even the inessential differences, such as differences in the amino acid order in enzymes, are minor and without known physicochemical significance.

Where, then, do we look for the factors that account for the overall 40-fold range of mammalian lifespans? The most obvious parameter of a system is the overall size. Mammals vary in weight by a factor of fifty million, which is the largest size range I know of for any system in the universe, animate or inanimate. The size factor accounts for a good part of the variation of lifespans, as I am sure is evident to all of you. However, the discrepancies are large and important. If we are to account for them, it must be in terms of a second system-parameter which is independent of body size. Most visceral organs show little significant variation independent of body size, and the slight degree of independence that does exist, such as in heart size, has no predictive significance for lifespan. The one organ of the mammalian body that shows a large range of variation independent of body size is the brain. Brain weight varies as much as 15-fold between species of like body weight. We saw above a good reason for considering a possible role for brain size in determining length of life, since there is evidence that mortality is in part a consequence of failure of homeostatic mechanisms, and it is at least conceivable that the homeostatic capacities of a species depend on the size of its brain. When the relation of lifespan to brain size was examined (Sacher, 1959), the discrepancies not accounted for in terms of body size were almost entirely accounted for. The 3-fold difference in lifespan between man and deer, the 4-fold difference between squirrel and rat, the 8-fold difference between cebus monkey and opossum, are accounted for with very little discrepancy. In other words, the most superficial look at the determiners of mammalian longevity, in terms of the two most obvious and accessible extensive parameters, yielded a well-nigh complete solution of the problem of mammalian longevity. This was done, moreover, in the course of testing a deduction from the stochastic theory of mortality, which is itself a systems-oriented theory.

What do we know that we did not know before? We know, at least in global terms, the nature of the factors that are the efficient causes of ageing, i.e. the factors that make ageing occur in each species at the observed rate. These factors may be reduced to the concepts of energy and entropy, or alternatively, energy and information. The size of a homeotherm mammal is an almost perfect measure of its metabolic rate, as Benedict, Brody and Kleiber have shown. The body size term says that big mammals live longer on the average because they metabolize more slowly. Yet two mammals may be the same size and have an 8-fold difference in lifespan, such as the opossum and the cebus monkey. We can now conclude that *Cebus* ages only one-eighth as fast per calorie of energy expended because its 70 g brain is working full time and all out to minimize the magnitude of its physiological fluctuations, and thus to give it a metabolic error rate only one-eighth as great as that experienced by the opossum, with its 6 g brain.

These results are modest in themselves, but they are important as portents of possible future developments in a gerontology that can develop the conceptual accommodation range that allows it to focus on the whole functioning organism as sharply as it does on the single molecule. This should not be impossible, for a wide accommodation range is a characteristic of youth, and gerontology is a young science still. After all, we

do acknowledge that mutation rates, like all reaction rates, are functions of the thermodynamic parameters of the environment. However, this thought is not complete until we add that the organism is far and away the most important constituent of its own environment, so that the molecule has a fate within the organism that is determined in great part by the systemic aspects of the phenome.

How then can gerontology become a complete science? It would be nonsense to say "Give up the molecular paradigm", for it alone is capable of answering the question "Why do we grow old?" The way to self-sufficiency as a discipline, ready to stand beside reproductive biology, developmental biology and the other major disciplines, is to insist on finding answers to *all* the questions that must be answered if we are ever to comprehend fully the biological, physical and chemical basis of the finitude of life. Two of these questions, which I discussed above, are on the way to being answered, but they give rise to other questions that should be appealing to neurophysiologists, endocrinologists, etc., who will for the first time have a way of relating to gerontology that is more significant than the past role of charting the downward trend of life processes with age.

When Shakespeare wrote the lines "The fault, dear Brutus, is not in our stars but in ourselves", tragic theatre crossed a fateful watershed. It left behind the classical view, of man pursued by his preordained fate, and took the first step toward the modern conception, of man attempting to cope with the irreconcilable facts of his existential finitude and freedom. Similarly, attempts by scientists to grasp the nature of ageing have up to now been imbued with a sense of ageing as a foreordained and abitrary external process, which the organism can only passively endure.

In view of what I have said about the active, self-preserving role of the organism as an integrated system, and remembering also that Szilard used the term "fault" to denote a mutation, we can with justice make the paraphrase that, in respect to ageing, *the fault is not in our molecules, but in ourselves*. This shift of view may only deepen our tragic sense of life, but at least it makes of man a protagonist, rather than a mere victim.

Vertebrates, and mammals in particular, have gained significant ground in the contest of the individual with nature. Perhaps the most dramatic advance was the approximate doubling of the human lifespan within the past two million years. The greatest tragedy of all would be the abandonment by our technological society of all efforts to continue and speed up this progress of individuation, just because it is more rewarding and egogratifying for a few scientists to manipulate the molecules of living things. The macromolecules are indeed the building blocks of living systems, but bricks do not imply architecture. Still less can molecular structure alone imply the exquisite intricacy and economy of the complete living organism. Understanding at the system level is the most urgent need of mankind at this critical period for civilization, and the understanding of systems can arise only from the study of systems.

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Summary—This is the text of a talk in which the author presents his views about the dialectical interplay between the molecular and the systemic views in contemporary biology, especially as they relate to the progress of research on ageing. The molecular approach is now in the intellectual ascendant, and has a magnificent record of accomplishment in some areas, yet it does not seem able to generate logically consistent theories of ageing. The systemic position has a much more slender record of accomplishment, yet it can point to the demonstration that the marked differences in rate of ageing between mammalian species are accounted for almost entirely by constitutional differences between the species. These factors can at present be specified in global terms, specifically as the rate of energy metabolism and the size of the brain. It is indisputable that the material basis of ageing is molecular degradation, but the differences in rate can now be seen to arise from the organizational properties of the various phenomes. A research strategy based on implications of this interaction will lead to a more rapid convergence on the solution to the problem of ageing.