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## SOME BIOLOGICAL FACTORS IN AGING<sup>1</sup>

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From the time we start life as germ cells, we are in the process of aging. We do not become conscious of this often until "age begins to overtake us," but aging occurs with each hour, day and year, from the union of the reproductive cells which mark the beginning of life until the final end of life marked by death.

There is no good definition for the term "aging." Usually we think of the term as designating an increase in age in terms of years, or chronological age, yet we know that physiologically many persons are as young at an advanced chronological age as others at a much younger age. There is much controversy as to whether aging is an inevitable and essentially a physiological process, or whether it is a disease in itself.

The fact that it is inevitable was expressed by Warthin in his book entitled "*Old Age*": "The senescent process is potent from the very beginning, involution is a biologic entity equally important with evolution—its processes are as physiologic as are those of growth. It is, therefore, inherent in the cell itself, an intrinsic inherited quality of the germ plasm, and no slur or stigma of pathology should be cast upon this process. Senescence is due primarily to the gradual weakening energy charge set in action by the moment of fertilization."

The fact that aging is a disease (as related to the brain) in itself was expressed by Tilney: "No evidence thus far adduced is sufficient to convince us that there is such a thing as a strictly old brain. The brain in aged people may present certain morbid changes, but these are in their turn incident to many pathological assaults upon the tissues sustained during life which, in some individuals more, in others less, are in all alike in consequence of infections, intoxications, or other morbid influences. All of this is a strong argument in favor of the theory which holds old age in the brain, as in other organs, to be the result of life's successive and cumulative intoxications. —According to this view, old age has a pathological background. It arises from definite conditions which may be combated or corrected."

It is not my purpose to attempt a discussion of these points of view. That is a job for the specialist, the pathologist. My interest in the problem of aging, aside from the fact that I am actively engaged in the process and thus like most of you have a natural interest, lies in the fact that I have done some research on certain phases of the problem as it relates to a very limited area of the body. That work gave me an interest to choose the topic for this talk. As I have surveyed the field of literature available, I am impressed with the fact that there are also a lot of other persons who are growing older. There is a tremendous bibliography

<sup>1</sup>Presidential address delivered at the Annual Meeting of The Ohio Academy of Science at Ohio Wesleyan University, Delaware, Ohio, April 22, 1955.

available on "Aging," ranging from biological studies, both anatomical and physiological, through psychological and into sociological studies.

In the introduction to the book entitled "*Problems of Ageing*," Dr. John Dewey wrote a very interesting statement on aging. I quote portions of this: "The underlying problem (in aging) both scientifically and philosophically, it seems to me, is that of the relation of aging and maturing. We are at present more or less in the unpleasant and illogical condition of extolling maturity and deprecating age. It seems obvious without argument that there is some connection between the two; that we cannot separate the processes of maturing from those of aging, even though the two processes are not identical. The split that now exists between the two, in terms of both individual activity and happiness and of social usefulness, would appear to be socially or culturally produced, rather than to be biologically intrinsic. That there should be a gradual wearing down of energies, physical and mental, in the old age period, it is reasonable to expect upon biological grounds. That maturing changes, at some particular age, into incapacity for continued growth in every direction is a very different proposition. We may not be able to affirm with the poet—

Grow old with me  
The best is yet to come

but there is something abnormal in the situation if we are obliged to admit that after a certain period nothing better in any direction, individual and social, can occur because of the process of growing old."

Early in my graduate training I had a course in Embryology with the late Dr. B. F. Kingsbury at Cornell University during which he made a statement that at the time surprised me, as well as interested me very much. He, one day in lecture, indicated that "We grow oldest fastest while we are youngest." As we analyze the rapid rate of early development, beginning with an unfertilized ovum and a viable spermatozoon, and realize that in about four months' time the entire pattern of the human body has taken form, we then realize that the greatest progress in growth of the body, not quantitative growth but qualitative growth, does occur in a very short span. True, there are important developmental changes which occur during the remainder of the prenatal period, yet the basic fundamental plan isn't greatly altered.

In many, in fact, in most of the body systems, there are few important basic changes except in quantitative growth after birth. In the nervous system, for instance, it is well established that we are born with as many nerve cells as we will ever possess, and this number is far in excess of the number needed or used. Any cells which may be destroyed are never replaced. The fact that we have this marked surplus in number of cells gives us great comfort, yet degeneration in some of the vital areas and usually quite limited areas, may leave us at any age in a very helpless condition.

All living organisms pass through a sequence of changes which include development, growth, maturation, and senescence. These are commonly used biological terms and cannot be regarded as highly technical when we think of the process of life and of living. Since all these factors are involved in the life span, the question of aging presents a very broad biological problem. The rate and expression of aging vary greatly in different organisms, so that no general theory of aging is available and the problem of senescence in any group of animals must be regarded as a distinct problem within the larger biological question.

Since growth and the aging process are very rapid in early development, I have chosen to discuss some of the biological factors which operate during prenatal growth. Development is a structural or anatomical and a physiological process. The anatomical process deals with form, structure, and relations. The physio-

logical process is concerned with the way parts interact in the developing or evolving embryo.

I should like here to draw very heavily from the embryologists who are concerned with the origin and development of the individual as an organism. It is a well known biological maxim that all life comes from preexisting life and that the process of growth, that is a developmental increase in mass, is an important factor in development. As pointed out by Just, Lillie, and many other embryologists who have been concerned with the very early developmental processes, growth is accomplished in several ways: 1) synthesis of new living material (protoplasm) from foodstuffs, the foodstuff providing the nutritive factor; 2) growth by water uptake, this being particularly important in the very early weeks of development when fluid constitutes nearly 98 per cent of the human embryo; and 3) growth by manufacture and deposit of non-living substances, the material being of the nature primarily of intercellular substances, as the ground substance in skeletal tissues.

Growth is not of the same rate and of the same relative importance in different parts of the same organism, so that it is evident that uniform growth cannot produce changes which result in progressive alteration of form and proportions. The various rates constitute what may be termed *differential growth* and this is accomplished in spite of the fact that various parts of the body appear and begin to grow at different times.

Growth is made possible by and is under control of certain factors, a few of which will be discussed briefly:

1) The constitutional factor. Every zoological species has its characteristic rates and limits of growth. Under identical conditions of development the speed of growth is approximately the same in all individuals of a species, and there is little difference in the final size attained. This is due to inherited qualities that predispose toward a definite basic rate of cell division and growth.

2) Temperature. Growth rates vary with temperature, there being an optimum temperature in which growth is most favorable. In the mammal in which we have internal development within the female reproductive tract, there is a very fixed temperature and the rate of growth is constant, and the end of development preceding birth and the time when birth can be anticipated is so constant that a formula has been developed, which with rather minor variations, can be counted on as being a reliable guide as to when birth can be anticipated. On the other hand, in a form in which development occurs outside the fixed temperature conditions afforded by internal development, variations in temperature exert a marked influence on the rate of development. In the incubation of the chick, for instance, the optimum temperature is near 103° F. If this temperature is lowered, yet not low enough to arrest development completely but only to retard the rate, a longer time is required for hatching.

3) Nutritional factors. The requirements for growth through new tissue building are more demanding than those that suffice for the maintenance and repair of protoplasm which is already present. Food must not only be suitable but also adequate in amount if growth is to occur. There is a minimum below which growth fails. Above this level growth accelerates, but it cannot exceed an optimum rate, characteristic of the organism, even if excess food is available.

4) Growth-promoting factors. There are certain substances which are non-nutritive which further the process resulting in the production of new basic living materials:

a) The embryonic factor. The exact nature of this factor is not known but it has been demonstrated that when tissue is grown outside the body in a nutrient medium, that growth is stimulated by the addition of juices from the body to the medium. It is presumed that this same factor has an influence within the body.

b) Hormones. Some of the endocrine secretions are promoters and regulators of growth. The secretion of the thyroid and of a portion of the pituitary are particularly significant in this respect.

c) Vitamins. These are of plant origin in the animal diet. The absence of vitamin A in the young animal results in a failure to gain weight. An absence of vitamin B<sub>2</sub> results in growth failure.

Cell growth as an embryonic factor and as an adult factor is quite different. In embryonic growth there is not the highly developed level of specialization as is found in post-natal growth. There is a fundamental antagonism between cell differentiation and cell proliferation and the factors which promote differentiation make proliferation increasingly difficult. The cell types resulting from the process of differentiation are distinct and specific entities, and not transitional forms; this means, for instance, that a cell is never a cross between an epithelial cell and a muscle cell. Once a cell is committed to any type of differentiation it cannot engage in another type, nor can it abandon its original line of specialization in favor of another course. Furthermore, a course of differentiation followed by a cell always follows the distinctive way that is characteristic of the species to which the embryo of which the cell is a part belongs.

Aging cannot be ascribed to any single structural or functional change or failure, and there are variations in functional activity of tissues and organ systems among individuals of the same chronological age. One of the most commonly accepted reasons for retarded senescence is adequate nutrition which not only reflects itself in the growth process but in the maintenance of youthful characteristics. As knowledge of nurture, and especially of nutrition, has advanced and is advancing, some of the better nurtured children may have a rate of senescence much more favorable and quite different from the present picture of aging.

Time is of the greatest significance in studies of growth and of aging. It may be assumed that members of a *species* of the same chronological age may constitute a homogeneous group in the aging process, but studies on children and different animals have indicated that individuals grow, develop and mature at different rates and thus differ decidedly at the same chronological age. Dr. Alexis Carrell and Dr. Lecomte du Nouy have tried to differentiate time rate within individual organisms in their concepts of "physiological time" and of "biological time." It has been asserted that "time produces no effects—events occur in it but not because of it," which implies that time is a frame of reference for measurement of change but may be relative to the individual organism.

It is interesting to compare and contrast some of the factors which operate in aging in plants and in animals, and in lower animals and higher animals, and from such comparisons and contrasts we can observe, or perhaps draw some conclusions relative to the aging process.

Not being a botanist, I hesitate to attempt to make mention of the problem of aging in plants, but I feel on safe ground if I may be allowed to summarize some of the discussion given in a most interesting article by Dr. William Crocker, the late managing director of the Boyce Thompson Institute for Plant Research, Yonkers, New York. Dr. Crocker indicates that it is impossible to discuss aging in all plants under one concept because there is such a range of plants as to life course and life duration. The problem of aging in plants is rendered complex by the fact that the life span of a given plant in nature may be modified greatly by growing it under conditions that vary considerably, or in some cases even slightly from the conditions it meets in nature.

In the main, plants form an open system, that is, they continually develop new growing points, whereas animals more often form a closed system. This means that plants in general do not have a definite or even an approximate life span in contrast with animals. Certain plants are theoretically immortal, that is, they die only because of unfavorable external conditions. This is true of plants in which

all the cells remain embryonic instead of differentiating into reproductive and somatic cells. Even some plants that in nature differentiate into somatic and reproductive cells can be grown continuously vegetatively by the proper cultural conditions. Hartmann grew *Eudorina elegans*, a colonial alga, for 1300 generations over a period of five years, without any differentiation of cells beyond embryonic cells.

As we pass from plants to a consideration of animals, let us begin with the single celled animals or the Protozoa. In view of the nature of the life cycle of the Protozoa, the age problem has a two-fold bearing:

1) The individual is a free cell, which performs all the fundamental operations of life; and 2) more important is the following: The single cellular individual as a rule does not as such die; instead it grows and divides into two individuals. This continues so that chains of free individuals are produced, stretching for many cell generations. These are interrupted at long intervals by the union of two individuals in sexual reproduction. After this, the chain of free individuals continues. The question then is: Does the chain of successive living cells, through the process of living, gradually become senescent in its later links, so that it declines and finally dies, unless something intervenes to save it?

During fission or simple reproduction in the Protozoa, many of the characteristics of the adult do not at first appear in the offspring, but such characteristics, both internal and external, do gradually reappear as the individual grows older, thus the young offspring are at first "young" as compared with the parent. But the question remains whether the rejuvenescence so produced fully restores the primitive condition. The chain of living cells extends for hundreds or thousands of generations. Are the later members of the chain as young physiologically as the earlier members? The following are a few observations relating to the answer to this question in the Protozoa, and to similar questions in higher animals:

1) When chains of living cells are kept under observation in the laboratory, so that their fate can be determined, as has been done with many species of Protozoa, it is found as a rule that after some hundreds of generations they do decline. Fission and other life processes become slower, resistance decreases, functions are imperfectly performed. Various structural changes occur. All these factors give a picture of senescence which finally extends to death.

2) In Protozoa, it has been demonstrated that in full active living there are always kept in store fresh unexhausted parts which do not participate in the major activities of life and which can be brought into later use. In the higher organisms these are complete cells. *The presence of such fresh unexhausted parts is the secret of continued life.*

3) In the invertebrates, we find extensive if not universal use of the device of keeping certain parts of the organism out of the main current of the life activities, forming a reserve, which is substituted at intervals for worn parts. In the multicellular organism these reserve cells have the capability of developing and taking on all the activities of the organism. These are known to us as germ cells, but many organisms have other reserve cells known as embryonic or regenerative cells, which remain dormant but can be roused to active life by appropriate conditions. In the metazoa, the cells which take an active part in the life of the individual are subject as a rule to decline or senescence. In addition to the senescence of the individual cell, or in consequence of it, there is, as in the vertebrates, a general senescence of the entire body, culminating in death.

4) By contrast with the situation in plants, in animals the embryonic condition is not maintained in the metazoa or multicellular animals. In these we recognize somatic and reproductive cells almost from the beginning of development and the somatic cells are of various types and are organized into more complex units, the tissues. Tissues in turn are organized into still more complex units known as organs; as the heart, stomach, etc., such organs often presenting a combination of

all the fundamental types of tissues, so when we recognize senescence in an individual, it may be due to a degenerative process in an individual tissue, but more often many tissues are involved, and apparent aging in one organ or system may actually be a secondary effect resulting from aging in another organ or system.

It is of interest to review here some brief observations relative to the process of aging in man. Only a few of the body systems will be mentioned. Certain factors in aging will be apparent from these observations. Aside from the predominance of the congenital conditions as a cause of death in early infancy, deaths at ages under 40 are largely of infectious or accidental origin. Beginning with age 40, the cardiovascular-renal diseases (*i.e.*, chronic diseases of heart, chronic nephritis, cerebral hemorrhage and paralysis without specified cause, diseases of the arteries, and angina pectoris) assume rapidly increasing importance. More than one-fourth of the deaths in age group 40-49 arise from degenerative conditions in this category. The proportion of deaths from such diseases thereafter mounts until in age group 80-89 they account for two-thirds of all deaths. Cancer first becomes an important factor at age 40. Among females between 40-59, cancer causes about one-fifth of all deaths; among males between 50-69, about one-eighth of all deaths result from this cause. Accidents, important in mortality during youth and early maturity, are of importance again in old age.

Death in the aged is apparently only rarely due to a wearing out of the digestive system. Most elderly persons die with a digestive system when not directly affected by cancer, by a toxic or by an infectious process, that is capable of functioning beyond the ordinary life span. The consequences of aging *per se*, are not serious. It is striking that during life, symptoms referable to the gastrointestinal tract occur more frequently than to any other system in the body. This is because the alimentary tract is so readily influenced reflexly by mental states and by disease elsewhere in the body, and because many of the symptoms of disturbance of the tract are functional in nature and tend to respond readily to diet and rest. This is why Josh Billings wrote: "I have finally kum to the konklusion that a good reliable set of bowels is more to a man than enny quantity of brains."

In lower vertebrates and in the embryonic mammal, degenerative changes are observed with aging of the kidney. Senescence has been looked upon as involution due to a decrease in the vital energy of the cells. If such a primary senescent involution occurs in the kidney of man, it is obscured and its effects over-shadowed by secondary tissue changes that develop as a result of the normal aging of the renal arteries. Aging of the human kidney becomes, therefore, a special case of aging of the vascular system.

Age changes in tissues of the body, excluding blood and body fluids, are chiefly those of dehydration with reduction of intracellular fluid and an increase of intercellular fluid and in addition a certain faltering in the orderliness of tissue pattern. These changes also indicate the course of transformation from the orderly and reversible phenomena of health into the disorderly and irreversible which are the stigmata of disease.

Tendons and ligaments, synovial membrane and connective tissue, show no clearly defined age changes, but do present, as age advances, the cumulative effects of imperfect repair and constitutional defect. Smooth muscle is another tissue for which no age changes have been recorded. Chemical changes in skeletal muscle with age indicate a decrease of intracellular fluid and an increase of intercellular fluid.

Dr. Hefner, as retiring president of the Academy last year, made a significant point in his presidential address to the effect that no selective factor is so fatal to the maintenance of the proportion of persons with higher intellectual qualities as not being born. But after a person is born, if he is to make the greatest contribu-

tion to society it is important that he have a relatively long life span in which to make this contribution.

Our present knowledge of aging and death indicates the importance of the genetic or hereditary factor. There can be no doubt that in all animals from the single celled Protozoa, through the invertebrates and vertebrates to man, the length of life is largely determined by inheritance. In fruit flies a single gene may make a great difference in length of life. In humans there are long and short lived families and the genetic constitution is an important factor in aging. Another important factor that has been mentioned in early development and in the adult is the nutritive factor.

If we could be fortunate enough to be born and to be able to select our parents on the basis of the genetic factor for longevity and the financial factor to provide good nutrition, we could have a reasonable chance to reach a ripe old age, if we could avoid the accident factor. The fact that we are here indicates we got by the first hurdle of being born—how long we will be here will be largely determined by the other three factors.

To those of us who are old enough or are aging rapidly enough to be conscious of the process taking place—and often with great speed as we feel at times, we may be encouraged for the younger generation by the following from the March-April, 1954, issue of the Bulletin for Medical Research:

“The chances of anyone’s living to the age of 65 continues to get better and life expectancy past that point is on the increase. More than three-fourths of all women born last year will live to be at least 65, and nearly two-thirds of all men born last year have the same chance. Furthermore, half of the women who reach 65 will go on to age 80, and quite a few of them will celebrate their 88th birthdays. Half of the men reaching 65 will survive to 77.”

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