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AGE, CHANGE AND THE ADAPTED LIFE[1]

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THE interest in ageing which has expressed itself here in such a happy and helpful fashion during the past two days is not new as an intellectual adventure. The application of such understanding is in the period of its anticipated commencement. To date it has not related itself to life in the form of a basic consideration of such a process on which and from which specific interpretations of the varied manifestations of life at different age periods may be considered. The average individual, too frequently the biologist and usually the pathologist, limits his interest and confines his intelligence of ageing to narrow categories of thought. He fails to appreciate the yearning of tissues for life and the amazing chemical and structural modifications they may participate in, even gross structural changes designated disease, in order to bring about organ adaptation and the adaptation of the individual as a whole to those changes which occur as the life span progresses. The certainty of the termination of this life span and the fact that all living things are concerned with it has stimulated the imagination of poets and philosophers. Their inquisitiveness has been either romantic or dominated by resignation and has not been demonstrably helpful. Another period which concerns itself with the facts of life is in its beginning, and as these facts accumulate through chemical, biological and psychical research the romance of life will find sound ground on which to express its related beauty. Ultimate resignation will become lost in an interest in the transitory prolongation and effectiveness of the different periods of the life span. The Browning concept of the "last of life for which the first was made" will assume tangible significance.

For centuries before Cicero's great statement concerning old age thought had been given to this state of man, but only in what may be designated recent

[1] An address at the Symposium on Ageing, Washington University Medical School, Saint Louis, March 24 and 25, 1944.

years has the subject of ageing been considered in a relatedly helpful fashion. Metchnikoff[2] and Minot[3] gave serious thought to the ageing process, not only as a change in form, the morphology of senescence, but the former investigator made suggestions for the prolongation of the life of man. He was not greatly concerned with the effectiveness and pleasant relatedness of this life as years were added to it. Such a projection of the life span into and by prolonging the senile state is not helpful to the individual or to the social organization of which he is a part. In recent years several monographs[4, 5, 6] have appeared that gather together information concerning ageing and the senile individual and have served to bolster up some interest of a rather detached and philosophical nature in life processes. The masterly volume of Child[7] on "Senescence and Rejuvenescence" stands as a contribution of an experimental scientific order in an attempt by such a method to gain an insight into the phenomenon of ageing. Real and durably satisfying interest of a lasting and accurate nature in these processes has in this country come about through the concern of the Josiah Macy Jr. Foundation and the hearty appreciation of this interest by Professor E. V. Cowdry, which has culminated in the publication of two editions of his book "Problems of Ageing."[8] Here one finds not poetry or delightful prose dealing with these problems but investigations by earnest scientists into the particularities of ageing which, when considered in a composite fashion, give great understanding of these changes as a whole in both animal and plant organizations. Likely certain of these important contributions came about not primarily as previously planned studies on ageing, but as the life of plants and animals was in the process of investigation, these factors of change with age insinuated themselves for detailed consideration. They forced the investigator to take an excursion into one of the many bypaths which develop during research and which if their significance is realized may lead to plateaus affording broad vision of problems that await solution of greater worthwhileness than the meticulous problem which prompted the initial investigation. The factors of age are concealed by many chemical and later morphological manifestations of cell life, whatever they may be: they are ever present.

In Great Britain and Continental Europe one finds the counterpart of Professor Cowdry for this country in Professor V. Korenchevsky, head of the division of pathology at the Lister Institute, London, who now for reasons of greater safety and less disturbance carries on his work at Oxford University. He had once been a student of Metchnikoff and perhaps here was the source of the spark that flamed his interest in ageing. As a result of this interest Korenchevsky has formed not another society, but an intimate club-like international organization designated by him the "Club for Research on Ageing." He personally established in this country the American Division of this club which has functioned effectively for the past nine years. In addition to these interests in ageing the National Research Council, through the Division of Biology and Agriculture, has established a Committee on the Biological Processes of Ageing that affords another channel through which interest in ageing may express itself. This short and entirely inadequate statement in retrospect has been made to indicate the geographically wide concern which exists in connection with the ageing process and in turn to congratulate this medical school and those individuals who with wisdom made this conference possible.

The usual concept of age is that of a fixed, natural and irreversible process, chronologically determined by the species of animal which within certain fairly constant limitations terminates in death. Age and the processes constituting it should be seen and appreciated as living, fluid, elastic states of give-and-take for the sake of adjustment as an organism passes through its life span with those changes indicative of ageing being in some measure manifestations of an attempt of such an organism, man, to effect a working adaptation to these years. Certain of these signs of ageing represent failures in such an attempt. The important consideration for the student of ageing is to ascertain the reason for such failures and the cause for those states of premature ageing and instability which unrelate the individual to that environment in which he has to live and maintain a functional adjustment. Very recently Stieglitz in his volume on "Geriatric Medicine"[9] has brought to a focus the clinical application to date of information which we have in this domain.

The desire of tissues for life and relatedness is abundant.[10, 11, 12] They withstand repeated and con-

[2] Élie Metchnikoff, "The Prolongation of Life," G. P. Putnam's Sons, 1910.

[3] Charles S. Minot, "The Problem of Age, Growth and Death," G. P. Putnam's Sons, 1908.

[4] Aldred Scott Warthin, "Old Age the Major Invaluation," Paul B. Hober, Inc., 1930.

[5] Raymond Pearl, "The Biology of Death," J. B. Lippincott Company, 1922.

[6] Sir Humphry Rolleston, "Medical Aspects of Old Age," Macmillan and Company, 1932.

[7] Charles M. Child, "Senescence and Rejuvenescence," University of Chicago Press, 1915.

[8] E. V. Cowdry, "Problems of Ageing," second edition, Williams and Wilkins Company, 1942.

[9] Edward J. Stieglitz, "Geriatric Medicine," W. B. Saunders Company, 1943.

[10] Samuel Meltzer, Jr., "The Factors of Safety in Animal and Animal Economy," The Harvey Lectures, 1906–1907. J. B. Lippincott Company, 1908.

tinuous psychical and somatic insults for years before the signs of such injury develop. Even though the order of tissue change which may assert itself is of such an abnormal structure as to warrant its designation "disease," yet it may be a morphological defense mechanism to maintain life and to stabilize it at a lower level of physiological effectiveness.[13] Such changes are not infrequently seen as tissue reactions of repair to severe injury. The important and necessary understanding of ageing must come about years before such evident tissue interference develops. This information must be acquired when changes in cell life and in the individual as a whole are of a predominantly chemical order, when they are not structurally irreversible and when they afford an opportunity for chemical modification towards that normal which different animal species have established for designated age periods.

Ageing of the animal organism, of man, commences not at forty years or at some other advanced chronological period but when the male spermatozoan unites with and fertilizes the female ovum. There then commences a process of ageing with tissue differentiation and organ formation towards perfection which culminates for one period of this process at the end of the gestation period. The organism as individual at birth has so aged through constructive processes that it can now attempt to cope with a changing outside environment and by changes within itself, by processes of a physiological order, effect a functional adjustment, designated an adapted and related life. There is in such an organism no fixity of intent or purpose except to live an animal type of existence. Later with structural cerebral differentiation, the acquisition of a receptiveness on the part of such tissue, mind as learning, reason and emotion guide or fail to guide this animal body in a related fashion. The duration of the period after birth for constructive ageing towards perfection in adult life not only varies with the species of animal but with animals of the same species. In the case of man, certain families age more rapidly than others. They reach maturity more rapidly and retrogressive changes supervene at relatively earlier age periods. There is no understanding at present of the differences in the chemical constitution of the tissues of such families which determine the advent and the rapidity of the ageing process. The life span after birth furnishes a period for constructive ageing to adulthood at which time the individual shoud have reached a hypothecated normal as a balanced and related life.

During the periods of infancy, childhood and youth, life areas of a predominantly normal nature, such tissues are, in terms of their age, susceptible to accidents, designated "diseases of infancy and childhood." These transitory interruptions of this normal are usually of an infectious order and may now in many instances be specifically protected against or terminated after their development. Certain invading organisms, bacteria and viruses, appear to find tissue culture media at these age periods especially adapted, appropriately chemically constituted for their invasion and rapid multiplication. This observation at once raises the question in connection with ageing at these periods as to the chemical nature of the tissue which permits such invasions and subsequent growth of organisms. Why do we speak of poliomyelitis as infantile paralysis and thereby in terms of designation exclude on the basis of its frequency of occurrence the same specific virus disease in middle age and in senility? Such questions are rarely asked. Their solution presents an open field for research of a basic nature. An answer of a chemical order which may be found within such fixed cells that constitutes a specific affinity for the invading cells has not been approached in terms of an answer. Our attention very naturally has been focused on the organisms causing these specific diseases and on immune, protective bodies which may be produced as reactions to such tissue invasions, but we have not gone behind the appearance of these bodies to the chemical nature of cells at different age periods responsible for their production or lack of formation. The age factor, whatever that may represent in terms of chemical constitution, is the determining influence which in large measure segregates certain infectious processes.

During the age periods of infancy and childhood, over and above the accidents represented by the infectious diseases there was until some thirty or forty years ago a very high mortality in such age groups, due to imperfect feeding and disturbances of nutrition. These changes in turn certainly predisposed to the development of the specific infections. The feeding of such young tissues based on their caloric demand and the specific nutritional requirements for different chemical materials as foodstuffs was in large measure unknown. The significant influence of a general, as well as of a specific, nature of the various vitamins was unheard of. An understanding attempt could not be made to aid this young tissue in relating itself into the period of adult life. This failure was so apparent and the death rate was so high in infants and young children that a medical specialty developed, designated pediatrics. Understanding in this domain did not come about from knowledge of the adult organism. It came through the interest of in-

[11] W. B. Cannon, "The Wisdom of the Body," W. W. Norton and Company, 1932.
[12] Wm. deB. MacNider, *Annals Int. Med.*, 17: 989, 1942.
[13] Wm. deB. MacNider, *Jour. Pharm. and Exp. Therap.*, 56; 383, 1936.

vestigators in detached laboratories and later at the bedside as clinical research by individuals who were willing to concern themselves with life processes, in this instance the ageing of infants and young children, the type and amount of food materials, the fluid requirements and the vitamins necessary for such young tissues as they constructively aged. In this country Jacobi, the elder Holt and now the younger Holt, Booker, Hess and of particular significance Howland, and later his great pupil and associate, W. McKim Marriott, who made with the assistance of its present head and director, the department and clinic of pediatrics at this university. To this clinic came biological chemists, physical chemists and clinicians from throughout this country and abroad to acquire an understanding of the science of pediatrics and with such knowledge to guide and relate tissues as organisms, individuals, of the early age groups as they aged towards a hoped-for perfection. Such information came through research in segments of life that could readily respond to such applied science, a young age group, individuals with an inherent chemical urge[14] for normal development and relatedness. The same order of investigation is imperative, even though it is with more difficulty applied, for those individuals who have reached their summit of constructive development and at different chronological periods commence their descent towards senility. Here the biochemical tendency is away from the normal. The trend is not for life, it is against it. There must develop a group of scientifically trained people from and through the laboratory and into the clinic as has been accomplished by the pediatricians, who will concern themselves with an understanding of those retrogressive changes that make not their chemical, but their gross appearance at what is designated "middle age." The chemical basis for such changes must develop years before the appearance of the structural changes. Such retrogressive tissue modifications progress with periods of transitory tissue adjustment and maladjustment until the latter state becomes permanent, fixed and only stabilized as a state of disease or as physiological senility. Such states are not reversible, even though they may as such represent periods of tissue reaction in an attempt at stabilization.

In a discussion of this order it would be unfortunate to attempt to designate by age segments from adult life into senility the nature of the physical disturbances which may supervene. There does, however, in general occur in the life span of the human being a critical period of change that has so progressed chemically between the ages of forty and fifty-five that it may with fair certainty be recognized by structural changes. Concerning the chemical shifts that develop as molecular modifications in such living tissues and that culminate in the degenerative diseases we know little in terms of certainty. Of the very greatest importance is the fact that at such periods or later is the time incidence for the development of cancer. What chemical bodies assert their action at such periods which lead to cell growth of an unguided, unrestrained order? What chemical bodies cease to exert their restraining influence on tissues at such age periods which release them for a certain wildness of life, designated malignancy? The fact of cancer is intimately associated with the factor of age. Investigation in this domain is of such a specialized nature that it requires a type of investigator of highly specialized training. An understanding, however, of the critical middle-age period in man is of a more general order and primarily concerns the biochemist and the expert in nutrition. These were the individuals who were found necessary to gain an understanding of the early age periods of constructive development.

The symptoms and signs of departures from the retrogressive, the ageing normal, are of their nature both varied and variable. They are varied, depending upon which organ, organ system or tissue expresses itself in such change and their modification, their variability in such tissues, their intensity, the readiness with which they develop, is in part genetic in origin and can be influenced by thoughtful mating. In addition to the factor of heredity, there can be little doubt of the development in certain tissues, at the middle-age period, of changes in the metabolism of cells of great significance. Such states should be amenable to the use of appropriate diets aided by accurately determined inorganic and vitamin supplements. Such was the case in infancy and childhood. We know very little concerning the food requirements for older individuals, those at their critical period of change and during their advance towards senility. Biochemical and nutritional research for such age groups is not only necessary, it is imperative if we are to prevent a considerable proportion of the degenerative diseases of middle age, stabilize individuals at such periods for toil and for happiness, and which defer the advent of those years of unrelatedness designated senility.

When accidents of a major and fatal order superimpose themselves in such individuals or when by the natural extension of pathological processes life comes to an end with all its antecedent years of incapacity, the pathologist takes over and with accuracy records these changes at the autopsy table. They remain as a record of terminal events and take their place in

[14] Joseph Needham, "Biochemistry and Morphogenesis," Cambridge University Press, 1942.

a card-indexing system. Such observations are most worthwhile, but they only serve as inelastic checks on pre-existing clinical states. Such records have little significance for, and they fail to throw the light of information on, the commencement of those bodily reactions which finally culminate in such structural changes of a gross order that the pathologist can recognize them. Sir James Mackenzie, after his stay in London as the world's most illuminating and eminent cardiologist, went back to his Aberdeen to establish an institute for the study of the commencement of disease. His thought was good. It failed to come to fulfilment. He died at a relatively early age from coronary occlusion. In considering these middle-age breakdowns or the gradual progression of degenerative diseases commencing in and before this period, one fundamental type of understanding is essential. This consists in learning through research on the lower animals as well as in man the basic chemical differences in cell life as that life advances through age periods as infancy, youth and maturity to a chronological period in the life span where such chemical changes shift qualitatively, quantitatively or both, with the advent of first the symptoms and usually much later the signs, as modified structure, of commencing tissue retrogression as degeneration. Such studies are just as possible and feasible for the age periods prior to and into those of tissue degeneration which result in maladjusted individuals as they have been for the constructive age periods of tissue development and adjustment. These studies have not been made. When such segments of information are obtainable they may then be fitted together and two orders of helpfulness made available for the ageing individual—firstly, prophylactic advice and the use of natural measures for tissue protection, and secondly and with regret, attempted treatment, nutritional replacements for the existing tissue change. Repair may be difficult.

Prior to and during the Hippocratic period medical thought had to content itself with the observation and interpretation of surface, bodily phenomena. Different types of individuals were recognized and evaluations were made of their susceptibility or lack of susceptibility to disease. Finally, with the advent and establishment of such changes a prognosis was made possible concerning the outcome of the process. Later, when regulated dissection of the human body was permitted, the anatomists and their offspring, the pathologists, had an opportunity to observe gross organ and tissue changes and attempt to correlate these with the symptoms and signs of disease. Still later, with the development of the microscope these gross changes were found to be a collective reaction, in some instances similar in character, of the cell units in organs and tissues. It is at this point that pathology in general has rested its case. Such observations are essential for the morphological, the anatomical, understanding of disease. They are lifeless reactions. They are no longer a part of the elastic, adapting, living organism as individual. They afford little understanding of those pathological life processes of a chemical order which finally assume such a degree of chemical intensity as to modify cell structure and demonstrate by physical change their chemical presence. Such is the order of the commencement of disease frequently encountered in the middle-aged group of individuals. The pathology, the physiology and pharmacology of the not very distant future will be of a biochemical and biophysical order. Such a concept with the type of research which fits into it and gives understanding to it is necessary if information is to be obtained of the changing, chemical life of tissues as they advance from one age period to another, and as these periods are modified by departures from the normal. With such knowledge these changes within cells of a chemical order can to an extent be regulated and guided. The object of such regulation and tissue guidance is not to prolong life into a useless and likely unhappy senile state, but to conserve and protect it at periods in the life span where it may effectively relate itself in toil as helpfulness for the individual and the family, the economic and social order in which it lives, the industry which it serves or the profession of which it is a part.

The first essential for research is a thought. For the activation and operation of a thought as its validity is tested, financial support is essential. At the present time after man has passed the periods of infancy and childhood and has given up the guidance of the pediatrician, the rest of his life span for which the first was made is permitted to run its course without an understanding of succeeding age periods and therefore without basic guidance. The segments of life as age advances can just as certainly be understood, guided, transitorily stabilized and made increasingly effective as has been demonstrated for the earlier periods. Inquisitive individuals adequately trained with financial support for their undertakings as research will be able to prolong and relate purposefully individuals in the middle-age period of the life span, the life area which at the present time is either terminated abruptly or too frequently prepares the individual for a rapidly advancing state of premature senility. Human conservation of this order is a thrilling adventure and one which challenges the generosity of thoughtful human beings.