

GERONTOTHERAPEUTICS*

THE recent growth of interest in the medical aspects of aging is a natural consequence of the increasing age level of the population. Efforts to widen the healthy middle span of life will decrease the period of senility as well as increase the average life span. The application of scientific and medical research to pediatrics has given such good results that further work, although necessary and desirable, may be expected to reach a point of diminishing returns for the time, effort, and money involved. The next big general problem in the field of medicine, therefore, is the prevention and control of the changes in the human organism brought about by age.

Research work in the field of aging divides itself into four attacks upon the problem. The first and most obvious approach is geriatrics, which consists in the therapeutic treatment of the infirmities and diseases associated with age, irrespective of their origin. The treatment of the aged, or geriatric medicine, has already become one of the major interests of the clinician and the practitioner. Research in geriatrics may be best carried out by the physician in the clinic and in general practice. All fields of medicine contribute to geriatrics, and rapid advancement in this branch has taken place in the past few years. The importance of geriatric medicine will increase with time. Unfortunately, geriatric medicine is a case of locking the stable door after the horse has been stolen. It can alleviate the ills of age, but by the time the physician begins treatment the effects of the aging process are already far advanced. Research in geriatrics may be safely left to the medical profession with appropriate contributory help from the research scientist.

A second phase of aging research is the psychological and psychiatric treatment of the aged. Only skilled psychologists and psychiatrists can investigate this aspect of the problem, which may be called "psychogeriatrics." At best such research, and treatments developed, are only adjustments and compensation processes for an established syndrome. This work will become more important as the average age of the population increases.

The key field of investigation is gerontology, a third phase. Gerontology is concerned with the biology of the aging process, the changes in the tissues with time, and the effects of age on the body as a physical mechanism. Within the past

few years this field has developed greatly, and various foundations have subscribed to the work. An understanding of the biology of the aging process is essential to the treatment of the aged in geriatrics, as well as to a successful attack on the control of the aging process involved in the fourth attack on the problem, or gerontotherapeutics.

Gerontotherapeutics is a term invented by Benjamin^{1,2} to describe the treatment of the aging process as an entity, the treatment of the individual to slow down and to prevent the development of many of the aspects of senescence. It is the practical application of the results of gerontological research to the human being. It includes the determination of the optimum dosages and treatment of antiaging agents on old animals so as to discover the limits of usefulness and the mode of application of such agents. The final step in gerontotherapeutics is the clinical testing on patients so that the beneficial and useful treatments may be released to the medical profession for general use. Until the present time this phase of the aging problem has been almost totally neglected. Neither men nor funds have been provided for the practical utilization of the scientific discoveries already made in gerontology.

There are at least four elements in the problem of gerontotherapeutics that must be investigated further by appropriate work on old animals and then carried through the clinical stage for human use. The vitamin field is being investigated for therapeutic treatment in geriatrics, but it has been neglected as a preventive measure in gerontotherapeutics. Sherman³ screened vitamin A on various dosage levels in rats and found that an increased intake up to a certain level increased the life span of rats about 10 per cent. A similar increase on a different strain of animals was also found by the Pauls for vitamin A.⁴ On another life form vitamin B₆ (pyridoxin) and pantothenic acid increased the life span from 10 to 25 per cent.⁵ A combination of sodium yeast nucleate, pyridoxin, and calcium pantothenate gave an increase of about 46 per cent in the average life in the same research.

It is evident that a complete screening of the various vitamins is necessary, with the establishment of optimum intakes to slow down the aging process. A complete analysis of the work required for the use of vitamins as antiaging factors has been made.⁶ In this program investigations on other nutrient factors, such as yeast nucleic acid, should also be carried out. If fed in large doses

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from birth, yeast nucleic acid has been demonstrated to increase the life span of mice to an extent of about 15 per cent of the average life span.⁷ A smaller daily intake shows about a 10 per cent increase of the average life span in old mice.^{8, 9}

Hormones have not been effectively screened for their influence on the average span of life, although it has been demonstrated that testosterone¹⁰ and progesterone¹¹ may show some beneficial effects upon the senescent period. Some excellent work on hormones and the aging process has been carried out by Korenchevsky and his associates. Complete evaluation of hormones in the aging process must still be determined.

The major cause of death in any civilized country may be traced to some form of breakdown of the cardiovascular system. The prevention or elimination of this type of breakdown must be a major objective of gerontotherapeutic research. The Foundation recently formed by the American Pharmaceutical Manufacturers Association plans to undertake work in the geriatric and gerontological phases of this problem. An investigation of the gerontotherapeutic side is also necessary. The use of choline^{13,14} and inositol^{13,15} to remove cholesterol deposited in the circulatory system in the treatment of arteriosclerosis and coronary thrombosis has reached the clinical stage. Their use to *prevent* the development of cardiovascular breakdown in man is yet to be investigated, although positive evidence has been obtained in animals. The roles of pyridoxin¹⁶ and tocopherol in the prevention of heart disease have still to be evaluated.

The successful solution of the cardiovascular problem would do more to lengthen life than any other phase of the aging problem, unless it were to be the complete solution of the growth factors phase discovered by Carrel and his co-workers.¹⁷ The investigation, identification, and production of the antiaging factors found in plasma will result in the renewal of tissue by growth, which is the final solution of the aging problem. This fourth phase of the problem will take the greatest length of time to develop, but its solution offers the greatest returns. Serological investigations should also be carried out in order to increase the resistance to internal breakdown.

The four parameters discussed will automatically expand with increasing work in gerontology and gerontotherapeutics. Fortunately methods are now known for clinically testing the rate of aging, so that the efficacy of a project in gerontotherapeutics can be verified on human beings in a clinic, as well as upon animals. The rate of healing of wounds¹⁸ and the change of the refractive index of the lens

of the eye¹⁹ are functions of physiological age. Therefore, these two tests may be used to evaluate on clinical patients anything that shows up favorably in animal work. This evaluation can be carried out in three to five years instead of waiting for about two hundred years for something to show up in the general population, as many investigators have assumed to be necessary.

In investigations on laboratory animals the healthy life span has been increased by the use of longevity factors instead of increasing the period of senility, as many people who are unfamiliar with the work think is being done. The animals remain healthier, more vigorous, retain sexual virility, and do not exhibit the general debility before death noted in the control, or untreated, animals. This gain in real living is in addition to the increase in the average life span.

Research in gerontotherapeutics is also an indirect method of attacking the cancer problem, for the incidence of tumors increases with age in humans. Animals treated with longevity factors do not develop as many tumors as the control, or untreated, animals. This may mean that the longer the animal lives as a healthy, vigorous specimen the younger the cell types retained by the body, and thus a decreased probability for the development of tumors.

The first major attack on the aging syndrome using the methods of gerontotherapeutics will be by the newly created National Foundation for Anti-Aging Research, Inc., New York City. This organization will carry out large-scale animal screening and clinical testing on the positive vectors hitherto uncovered by gerontology and early gerontotherapeutic research. The objectives of the new foundation include the development of practical and useful antiaging agents that may be used by the general population under the supervision of the medical profession. The foundation will concentrate upon the general improvements of health and the life span at various levels of the population from about thirty years of age up. Improvement in health and life span are inversely related to the age of the patient at the beginning of the gerontotherapeutic treatment. Therefore gerontotherapeutics is essentially preventive medicine.

The increase in the average span of life from such a gerontotherapeutic program is a matter of discussion for investigators in the aging field. The pessimistic ones estimate an increase of average life span in the range of about ten years, whereas the more optimistic believe that there is a good probability of doubling the average life span. Nearly all

agree, however, that man dies too early, and that the average span of life can be increased. The organs of the body are designed for an average length of life equal to approximately twice the present average. If the rate of aging can be reduced, and there is scientific evidence that it can, then the average length of life should approach eventually the upper limits of several hundred years found by Simms²⁰ in his analysis of death rates at various ages. In order to achieve any scientific objective, money, men with the desired mental outlook and scientific training, and time are needed. There is no field of medical research known today than can offer hope of such rich rewards for the expenditure of such meager sums as gerontotherapeutics, and the goal is certainly worthy of the effort.

Two national factors should also be considered. If we are confronted with a long war, or a series of small wars, it will be necessary for the older age

groups to carry out a major part of the production prerequisite to national survival. The older groups can do this if they are well, healthy, and younger than their years! Also, the increasing age level of the population poses two alternatives. In one we have a large number of senile people in poor health who must have medical and nursing care and attention. This condition cuts down on our ability to produce for the abundant life by taking out of production and creation of national wealth a large number of people—both patients and their attendants. If, however, the older age groups are healthy, active, and younger than their years they will continue to contribute to our human resources, which are basically the primary source of our national well-being and economy. Both problems can only be successfully solved by gerontotherapeutics.

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