THE PROBLEM OF AGEING

BASIC DIFFICULTIES OF RESEARCH

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Great interest in the problems of gerontology is being shown in medical and scientific circles and by the public at large. Misunderstandings on the subject among non-specialists, however, are sometimes considerable. Therefore a summary of some of the main difficulties of the problem and of gerontological research might be of interest to those who have no time to study the matter in detail.

Theories of Senescence

There are several theories of senescence. Professor Warthin (1929, p. 160) sums up his critical review in the following pertinent words: "In general they are all built upon insecure foundations, hypothetical substances and hypothetical changes that may be due to the processes [effects, V.K.] of senescence and not its cause. Not a single one of all these theories of senescence so far offered has a leg to stand upon; for the greater part they are pure hypotheses constructed about some single fact."

Professor Medawar (1946), in his conclusions, is equally emphatic: "The problems of old age and natural death are hardly yet acknowledged to be within the province of genuine scientific inquiry." He emphasizes that the gerontologist requires many accurate data, scientifically controlled, for his conclusions; he has no time for "anecdotes" and loose statements, such as those concerning very old age in some animals and human beings, various sweeping theories of senescence, etc. He rightly says that the present-day gerontologist is quite aware of the fact that he has to begin "the study of the problem of ageing from scratch," and that gerontologists "would first of all try to piece together a full empirical description of the phenomenon of ageing as it is reflected in structural changes of tissues and cells and, more particularly, in the type and intensity of tissue and cellular metabolism. Only scraps of such information are now available."

The theory recently suggested by Bab (1948) belongs to the same category as defined by Warthin: in this theory one of the two factors on which, according to him, ageing depends is the diencephalon, about which so far we know comparatively little, and the changes in which most probably are the effects of ageing and not one of its primary causes.

Thus it is clear that, until the main facts concerning this problem are discovered and pieced together by experimental and clinical research, gerontologists will not be able to construct any reliable theory of senescence.

Pathological Character of Present Ageing

The greatest difficulty, however, of gerontology is, that we know practically nothing of normal physiological senescence and the normal span of life. Referring to man, Mueller-Deham and Rabson (1942) state that, "in the first place, the old patient is a sick one; and, secondly, the sick patient is an old one." The latter sentence would be more correct in a modified form: "and, secondly, the sick patient is ageing more rapidly."

It is obviously impossible to discover normal features and establish normal standards of physiological senescence unless normal individuals are available: they should possess the best hereditary characters, should live a normal span of life in normal conditions of nutrition and environment, and should be free from any disease that might leave after-effects on their tissues and organs.

It is clear that from this point of view those centenarians who are available at present are deficient in various respects for human gerontological research. To begin with, we do not know whether 109-112 years, the longest span of human life so far registered with reasonable accuracy (Korenchevsky, 1947), really is the longest one and cannot be extended further under

those more normal conditions of existence which will be discovered by science and medicine (Fisher, 1923; Dublin, 1942). The basic elements of normal life, such as proper hygiene and nutrition, are most probably still very far from ideal, in spite of the truly remarkable progress in these fields of physiology and medicine.

Moreover, senescence is complicated and accelerated by those pathological features and diseases which are not necessarily associated with normal old age, since they are not present even in some rare cases of less-pronounced pathological ageing (for example, senile mental deterioration, effects of improper nutrition, accumulation of and auto-intoxication with metabolic products, gastro-intestinal auto-intoxication, hypertension, arteriosclerosis, and certain disorders in the functioning of the heart, liver, kidneys, and glands of internal secretion). Hirsch (1945) shows this fact clearly for arteriosclerosis in one of his careful investigations dealing with the relation of this disease to the processes of ageing.

There are several promising lines of research concerning pathological senility, but only two examples will be mentioned.

1. *Auto-intoxication with Metabolic Waste Products.*—Some results of primary importance have been obtained with tissue cultures in the brilliant experiments of Carrel and his co-workers (1921, 1922, 1937), extended and supplemented by Cohn and Murray (1925), Hoffman *et al.* (1937), Goldschmidt *et al.* (1937), Medawar (1940), and others, and well summarized by Medawar (1946). In cells isolated from the organism and living *in vitro* as a tissue culture senescence and death could be greatly postponed ("indefinitely" as suggested by Carrel, 1937, p. 4) if the metabolic waste products were not allowed to accumulate. In such conditions the "old" cells (i.e., those from older animals) have just as high a capacity of growth as young ones. The old cells merely take a longer time than do the young ones in starting their growth. Professor Pearl (1922), similarly to Carrel, concludes that (p. 75) "senescence appears not to be a primary attribute to the physiological economy of cells as such," and (p. 67) "that the individual cells and tissues of the body, in and by themselves, are potentially immortal."

In connexion with these experiments *in vitro*, Carrel performed a striking although drastic experiment *in vivo*. The experiment has been described by one of his co-workers (Du Nouy, 1936). At the Rockefeller Institute there was a dog nearly 18 years old. The animal never stirred from its corner and could hardly get up to eat. It slept all day, its coat was coming out, its eyes were dim, and the eyelids were stuck together. Nearly two-thirds of its blood was removed, the red cells centrifuged, washed in Ringer solution, then mixed with fresh Ringer solution so as to re-establish the initial volume of the blood and re injected into the dog. After recuperation the operation was repeated. After the second operation the dog not only lived but, when completely recovered, was quite different: it ran and barked, became lively and active—in particular, sexually active—its lids cleared, and its fur started to grow again. Although such a relief could be of a temporary character only, and the actual operation could not be considered for human geriatric research, the significance of the experiment is considerable.

2. *Nutritional Experiments.*—The experiments of Sherman and others (1937, 1939) and McCay (1942) and their co-workers suggest another promising line of gerontological research. They were able to obtain prolongation of the life-span and improvement of the health of rats either by adding an extra amount of vitamins and calcium to a diet already adequate in all respects (Sherman) or by quantitatively restricting such a diet (McCay). Carrel (1937) in experiments on mice obtained results similar to those of McCay.

Of course, the results of experiments on animals do not necessarily mean that the same effects will be obtained on human beings. Research on animals, however, must precede geriatric trials on human beings. Experiments on such short-lived animals as rats and mice give hope for a comparatively more rapid success in obtaining normal individuals with physiological senescence than do clinical trials on human beings. Moreover, attempts to change a pathological senility into a physiological one may perhaps bring about considerable changes in the human organism. This indicates the

possibility of grave danger, perhaps fatal, and necessitates therefore the greatest caution, and only by preliminary research on animals can we ensure absence of dangerous effects. It must also be emphasized that in research on gerontology the study of pathological senescence is as important as that of physiological ageing.

Definition of Old Age, and Tests for the Process of Ageing

At present, gerontologists must unavoidably be satisfied with a definition which disregards the most fundamental fact—namely, that we do not know the causes, features, and standards of normal physiological senescence. It can be expressed only in terms of the processes (effects) of ageing as we can observe them now. Because of this, until our knowledge of the subject is more complete such a definition can only be of a temporary character. Moreover, this definition should be based on facts which have been studied with reasonable accuracy.

From the point of view of these requirements the best definition of ageing has been given by Professor Warthin (1929, p. 74). He constructs it on pathological and clinical observations which have been obtained by all the investigators of the subject; namely, it is agreed that hypoplasia, or atrophy of organs, is one of the most important and typical changes and features of ageing. Hence Warthin defines ageing as a "major involution" of the living organism, of all its organs, tissues, and functions. Since all of them are correlated with and dependent on each other, the involution of each single organ, "once well initiated, may through the weakening or loss of the given function initiate or strengthen retrogressive changes in other organs. The various lines of involution are not wholly independent, but, in the general economy of the organism, aid and supplement one another until various vicious circles and correlations of retrogression are produced." Although this definition deals only with the simplest factual effects of ageing, it is very helpful in indicating various urgent schemes of gerontological research.

In the first place, a detailed investigation of hypoplastic and atrophic changes in the organs and tissues is very important, especially in the earliest latent form of relative hypoplasia as measured by changes in weight or linear measurements of organs and cells. The first results of such research were based on the data independently obtained in two American laboratories (Donaldson, 1924; Freudenberger and Billiter, 1935; Freudenberger and Clausen, 1937a, 1937b; Freudenberger and Hashimoto, 1937, 1939; Freudenberger and Howard, 1937) and in the Oxford Gerontological Research Unit (Korenchevsky, 1942, 1948; Korenchevsky and Jones, 1946, 1947, 1948). These data are in complete agreement and show that the relative decrease in weight of organs (relative involution) can be used as one of the tests for and indications of ageing in rats. Most probably this test will be reliable also for human material, as shown by investigations and recalculations (Korenchevsky, 1942) of the data so far available.

The test appears to be not only as good as many other tests of ageing but of great importance because it deals with one of the main changes and features both of ageing and of old age. It has to be supplemented, however, at least by histological examination.

At present, however, every test or indicator of ageing is handicapped by two difficulties. First, it is not known whether our tests will be valid for the processes of normal physiological senescence. Secondly, practically no feature of present-day senescence can be regarded as specific for old age only. Any of them might be present in or after some diseases, or occur in the changes produced by mental or physical stress and duress, or develop in or after some other pathological conditions. For example, in some rare cases the hair does not become grey in old age, whilst in some young ones it becomes grey in a very short time under the stress of an emotional crisis. In young rats certain vitamin deficiencies produce greying of fur (Unna *et al.*, 1941; Ansbacher, 1941; Ralli and Graef, 1943), atrophic skin (Morgan and Simms, 1939), and osteoporosis (Korenchevsky, 1922). Baldness might start to develop at an early age, or (Hamilton, 1942) can be produced by suitable doses of androgens.

A premature appearance of senile wrinkled skin was observed and described by Merschejewsky (1876), Pelikan (1876), Pittard

(1934), and Tandler and Grosz (1913) in castrated men. Arteriosclerosis, hypertension, senile kidneys, senile heart, etc., might be almost absent in some cases of senescence. For instance, Hirsch (1945) did not find any signs of arteriosclerosis in 9.5% of autopsies in 400 old men aged more than 65 and examined by him.

From all the above-mentioned facts it follows that in present-day gerontological research a correct understanding and an accurate definition of the processes of ageing, or of the anti-ageing properties of any factor examined, could be obtained only after performance of several morphological, physiological, and biochemical investigations, both experimental and clinical (Korenchevsky, 1948). Since such a manifold investigation is technically impossible for a single research worker, the conclusions which he makes have to be drawn with reservations as judged by the test (or tests) of ageing applied in the experiments performed.

Causes of Ageing

So far we do not know the *main primary causes* of ageing, nor are we able to begin investigation of them before cases of normal physiological senescence are available. Heredity, according to some research workers (e.g., Pearl, 1922, 1931; Pearl and de Witt Pearl, 1934), influences longevity. If this is so, future research might discover a hereditary factor which has a connexion with the primary causes of ageing. Dublin and Marks (1942), however, emphasize difficulties of such research in man: "There may be strong beneficial influences from survivorship of parents on longevity of offspring . . . and these influences may have nothing whatever to do with heredity."

Professor Child (1915), one of the first gerontologists to have a sharp insight into and clear understanding of the problems of ageing, concludes in these words in dealing with the importance of heredity for geriatric research (p. 310): "The advance of knowledge and of experimental technique may make it possible at some future time to bring about a greater degree of rejuvenescence and retardation of senescence in man and the higher animals than is now possible, but when we remember that the present condition of the protoplasmic substratum of these organisms is the result of millions of years of evolutionary equilibration we cannot but admit that this task may prove to be one of considerable difficulty."

In the case of the *secondary causes of ageing* the possibilities for gerontological research are more satisfactory. These causes should be defined as non-specific but capable only of hastening the process of ageing. A great number of the secondary causes might include any of those non-specific factors which increase "wear and tear" and involution, general or only of one or more organs or tissues. They *accelerate* the main process of ageing, chiefly by producing "secondary vicious circles of ageing" (Warthin).

Infectious diseases, intoxications, deficiencies of vitamins or hormones or any other vital factor, any pathological changes in any tissue, organ, or blood vessels, physical or mental traumas, etc., might belong to this category. For example, hypothyroidism might produce a number of features of senility, even (Hertoghe, 1899) in the form of mild deficiency. Castrated men often develop some senile changes prematurely (Merschejewsky, 1876; Korsakow, 1898; Pittard, 1934), although they might preserve their mental faculties. Thus Korsakow writes (p. 340): "The eunuchs are ageing early, at the age of 40 producing an impression of 60-year-old men." Professor Pittard (p. 327) records: "The men castrated after puberty appear to age very rapidly, as also their congeneric fellows do, who have been castrated early. They become prematurely wrinkled and acquire soon the appearance of old women." In a patient with diphtheria the toxin producing degenerative changes in the heart accelerates its ageing, but obviously this is not one of the primary causes of physiological senile changes in that organ.

It is obviously illogical, however, to expect (as some authors do) that a secondary cause can *produce the whole* complex of ageing in all organs, tissues, and their functions when this cause is able to accelerate sometimes only a single process of senescence in one organ or tissue. Moreover, the secondary causes of senescence, not being the primary causes of ageing, produce chiefly their own primary action according to their functional nature (for example, effects specific for each

hormone or vitamin, or their deficiency). This action, although accelerating senile change or changes in some organs, in one or two other organs simultaneously might produce an effect which is typical of the specific function only but not of senility (e.g., a delay in thymus involution and, in male rats, adrenal hypertrophy after castration). It is an urgent task to investigate all these secondary causes and their vicious circles in order to illuminate their possible role in the senility complex and to understand how to break these vicious circles for geriatric purposes. From this point of view investigation of endocrine organs is specially important.

In the Oxford Gerontological Research Unit (Korenchevsky and Jones, 1946, 1947, 1948) an approach to this problem gave some significant results. Changes in the relative weights, and histological examination, showed that in female rats ovariectomy accelerates, and the combination of sex and thyroid hormones reverse more or less completely, the relative involution in the organs investigated. It was, however, strongly emphasized that in these experiments, as in any other research on ageing, the gerontological interpretation of the results obtained is impossible without manifold morphological, physiological, and biochemical experiments (Korenchevsky, 1948). It is obvious that ovariectomy might belong only to the group of secondary causes of ageing and therefore alone could never produce the whole syndrome of ageing, nor, for the same reasons, could hormones reverse this syndrome.

Moreover, since the action of the secondary causes, in particular that of ovariectomy, is not specifically ageing, and since the hormones might belong to the secondary reverse factors only—i.e., non-specific ones—discrepancies between the changes produced by them and the ageing or anti-ageing effects respectively are always possible. For example, androgens increase the involution of adrenals, whilst exerting an anti-involutionary effect on other organs investigated; ovariectomy at the beginning delays the involution of the thymus, but accelerates that process in some other organs. The clear predominance and importance of the special effects decide the gerontological significance of the factor concerned.

Summary

Gerontological research is handicapped by the basic difficulties of the problem; the span of life and the process of ageing are abnormal, and therefore the normal standard features and the primary causes of physiological senescence and old age are unknown.

It is possible, however, to investigate the secondary causes of ageing and pathological senescence as observed at present. This research is as important to gerontology as is that on physiological old age.

A definition of the secondary causes of ageing is given and the value of the present-day tests for ageing is discussed.

REFERENCES

- Ansbacher, S. (1941). *Science*, **93**, 164.
 Bab, H. (1948). *British Medical Journal*, **1**, 1000.
 Carrel, A., and Ebeling, A. H. (1921). *J. exp. Med.*, **34**, 599.
 — (1922). *Ibid.*, **35**, 17.
 — (1937). *The Problem of the Prolongation of Life*. New York.
 Child, C. M. (1915). *Senescence and Rejuvenescence*. Chicago.
 Cohn, A. E., and Murray, H. A. (1925). *J. exp. Med.*, **42**, 275.
 Donaldson, H. H. (1924). *The Rat*. Philadelphia.
 Dublin, L. I. (1942). In E. V. Cowdry's *Problems of Ageing*, p. 108. Baltimore.
 — and Marks, H. H. (1942). *The Inheritance of Longevity*, p. 32. New York.
 Du Nouy, L. (1936). *Biological Time*, p. 115. London.
 Fisher, I. (1923). *Report on National Vitality, Its Wastes and Conservation*, p. 103. Washington.
 Freudenberg, C. B., and Billiter, O. A. (1935). *Endocrinology*, **19**, 347.
 — and Clausen, F. W. (1937a). *Anat. Rec.*, **68**, 133.
 — (1937b). *Ibid.*, **69**, 171.
 — and Hashimoto, E. I. (1937). *Amer. J. Anat.*, **62**, 93.
 — (1939). *Proc. Soc. exp. Biol., N.Y.*, **41**, 530.
 — and Howard, P. M. (1937). *Ibid.*, **36**, 144.
 Goldschmidt, J., Hoffman, R., and Doljanski, L. (1937). *C.R. Soc. Biol., Paris*, **126**, 389.
 Hamilton, J. B. (1942). *Amer. J. Anat.*, **71**, 451.
 Hertoghe, E. (1899). *Nouv. Iconogr. Salpêtr.*, **12**, 267.
 Hirsch, S. (1945). *Brux.-med.*, **25**, 419.
 Hoffman, R. S., Goldschmidt, J., and Doljanski, L. (1937). *Growth*, **1**, 228.
 Korenchevsky, V. (1922). "The Aetiology and Pathology of Rickets from the Experimental Point of View." *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 71, London.
 — (1942). *J. Path. Bact.*, **54**, 13.
 — (1947). *British Medical Journal*, **2**, 14.
 — (1948). *Ibid.*, **1**, 728.
 — and Jones, V. E. (1946). *J. Geront.*, **1**, 319, 336.
 — (1947). *Ibid.*, **2**, 116.
 — (1948). *Ibid.*, **3**, 21.
 Korsakow, W. (1898). *Dtsch. med. Wschr.*, **24**, 338.
 McCay, C. M. (1942). In E. V. Cowdry's *Problems of Ageing*, p. 680. Baltimore.
 Medawar, P. B. (1940). *Proc. roy. Soc. B*, **129**, 332.
 — (1946). *Mod. Quart.*, **1**, 30.
 Merschejewsky, W. O. (1876). "Beilagen" in Pelikan's (1876) book, p. 15.
 Morgan, A. F., and Simms, H. D. (1939). *Science*, **89**, 565.
 Mueller-Deham, A., and Rabson, S. M. (1942). *Internal Medicine in Old Age*, p. 40. Baltimore.
 Pearl, R. (1922). *The Biology of Death*. Philadelphia.
 — (1931). *Hum. Biol.*, **3**, 245.
 — and De Witt Pearl, R. (1934). *The Ancestry of the Long-lived*. Baltimore.
 Pelikan, E. (1876). *Gerichtlich-medizinische Untersuchungen über das Skopzen-thum in Russland*. Giessen.
 Pittard, E. (1934). *La castration chez l'homme et les modifications morphologiques qu'elle entraîne*. Paris.
 Ralli, E. P., and Graef, I. (1943). *Endocrinology*, **32**, 1.
 Sherman, H. C., and Campbell, H. L. (1937). *J. Nutr.*, **14**, 609.
 — and Lanford, P. S. (1939). *Proc. Amer. Acad. Sci.*, **25**, 16.
 Tandler, J., and Grosz, S. (1913). *Die biologischen Grundlagen der sekundären Geschlechtscharaktere*. Berlin.
 Unna, K., Richards, G. V., and Sampson, W. L. (1941). *J. Nutr.*, **22**, 553.
 Warthin, A. S. (1929). *Old Age, the Major Involution*. New York.

MEDICAL NEW YEAR HONOURS

The names of the following members of the medical profession were included in a New Year Honours List published in the *London Gazette* on Jan. 1.

Baron

Sir JOHN BOYD ORR, D.S.O., M.C., M.D., D.Sc., LL.D., F.R.S. Lately Director-General of the Food and Agriculture Organization of the United Nations.

Privy Councillor

EDITH CLARA SUMMERSKILL, M.R.C.S., L.R.C.P., M.P. Member of Parliament for West Fulham since 1938. Parliamentary Secretary, Ministry of Food, since 1945.

G.B.E. (Civil Division)

Sir WILLIAM WILSON JAMESON, K.C.B., M.D., F.R.C.P. Honorary Physician to the King. Chief Medical Officer, Ministry of Health and Ministry of Education.

K.C.V.O.

Sir WILLIAM GILLIATT, C.V.O., M.D., M.S., F.R.C.P., F.R.C.S. President of the Royal College of Obstetricians and Gynaecologists.

Knighthood

HENRY COHEN, M.D., F.R.C.P. Professor of Medicine in the University of Liverpool.

HUGH ERNEST GRIFFITHS, C.B.E., M.S., F.R.C.S., Surgeon, Albert Dock Hospital, London, E. For services in the industrial rehabilitation of disabled persons.

SYDNEY ALFRED SMITH, C.B.E., M.D., F.R.C.P.Ed. Regius Professor of Forensic Medicine and Dean of the Faculty of Medicine in the University of Edinburgh.

C.B. (Military Division)

FREDERICK HARRIS, C.B.E., M.C., M.B., B.Ch., late Royal Army Medical Corps. Honorary Surgeon to the King.

LIONEL FREDERICK STRUGNELL, M.B., B.S. Surgeon Rear-Admiral, Royal Navy. Honorary Physician to the King.

C.M.G.

ARTHUR BARTON PILGRIM AMIES, D.D.Sc., F.R.A.C.S., F.A.C.D., D.L.O. Professor of Dental Science in the University of Melbourne.

THOMAS AITKEN AUSTIN, L.R.C.P.&S.I., D.P.H., D.T.M., D.T.H. Colonial Medical Service. Director of Medical Services, Uganda.

RICHARD BRUNEL HAWES, M.B., B.S., F.R.C.P., D.T.M.&H. Consulting Physician to the Colonial Office.

MONTAGU TRAVERS MORGAN, M.C., M.D., D.P.H. Medical Officer of Health, Port of London. Medical Adviser, Ministry of Transport.

C.B.E. (Military Division)

ROBERT WALSH MUSSEN, M.D., M.R.C.P. Surgeon Captain, Royal Navy.

C.B.E. (Civil Division)

WILLIAM ARTHUR BULLOUGH, M.Sc., M.B., Ch.B., D.P.H. County Medical Officer for Essex.

JOHN BURTON CLELAND, M.D., Ch.M. Formerly Professor of Pathology in the University of Adelaide.

EMILY HANCOCK MCKINNON, M.B., B.Ch., of Dunedin, New Zealand. For services in the field of medicine and welfare of women.

NORMAN MANSON, M.B., Ch.B., D.O.M.S. Warden, Hospital of St. John, Jerusalem.

WILLIAM BENTLEY PURCHASE, M.C., M.B., D.P.H. H.M. Coroner for the Northern District of London.

WILLIAM ROBERTS, M.D., F.R.C.S. Medical Superintendent, Grace Hospital, Newfoundland.

O.B.E. (Military Division)

STEPHEN MACKENZIE, M.R.C.S., L.R.C.P., D.C.H. Lieutenant-Colonel (temporary) (now Major), Royal Army Medical Corps.

SIDNEY RICHARD CARLYLE NELSON, M.D., M.C.P.&S. Wing Commander, Royal Air Force.