THE BIOLOGY OF SENESCENCE

A review of the biology of Ageing in man and animals

Alex Comfort

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by

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PREFACE

THIS book is a compilation. It was written as an aid to my own research, in a subject where it is difficult to know where to begin, but I hope that the references, at least, will be useful to others.

The denunciation of a subject and its current theoretical basis as 'unsatisfactory' is a relatively easy exercise—dealing with it satisfactorily is quite another matter. No biological treatment of senescence can hope to be satisfactory in the absence of a great deal of factual information which at present is not there. I have attempted to collect as much of this information as possible: since most of it comes from fields in which I have no experience, there are bound to be errors both of fact and of deduction in such a survey, and I hope that they will be pointed out to me.

I am deeply grateful to Professor Peter Medawar, F.R.S., under whom I have worked, to Professor J. B. S. Haldane, F.R.S., for kindly drawing my attention to a number of references I would not otherwise have seen, and to many colleagues whom I have molested for information or criticism, and whose help and advice has been invaluable, though they bear no responsibility for the result. I am also profoundly indebted to the Nuffield Foundation for several years' financial support, to Dr. Harrison Matthews, Director of the London Zoo, for access to its records, and to Miss Rosemary Birbeck for much help in preparing the manuscript and bibliography.

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MAN throughout history, and every individual since his childhood, has been aware that he himself, and those animals which he has kept in domestication, will undergo an adverse change with the passage of time. Their fertility, strength and activity decreases, and their liability to die from causes which, earlier in life, they could have resisted, increases.

This process of change is senescence, and senescence enters human experience through the fact that man exhibits it himself. This close involvement with human fears and aspirations may account for the very extensive metaphysical literature of ageing. It certainly accounts for the profound concern with which humanity has tended to regard the subject. To a great extent human history and psychology must always have been determined and moulded by the awareness that the life-span of any individual is determinate, and that the expectation of life tends to decrease with increasing age. The Oriental could say 'O King, live for ever!' in the knowledge that every personal tyranny has its term. Every child since the emergence of language has probably asked 'Why did that man die?' and has been told 'He died because he was old.'

Interesting psychological and historical speculation could be made on the part which this awareness has played in human affairs. From the biologist's standpoint, its main importance has been the bias which it has injected into the study of senescence. The child who asks the question, and receives the answer, is familiar with 'old' clothes and 'old' toys. He has always known that he, his pets, his cattle and his neighbours will become increasingly prone to breakdown and ultimate death the older they get. He has observed from the nursery that inanimate and

mechanical systems also deteriorate with the passage of time. He appears at a later age to derive some degree of comfort from the contemplation of the supposed generality, universality and fundamental inherence of ageing—or alternatively from drawing a contrast between Divine or cosmic permanence and his own transience. However inspiring this type of thinking may have been—and it features largely in the past artistic and philosophical productions of all cultures—its influence and its incorporation as second nature into the thought of biologists throughout history has seriously handicapped the attempt to understand what exactly takes place in senescence, which organisms exhibit it, and how far it is really analogous to processes of mechanical wear. One result of the involvement of senescence with philosophy and the 'things that matter' has been the prevalence of attempts to demonstrate general theories of senile change, including all metazoa and even inanimate objects, and having an edifying and a metaphysical cast. Prominent among these have been attempts to equate ageing with development, with the 'price' of multicellular existence, with hypothetical mechano-chemical changes in colloid systems, with the exhaustion induced by reproductive processes, and with various concepts tending to the philosophical contemplation of decline and death.

It is not unreasonable to point out that these theories have for the most part deeper psychological and anthropological than experimental and observational roots. Some of them have a few facts on their side. 'Reproductive exhaustion' does appear to induce senescence in fish and in mollusca, and flowering is a proximate cause of death in monocarpic plants, but the general concept, especially when it is made a universal, owes a large debt to the widespread belief in human cultures that sexuality 'has its price'. Extensions of mechanical analogies from the wearing out of tools to the wearing out of animal bodies are justifiable in a limited number of cases where structures such as teeth undergo demonstrable wear with use, and where this process limits the life of the organism; but they have also shown a tendency to become generalized in the hands of biologists who are devoted for philosophical, political or religious reasons, to mechanism in the interpretation of human behaviour. State-

ments that 'senescence is no more than the later stage of embryology' resemble Benjamin Rush's great discovery, that all disease is disordered function. They belong to the category of word-rearrangement games, which have long been played in those fields of study where there is as yet no 'hard news'.

Although the religious, poetic, metaphysical and philosophical literatures of senescence will not be examined here, the detection and examination of analogies based upon them, which have had a great, and generally adverse, influence on the growth of our knowledge of age processes, must clearly play a large part in any critical examination of the subject. The comments of Francis Bacon, who was both a philosophical originator of the scientific method, and the first systematic English gerontologist,[1] provide one of the best critiques of the influence of such analogies and thought-patterns, and they will be quoted without scruple here.

The practical importance of work upon the biology of senescence, beyond the fundamental information which such work might give about the mechanisms of cell differentiation and renewal, can best be seen from the diagrams at Fig. 1–3 and 7. The advance of public health has produced a conspicuous shift in the shape of the survival curve in man so far as the privileged countries are concerned, from the oblique to the rectangular form. This has been due almost entirely to a reduction in the mortality of the younger age groups—the human 'specific age' and the maximum life-span have not been appreciably altered. The medical importance of work on the nature of ageing lies at present less in the immediate prospect of spectacular interference with the process of senescence than in the fact that unless we understand old age we cannot treat its diseases or palliate its unpleasantness. At present age-linked diseases are coming to account for well over half the major clinical material in any Western medical practice. The physician is constantly referring to the biologist for a scientific basis for geriatrics, and finding

[1] I dislike this word, but it is probably too well grown for eradication. It should mean 'a student of old men' (*γέρων*) and gerontology the study of old men. For the study of age itself, the subject of this book, we require geratology (*γῆρας*), upon which it would be fruitless to insist.

that it is not there. The amount of material on which such a foundation could be built has increased, though not very rapidly, during the present century. Its quantity is still inversely proportional to the importance of the subject.

There are not many adequate reviews of the modern biological literature. The most recent are those of Lansing (1951, 52). A previous review of mine contains little which is not repeated here (Comfort, 1954). Some of the more celebrated 'general theories' have received spirited treatment in a review by Medawar (1945). The literature of animal population statistics has been reviewed by Deevey (1947) and that of invertebrate senescence by Szabó (1935) and by Harms (1949). It is a pleasure to acknowledge my indebtedness to these reviews and to the bibliography of Shock (1951). A great deal of clinico-pathological material upon the age-incidence of various human diseases and the weights of organs throughout life has been collected by Bürger (1954). In a depressingly large number of fields, there has been little new information in the last twenty years. Other reviews of specific topics will be cited in their place. The senescence of plants is not discussed here: it has been reviewed in some detail by Crocker (1939), to whose paper there seems little to add.

Senescence is probably best regarded as a general title for the group of effects which, in various phyla, lead to a decreasing expectation of life with increasing age. It is not, in this sense, a 'fundamental', 'inherent', or otherwise generalizable process, and attempts to find one underlying cellular property which explains all instances of such a change are probably misplaced. It is important and desirable to recognize the origins of many such general theories, which owe much to folk-lore on one hand and to the emotional make-up of their authors on the other. The demoralizing effect of the subject of senescence, even upon biologists of the highest competence and critical intelligence, is well illustrated by the following passage from Pearl (1928), the father of animal actuarial studies:

'(Somatic death in metazoa) is simply the price they pay for the privilege of enjoying those higher specializations of structure and function which have been added on as a sideline to the

main business of living things, which is to pass on in unbroken continuity the never-dimmed fire of life itself.'

Warthin (1929), whose insistence upon the fundamental impossibility of modifying the tempo of human ageing, now or at any time in the future, has an orgiastic tone quite out of keeping with the rashness of such a prediction, writes:

'We live but to create a new machine of a little later model than our own, a new life-machine that in some ineffable way can help along the great process of evolution of the species somehow more efficiently than we could do were we immortal. The Universe, by its very nature, demands mortality for the individual if the life of the species is to attain immortality through the ability to cope with the changing environment of successive ages. . . . It is evident that *involution* is a biologic entity equally important with *evolution* in the broad scheme of the immortal process of life. Its processes are as *physiologic* as 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 *pathologic* should be cast upon this process. What its exact chemicophysical mechanism is will be known only when we know the nature of the *energy-charge* and the *energy-release* of the cell. We may say, therefore, that age, the major involution, is due primarily to the gradually weakening *energy-charge* set in action by the moment of fertilization, and is dependent upon the potential fulfillment of function by the organism. The immortality of the germ plasm rests upon the renewal of this energy charge from generation to generation.'

This passage is highly typical of the literature of old age to the present day. There can be few branches of biology in which uplifting generalization of this kind has so long been treated as a respectable currency for scientific thought.

In general, the more elaborate the attempts to depict senescence in overall mathematical terms, the more intellectually disastrous they have proved. One of the most celebrated incursions of metaphysics into biology, that which postulates a separate 'biological time', is best expounded in the words of its sponsor, Lecomte du Noüy (1936):

'When we refer to sidereal time as being the canvas on which the pattern of our existence is spread, we notice that the time needed to effectuate a certain unit of physiological work of repair is about four times greater at fifty than at ten years of age. Everything, therefore, occurs as if sidereal time flowed four times faster for a man of fifty than for a child of ten. It is evident, on the other hand, that from a psychological point of view many more things happen to a child in a year than to an old man. The year therefore seems much longer to the child. . . . Thus we find that when we take physiological time as a unit of comparison, physical time no longer flows uniformly. This affirmation revolts one if the words are taken in a literal sense. But . . . the expression "flow of time" . . . is entirely false and does not correspond to a reality. When . . . we say that physical time measured by means of a unit borrowed from our physiological time no longer flows uniformly, it simply means that it does not *seem* to flow uniformly . . . Must one consider this fact as the indication of a difference of magnitude between our short individual period and the immense periods of the universe? Must we see a proof of the existence of such periods? Who knows? All that we can say at present is that our crude language, lacking appropriate words, translate this knowledge into improper, inadequate expressions such as "There are two species of time" or "Physiological time does not flow uniformly like physical time" . . . We must not let ourselves be duped by these words, etc. . . .'

It is startling how many distinguished biologists have subsequently quoted the notion of a distinct 'biological' time with apparent sanction. The alcoholic who draws on his bottle irregularly will find that its progress towards emptiness follows an irregular scale, 'alcoholic time', so that judged by the rate of emptying of the bottle, 'sidereal' time appears to progress unevenly. But variation in rate is hardly an occult, or even an unfamiliar, phenomenon. Like others before him, du Noüy has gone down clutching a platitude and come up embracing a metaphysical system.

In almost any other important biological field than that of senescence, it is possible to present the main theories historic-

ally, and to show a steady progression from a large number of speculative, to one or two highly probable, main hypotheses. In the case of senescence this cannot profitably be done. The general theories of its nature and cause which have been put forward from the time of Aristotle to the present day have fallen into a number of overall groups, and have been divided almost equally between fundamentalist theories which explain all senescence, or treat it as an inherent property of living matter or of metazoan cells, and epiphenomenalist theories which relate it to particular physiological systems or conditions. They are also fairly evenly divided between the various categories of Baconian idola. It is a striking feature of these theories that they show little or no historical development; they can much more readily be summarized as a catalogue than as a process of developing scientific awareness. To the fundamentalist group belong, in the first place, all theories which assume the existence of cellular 'wear and tear' (*Abnutzungstheorie*) without further particularization (Weismann, 1882; Pearl, 1928; Warthin, 1929); the mechanochemical deterioration of cell colloids (Bauer, Bergauer, 1924; Růžická, 1924; 1929; Dhar, 1932; Lepeschkin, 1931; Szabó, 1931; Marinesco, 1934; Kopaczewski, 1938; Georgiana, 1949); and pathological or histological elaborations of these, which attribute senescence to inherent changes in specified tissues, nervous (Muhlmann, 1900, 1910, 1914, 1927; Ribbert, 1908; Vogt and Vogt, 1946; Bab, 1948), endocrine (Lorand, 1904; Gley, 1922; Dunn, 1946; Findley, 1949; to cite only a few from an enormous literature in which the endocrine nature of mammalian senescence is discussed, stated or assumed), vascular (Demange, 1886), or even connective (Bogomolets, 1947). To the epiphenomenalist group belong toxic theories based on products of intestinal bacteria (Metchnikoff, 1904, 1907; Lorand, 1929; Metalnikov, 1937), accumulation of 'metaplasm' or of metabolites (Kassowitz, 1899; Jickeli, 1902; Montgomery, 1906; Muhlmann, 1910; Molisch, 1938; Heilbrunn, 1943; Lansing, 1942; etc.), the action of gravity (Darányi, 1930), the accumulation of heavy water (Hakh and Westling, 1934) and the deleterious effect of cosmic rays (Kunze, 1933). There are also general developmental theories which stress the continuity of senescence with

morphogenesis (Baer, 1864; Cholodkowsky, 1882; Roux, 1881; Delage, 1903; Warthin, 1929) or the operation of an Aristotelean entelechy (Driesch, 1941; Bürger, 1954), metabolic theories introducing the concept of a fixed-quantity reaction or of a rate/quantity relationship in determining longevity (Rubner, 1908; Loeb, 1908; Pearl, 1928; Robertson, 1923), attainment of a critical volume-surface relationship (Muhlmann, 1910 etc.), depletive theories relating senescence to reproduction (Orton, 1929) and finally an important group of theories which relate senescence to the cessation of somatic growth (Minot, 1908; Carrel and Ebeling, 1921; Brody, 1924; Bidder, 1932; Lansing, 1947, 1951). Most of the older theories have been reviewed, against a background of Drieschian neovitalism, in the textbook of Bürger (1954).

The distribution of dates in this catalogue sufficiently indicates the state of the subject. When Francis Bacon examined the relationship between animal specific longevity, growth-rate, size and gestation period, he concluded that the available facts were unfortunately insufficient to support a general theory. That conclusion remains valid in practically all the instances quoted, but Bacon's self-denial failed to set a precedent for his successors. Almost all these theories, judging from the literature, continue at some point to influence biological thinking: some can be partially, or even largely, justified by the suitable selection of instances. Others did not bear critical inspection at the time they were first formulated, bearing in mind the known behaviour of cells, and the known discrepancies in longevity and in rate of ageing between animals of similar size, histological complexity, and physiological organization. Relatively few are supported by any body of fundamental experiment. The devising of general theories of senescence has employed able men, chiefly in their spare time from laboratory research, for many years. It seems reasonable to assume that almost all the mechanisms which might theoretically be involved have been considered, and if we are to understand what does in fact occur in a given ageing organism, we now need a combination of general observation with planned causal analysis in experimental animals.

The main theories of ageing will be discussed in the text.

There are, however, a few which should be outlined in greater detail here—either because they are still of importance, or because, though untenable, they have a considerable surviving influence.

The most influential nineteenth-century contribution to this second category was probably that of Weismann, whose theory sprang directly from his distinction between germ plasm and soma. Weismann regarded senescence as an inherent property of metazoa, though not of living matter, since he failed to find it in protozoans and other unicellular organisms. Its evolution had gone hand in hand with the evolution of the soma as a distinct entity, and it was the product of natural selection, arising like other mutants by chance, but perpetuated as a positively beneficial adaptation, because 'unlimited duration of life of the individual would be a senseless luxury'. 'Death', according to this view, 'takes place because a worn-out tissue cannot forever renew itself. . . . Worn-out individuals are not only valueless to the species, but they are even harmful, for they take the place of those which are sound' (1882). This argument both assumes what it sets out to explain, that the survival value of an individual decreases with increasing age, and denies its own premise, by suggesting that worn-out individuals threaten the existence of the young. It had the advantage, however, of being an evolutionary theory, and we shall see later that this is the only type of theory which today seems likely to offer a general approach to the emergence of senescence in all the groups which exhibit it. The idea that all somatic cells must necessarily undergo irreversible senescence was challenged early in the century by the studies of Child (1915) upon planarians, and of Carrel (1912) upon tissue culture. The assumption that all higher metazoa must *ex hypothesi* exhibit senescence, however, dies hard, and the fallacious argument based on selection has been repeated as recently as 1937 (Metalnikov, 1936, 1937).

A considerable number of *metabolic theories* were based on the fact that an inverse relationship exists between length of life and 'rate of living'. On the basis of calorimetric experiments, Rubner (1908, 1909) calculated that the amount of energy required for the doubling of weight by body growth was approximately equal in a number of mammals. The energy