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Minireviews

The biological aging process

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In any particular field of research it is advisable, from time to time, to take stock and reconsider the 'state of the art', and to re-formulate, in the light of scientific developments and one's personal reflections, the aims and targets for future work. It seems to me that such a time has come for experimental research on aging, and I want to say, quite briefly, where, in my view, we stand today and suggest which directions research into the process of aging might take in the future. In the short space available here it will of course not be possible to deal exhaustively with such a complex problem. It is my intention to discuss a few selected points which presently appear to me of highest interest.

Perhaps the only fact that all those engaged in aging research will agree on is that the individual lifespan of animals (or at least of mammals) – and of man – is limited by biological factors. It has not required modern experimental science to uncover this fact; it is, for example, stated *expressis verbis* in Christoph Wilhelm Hufeland's admirable and still quite contemporary treatise 'Macrobiotics: The art of Prolonging Life'[1], first published in Jena, 1798. The great physician states clearly and as accepted fact that for each animal species and for mankind there is an upper limit to lifespan, that this limit is fixed, is different and specific for each species, and that for man it has not changed since the earliest written records of human history. Recent careful study by phylogenetic analysis, with the help of an empirical equation using brain- and body weight estimations from fossils, has led to the conclusion that for *Homo sapiens* the maximum potential lifespan (Hufeland's 'absolute' lifespan as opposed to 'relative' or average lifespan of a particular selected population) has remained unchanged at around 95 years for the past 100,000 years[2].

This is certainly the basic tenet of gerontology which has stood firm ever since the hapless search for the Fountain of Youth and the Philosopher's Stone of the Middle Ages. As long as we remain *Homo sapiens* we must face the fact that we are mortal, that our days are numbered, and that nothing can be done about it. There is a fixed, immutable upper limit to our length of life. I am quite aware that there are people who, for personal or ideological reasons, refuse to accept such a deterministic view, and who think that lifespan can be lengthened by a factor of 2–3 merely through the proper biochemical manipulation of metabolism. I am stating here my own views and beliefs.

Nobody has put this into clearer and more convincing terms than Fries and Crapo in their recent booklet, 'Vitality and Aging'[3]. I believe the time has come for all of us engaged in one way or another in aging research to accept their concept that attaining the 'rectangular society' is the real and practical aim of our work. The 'rectangular society' means that for any human (or mammalian) population, individual lifespans come as close to the species-specific lifespan potential as possible: then the shape of the survival

curve for that population approaches the shape of a rectangle, with almost all deaths occurring within a very short period of time close to the defined upper limit. We are all familiar with the graphs showing groups of survival curves for different human populations and the change in their pattern over the past 100 years[4], and we are aware that while average lifespan and life expectancy at birth have increased dramatically during this time, the ends of all curves still meet at the same age: around 100 years. Clearly, we are already approaching the 'rectangular society', and it does not seem to me to be the merit of aging research. This 'rectangularization' of human survival curves is the result of improved standards of living, of hygiene, of medical care, and of various sociological factors.

If mankind as a species is approaching its optimal survival curve, what than should the aims of experimental gerontology be? For one thing, it is obvious that there are still too many life-shortening factors active in even the most developed and healthy societies. As Fries and Crapo[3] point out, the linear decline - from about age 30 years onward - of the averages for many physiological functions, which has been one of the basic pieces of evidence in favor of a universal biological aging process, is not at all convincing or even necessarily correct: the increasing variability of physiological and biochemical parameters with increasing chronological age (the curse of every experimental gerontologist) makes averages increasingly meaningless, even in the most standardized of laboratory animal stocks. If we plot all individual points at all individual ages, another picture emerges, one of which we have probably always been aware, but which we have perhaps too often suppressed in favor of statistics, means and variances: in some individuals, there is scarcely any loss of functions up to the highest age, approaching the biological limit. In others, losses of functions occur well before the biologically normal age. The real, 'normal' biological aging process clearly lies in the top points of the plot and not in any of the lower, less-than-optimal points. If we then want to draw a graph or curve of 'normal' losses in physiological functions with increasing chronological age, we must use only these topmost points. Ideally, of course, this should be done in a longitudinal study of a cohort of many individuals up to the last death, but we know that this is not a practical possibility. We will probably find a linear age-dependent decrease in many functions even then, but with much more gradual age-slopes than for the usual averages. Ideally, each individual should age along the topmost slope of functional loss, the smallest possible loss per unit time: then we will have reached the rectangular survival curve. Fries and Crapo[3] suggest a tentative list of physiological parameters that cannot be manipulated and that represent 'true' aging, and another list of those where the present averages are well below the possible optima: here lies much room for improvement, and this is an area where much more research is needed: why do so many individuals still live and function well below their potential?

One can object at this point that it is surely the genetic variability of the average population that is at the root of the variability in physiological functions. Recently Lints[5] has extensively discussed the available evidence on a genetic control of aging and death. The difficulty is that we should treat these two factors separately. Neither the concept that death is merely the final result of a biological (genetically controlled?) aging process, nor, conversely, the concept that aging is an obligatory precursor of a (genetically controlled?) 'natural' death is necessarily true. Undoubtedly there must be some form of genetic control of maximum lifespan potential. But must then a physiological aging process also be under genetic control? There is room for doubt. The idea of specific 'aging genes', positively controlling deleterious 'aging events', may in any case be abandoned.

There are classical examples of animal species where lifespan seems to be directly controlled by defined physiological events: the Pacific migratory salmon which shows 'parental death' after first spawning; and bats, which have unusually long lifespans compared to small terrestrial rodents of similar body weight. Can we deduce from these a physiological control of maximal potential lifespan? When we look closely at these cases, it does not appear to be so. In the case of the migratory Pacific salmon, the rapid death after spawning is due to a more than 5-fold rise in adrenal corticoid steroid levels[6]. The animals die in a state of adrenal corticoid toxicosis. If sexual development is prevented by early castration, such salmon can live up to twice the 'natural' lifespan. If, on the other hand, nonmigratory rainbow trout, which 'normally' live much longer than the migratory salmon, are implanted with hydrocortisone pellets, the same degenerative changes are elicited. Thus we have here a hormone causing premature aging and death, well before the maximal potential lifespan. The unusually long maximal lifespans of the Chiroptera (bats), up to 20 years compared to about 4 years for mice, has been attributed to hibernation, with its slowing of metabolic rate. While bats do in fact have generally lower body temperatures and metabolic rates than small rodents[7], it is surprising that temperate zone bats (which hibernate) as well as tropical bats (which do not) have similar maximal lifespans[8]. In spite of the fact that the tropical species have higher metabolic rates, they do not show the expected lower lifespans. This does not support the classical hypothesis of Rubner (1908) that longevity is essentially determined by metabolic rate. The long lifespans of bats in general seem to be the result of daily torpor, with lowered body temperature

(partial poikilotherms), which is found in both temperate and tropical species.

If the 'rectangular society', and in consequence the rectangular individual life-curve, is the end of the way, then indeed we come to the concept of life as the 'Wonderful One Hoss Shay' that forms the theme of Fries' and Crapo's[3] book: In Oliver Wendell Holmes' poem by that name, the wonderful chaise falls completely apart exactly 100 years to the day after it was built: '... it went to pieces all at once, all at once and nothing first ...'. To repeat the main point: research must find out why so many individuals do not yet reach their individual rectangular life curve and become, instead, senescent (in its most negative sense) before their allotted time. Many factors, extrinsic and intrinsic, are involved, and much is left to do. Each one of us involved in this wide field will probably see a different aspect as the most important, depending upon whether we are biochemists, physiologists, pathologists, immunologists, endocrinologists, geriatricians, psychiatrists, or any other of the many specialties involved in aging research. If I may single out just one topic as an example: the increasing number of senile, demented people in our old age homes and psychogeriatric hospital wards is rapidly developing into what will be one of the most serious problems facing society in the coming years and generations. All of these unfortunate people die well before their individual rectangular lifecurve is fulfilled. Research into the causes and mechanisms of senile dementia is increasing at a rapid pace, as the increasing volume of research reports shows[9], but we still know very little about the etiology of this condition or its early diagnosis, and even less about prevention and treatment.

Another major problem which will come up with the rectangular society is this: what to do with the increasing numbers of healthy and vigorous 'old' ('old' only in terms of years) people? All our present, carefully constructed retirement and health-care systems will be outdated and even counterproductive. It will mean a major restructuring of society.

Much effort has been spent in the search for 'primary' mechanisms of aging, at the cellular or molecular level. In a recent collection of articles in this journal[10], experts from different fields of research came to the conclusion that we cannot expect to find 'the' cause of aging, that no single primary causal mechanism exists. Aging occurs at all levels of biological organization and seems to have both intrinsic and extrinsic causes. If we look at the most healthy and vigorous of our older citizens as representing the normal way of life and aging, we may find that, as mentioned above, certain functional losses we have so far considered as part of 'normal aging' are not really normal at all, and that the plateau of adult vigor is much more extended than we have assumed so far. If the natural end to life is a rapid, almost simultaneous, collapse of many functions and organs at a predetermined age rather than the result of a slow, linear, progressive decline, then a 'primary' mechanism must be something rather different from what I at least have thought it to be. There is here a striking similarity to the phenomenon of limited division potential of cells in vitro: loss of mitotic potential, cellular breakdown and death in fibroblast cultures occur rapidly within a short time at the end of a fixed period of regular growth. I do not wish to imply that the same basic mechanism operates in each case. It is merely the macroscopic pattern of survival and death that is similar.

If and when we do, eventually, understand what the causes of the final breakdown at the natural maximal age limit are, will we be able to do anything to prevent it, and should we try to extend the human lifespan potential? In my view, the motto 'Adding life to years' still seems to be better and wiser than 'Adding years to life'.

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