AN UNSOLVED PROBLEM OF BIOLOGY

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THE INAUGURAL LECTURE IS A COMPARATIVELY NEW institution in the College, but it has already come to acquire a certain ritual of delivery. One begins by wondering aloud what subject one is going to talk about and to which section of the audience the lecture should properly be addressed. Should one direct a scholarly harangue towards one's own professional colleagues, and so run the risk of leaving the rest of the audience fretful and bemused? Or should one make some attempt to address the University as a whole?

The latter choice is surely right, if only for this reason. The educated layman can perfectly well grasp the gist or sense of scientific discovery; he can get the hang of what it is all about. Sometimes he describes this achievement as 'mastering the principles' of a science, but that is going too far—the principles of a science are understood, if they are understood at all, only by its own practitioners of long standing. But scientific discovery as it reveals itself to the world at large represents the finished product of scientific activity; the layman has very little idea of how scientific problems are formulated and still less of how in practice they are solved. I therefore propose to take a single unsolved problem of biology and to set it out before you as a problem—that is, as the agenda of a certain scientific inquiry, and not as the minutes of laboratory practice or the formal record of something already done. Being in some degree crippled by the handicap of trying to be intelligible, I am bound to make statements which, if not baldly wrong, are true only with qualifications which I shall have no time to give them. This disability is not to be avoided; one gets nowhere if every sentence is to be qualified and refined.

The problem I propose to discuss is that of the origin and evolution of what is commonly spoken of as 'ageing'.[1] It is a problem of conspicuous sociological importance. Everyone now knows that the proportion of older people in our population is progressively

1 I have kept closely to my lecture as it was actually delivered, except that (*a*) I have left out an argument which, on further reflection, seems much less relevant and convincing than I formerly believed it, and (*b*) I have tried to answer in footnotes some particularly cogent criticisms by my colleagues. I have had the good fortune to consult with Professor L. S. Penrose on certain problems relating to the action of natural selection on human beings, and have had the most valuable advice from Professor J. B. S. Haldane, some of whose ideas are presented here as if they were my own.

increasing, that the centre of gravity of the population is shifting steadily towards old age. Using a plausible combination of hypotheses, one among several, the Statistics Committee of the Royal Commission on Population predicts that in half-a-century's time one-quarter of our population will be not less than 60 years of age. The economic consequences of such an age-structure are all too obvious. Now biological research is by no means uninfluenced by the economic importunities of the times, and there can be little doubt that the newly-awakened interest of biologists in ageing—or the hard cash that makes it possible for them to gratify it—is a direct reaction to this economic goad. Unfortunately, scientists have been slow to realize that the biologically important consequences of this secular increase in average longevity began to be apparent three-quarters of a century ago and are now on the threshold of completion. About seventy-five years ago, the mean expectation of life at birth in England and Wales began to exceed, as it now greatly exceeds, the age beyond which child-bearing virtually ceases. Women have had nearly all their children by the time they are 45, but may now expect, on the average, to live some quarter of a century longer. The fertility of men lasts beyond that of women and ends less sharply, but, roughly speaking, three-quarters of the male population is still alive at an age at which it can be credited with 99 per cent of its children. The principal causes of death have changed accordingly. Fifty years ago the major killing diseases were pneumonia and tuberculosis, both of infective origin; to-day they are cancer and what is compendiously called cardiovascular disease. Susceptibility to both cancer and the cardiovascular diseases is in some degree influenced by heredity, and should therefore be subject to those forces, of 'natural selection', that discriminate between the better and the genetically less well endowed. (To speak of 'discrimination' is, of course, to put the matter in too literary a way; let us say that people with different hereditary endowments do not have children in strict proportion to their numbers; some of them take more than their numerically fair share of the ancestry of future generations.) But cancer and the cardiovascular diseases are affections of middle and later life. Most people will already have had their children before the onset of these diseases can influence their candidature for selection. In the post-reproductive period of life, the

direct influence of natural selection has been reduced to zero,[1] and the principal causes of death to-day lie just beyond its grasp.

How it is that the force of natural selection becomes attenuated with increasing age I hope to explain very fully later. What is important in the meantime is that one should realize how, in the last seventy-five years, the whole pattern of the incidence of selective forces on civilized human beings has altered. We are not now waiting for our ageing population to produce biological changes of first-class importance, as some demographers seem to suggest. The changes have already happened. We have already entered a new era in the biological history of the human race.

II

It is a curious thing that there is no word in the English language that stands for the mere increase of years; that is, for ageing silenced of its overtones of increasing deterioration and decay. At present we are obliged to say that Dorian Gray did not exactly 'age', though to admit that he certainly grew older. We obviously need a word for mere ageing, and I propose to use 'ageing' itself for just that purpose. 'Ageing' hereafter stands for mere ageing, and has no other innuendo. I shall use the word 'senescence' to mean ageing accompanied by that decline of bodily faculties and sensibilities and energies which ageing colloquially entails. Dorian Gray aged, but only his portrait disclosed the changes of senescence. I hope that makes it clear.

Senescence means a decline of vitality. How is this to be more precisely defined and measured? One may set about trying to measure senescence in two entirely different sorts of ways.

[1] The word 'direct' is important. Grandparents, though no longer fertile, may yet promote (or impede) the welfare of their grandchildren, and so influence the mode of propagation of their genes. A gene for grandmotherly indulgence should therefore prevail over one for callous indifference, in spite of the fact that the gene is propagated *per procurationem* and not by the organism in which its developmental effect appears. Selection for grandmotherly indulgence I should describe as 'indirect', and the indirect action of selection becomes important whenever there is any high degree of social organization. The genes that make for efficient and industrious worker bees, for example, are of vital importance to the bee community, though not propagated by the worker bees themselves. Dr Kermack points out that the distinction between 'direct' and 'indirect' selection can easily be misleading, because in the outcome their effects are both the same. Let us admit, however, that there is a distinction of genetical procedure, though it might well have been embodied in better-chosen terms.

The first sort of measure is personal, in the sense that it is carried out on individual animals. Quite a number of schemes of measurement are at our disposal. For example, the rate at which wounds heal provides some sort of measure of what we vaguely mean by vitality, since it depends on the multiplication or migratory activity of cells. What sort of answer does it give? So far as we know, the answer is that the rate of wound healing is highest at birth and steadily declines thereafter. In terms of this measurement, therefore, senescence begins at birth and the 'prime of life' is something of a fiction. Or we might reasonably choose a measure founded on the acuity of the senses. The acoustical prime of life, for example, appears to be in the neighbourhood of the age of ten, for we are said to hear sounds of higher pitch at ten than earlier or thereafter. On the other hand physical strength, endurance, and the niceties of muscular co-ordination reach their peak at about age 25.

All these are very piecemeal measures. The best, perhaps, is that originally devised by Minot—the multiplicative power of the tissues of the body, that is, their capacity to increase by further growth in the manner in which they themselves were formed. Organisms tend to grow by compound interest, for that which is formed by growth is itself usually capable of further growing. But the rate of interest falls; the organism grows like a sum of money which, invested at birth at (say) 10 per cent compound interest, gathers in a lower rate of interest year by year. The rate of interest does indeed fall from birth, and it is at birth, if Minot is to be believed, that senescence must be said to begin. And so, in some perfectly respectable sense, it does; but if we pursue this train of thought by asking in what manner the rate of interest falls, we shall be led by Minot into an attractive paradox. The answer is that from birth onwards the rate of interest falls steadily at a rate which itself steadily falls. Not only does senescence begin at birth, but it is going on much faster in the early years of life than latterly. The child is hurrying precipitately towards his grave; his elders, appropriately enough, proceed there in a more decent and orderly fashion.

None of these personal measures is of more than limited value. They are together incomplete, and severally give different answers; nor can they be made to add up to give a single figure that represents a measure of senescence in the round. Let us therefore

turn to a scheme of measurement founded on wholly different principles.

III

The second sort of measure is not personal, but statistical. We have agreed that senescence is a decline of what may be vaguely called vitality, and must now ask what property it is that changes as a direct outcome of that decline. The property is, in a word, *vulnerability* to all the mortal hazards of life; and it is measured by the likelihood of dying within any chosen interval of age.

The measurement of vulnerability is in principle very easy. Imagine 100,000 animals, each of which is labelled or otherwise identified at birth and followed throughout its life; and suppose one keeps a record of the age at which each dies, keeping the record open until the death of the most long-lived. Such a record might well be called a Death Table, but, by an agreeable euphemism, it is in fact called a Life Table. If we plot the number of survivors against age, the curve so defined starts with age 0 at 100,000 and falls to zero at the age of about 100 years. Fig. 1 illustrates the shape of the life-table curve for human beings.

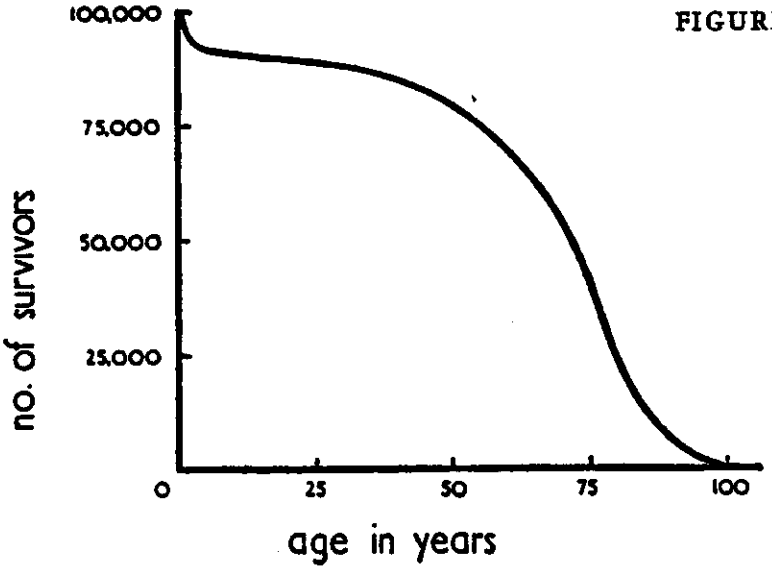

FIGURE 1

From such a curve one may compute the death-rate at any age of life, for that is simply its slope, the rate of decline of the number of survivors; the mean expectation of after-life at birth or at any other age; and the likelihood at any one age of living to any other. The

property that concerns us, however, is that which is called the specific death rate or, less aridly, the 'force of mortality', the likelihood of dying within each interval of age. In a first approximation, which is all that is necessary for our purpose, the force of mortality is the quotient of this fraction:

$$\frac{\text{Number of organisms that die within any chosen interval of age}}{\text{Number of organisms alive at the beginning of the interval}}$$

If, for example, 100 men reach age 89, but only 80 of them reach age 90, then the force of mortality in the 90th year of life is simply 0·2 (20 per cent, or 200 in every 1000). If there is no senescence in the population—if vitality does not decline, so that there is no greater likelihood of dying at any one age than any other—then the force of mortality must necessarily be constant. Its members die, to be sure; but a man who has just celebrated his 80th birthday anniversary is no more or less likely to celebrate his 81st than is a 7-year-old to celebrate his 8th. In my diagram, the force of mortality, being constant, would appear as a straight line parallel to the axis defining age.

In real life it is far otherwise. As Fig. 2 shows, the vulnerability of new-borns is not unexpectedly very high; not until nearly the 70th year of life does it become so high again. The curve of the force of mortality falls precipitously to a minimum around age 12 and then climbs upwards, slowly at first and latterly much faster. Age 12 (or thereabouts) is therefore the actuarial prime of life; at 12 one is more likely than at any other age to survive one further year, or month, or minute. But notice the smoothness of the curve that defines the force of mortality in later life. There is no break or singularity to give evidence that at any later age development and maturation are at last completed and that deterioration then sets in. Any complete theory of the origin and evolution of senescence must explain the smoothness and coherence of the curve of increasing vulnerability. It is not quite good enough merely to think up reasons why very elderly animals should die.

Because there are clearly special reasons why baby animals should be more vulnerable, though no less charged with vitality than their elders, I am proposing to neglect the arc of the curve of the force of mortality that lies before its minimum, but to use its later stretch as a measure of the degree of senility. This is a decision that cries aloud

for qualifications and reservations, and it is part of my purpose to reveal what some of these may be.

You will notice first that although the force of mortality may purport to measure a process that happens in the life of an individual animal (decline of 'vitality', or what you will) it is in fact

FIGURE 2

founded upon the age-frequency distribution of a single event in life—its end. It is a notorious fact that Maxwell's Demon can reduce all such measures to absurdity, since he can strike down perfectly vigorous, or indeed potentially immortal animals, at just such ages as will exactly imitate any chosen force-of-mortality curve.

There are many other serious reservations. The use of the force of mortality as a measure of senescence assumes that all members of the population are equally at risk. This is not true, because wage-earners are more exposed to risk than schoolchildren or those who have retired. A third difficulty is that if a life table is constructed in the way I have suggested—that is by following the life-histories of a cohort of the newly-born—it is only too likely to be corrupted by secular changes in the hazards of which human beings may be victims. Individuals aged 70 to-day were born in 1881, when the causes of the death of children, and their likelihood of surviving early youth, were very different from what they are to-day. A

fourth difficulty is that if the population is rather crudely subdivided into the innately (that is, genetically) less tough and tougher, then the population that reaches age 60 will be by no means a genetically fair sample of the cohort with which the life table began. Presumably each pattern of genetic constitution endows its owners with a characteristic mode of increase of vulnerability; but in a cohort of mixed origins all such distinctions must inevitably be confused.

These are grave difficulties, but all of them can be overcome in principle, and some in laboratory practice. I now turn to a much more important difficulty in the use of vulnerability as a measure of senescence: it is ingrained, and in practice ineradicable, and it leads us to distinguish between two *sorts* of causes of senescence.

IV

Consider wrinkles and lines on the skin, for these are familiar outward signs of ageing in its colloquial sense. People who often frown get lines between the eyebrows; the habitually supercilious reveal their temperament by furrows across the forehead; deep lines down the corners of the mouth are sometimes the consequence of having a ready smile. What is the history of wrinkles? Every time one grins or frowns some physical trace is left in the cellular or fibrous structure of the skin. These traces are cumulative, and if only one folds or creases the skin sufficiently often, they will add up to form a visible flexure line. One perfectly good reason why elderly people should have more lines and wrinkles is therefore simply that, being older, they have frowned and grinned more often. But we must also ask whether the skin of older people more readily takes the impress of creasing and folding. Does a *first* flexure in the skin of an older person leave a bolder trace than a first flexure in the skin of someone younger? We may be certain that it does. But the point is that *both* an increase in innate susceptibility to wrinkling *and* the cumulative effect of recurrent creasing have played a part in the history of wrinkles; and although we can distinguish the two sorts of causes in theory and in experimental practice, they cannot be disentangled merely by contemplating the wrinkle as a *fait accompli*.

Wrinkling is an unimportant example of a kind of disability that

affects all animals. Any injury that leaves a physical trace, as all but the most trivial do, increases the vulnerability of older animals, because injuries of one sort or another are recurrent hazards and older animals, having been exposed to them more often, will have built up a bigger actuarial debt. Skin scars may be individually trivial things, but the older animals will have more of them; and apart from that, germs gain easier access to the body during the time it takes for a wound to heal. Fractures of bone are slow to reunite and animals make easy prey until they have done so. The heightened blood-pressure that accompanies the shocks and alarms of natural living predisposes the blood-vessels to degenerative change. Cells may produce faulty copies of themselves in what should be an act of exactly symmetrical division; division is recurrent and faulty copies are perpetuated, so that their ill effects, summed over the cell population of the body, are bound to add up. The efficacy of most of the known cancer-provoking chemical compounds depends upon the repeated exposure of tissues to their action over long periods. Infections are recurrent hazards; most infections damage cells, and some do permanent damage of a sort that increases vulnerability in an obvious way. To go back to colloquial speech, all these effects are the effects of age but not necessarily the effects of ageing; they may take their toll even if ageing is not accompanied by an innate deterioration. Senescence, as it is measured by increase of vulnerability or the likelihood of an individual's dying, is therefore of at least twofold origin.[1] There is (*a*) the innate or ingrained senescence, which is, in a general sense,developmental or the effect of 'nature'; and (*b*) the senescence comprised of the accumulated sum of the effects of recurrent stress or injury or infection. The latter is environmental in origin and thus, in a paradoxically technical sense, the effect of 'nurture'. There is always an empirical test for distinguishing between the two in principle—one has only to find out whether a *first* injury or physiological abuse or stress is less well

[1] Dr Whitear has pointed out that a third and quite distinct sort of change with ageing which influences and will ultimately increase the vulnerability of older animals is that entailed by the differential growth and changing proportions of the several organs of the body or ingredients of a complex tissue. As a general rule, it may be said that every fixed regime of differential growth will, if growth is indeterminate, inevitably lead to mechanical or physiological ineptitude of one sort or another, although not necessarily involving a loss of 'vitality' at the cellular or tissue level. The problem is discussed more fully later.

tolerated by older animals than their juniors—but in the actual records of vulnerability the two are inextricably combined.[1]

That one is obliged by the terms of my definition to admit that there are two sorts of causes of senescence has, it will turn out, no more than a minor nuisance value. I am of course chiefly concerned with senescence of sort (*a*), and you will see that the arguments put forward to account for its origin and evolution are greatly strengthened by the fact that there may already exist a senescence of sort (*b*).

The time has now come for a formal definition of senescence, and I shall adopt the usual practice of translating a statement about the frequency of the occurrence of an event in a population into a statement about the likelihood of its happening to an individual. Senescence, then, may be defined as that change of the bodily faculties and sensibilities and energies which accompanies ageing, and which renders the individual progressively more likely to die from accidental causes of random incidence. Strictly speaking, the word 'accidental' is redundant, for all deaths are in some degree accidental. No death is wholly 'natural'; no one dies *merely* of the burden of the years.

V

By way of an interlude let me now, as a zoologist, apologize for appealing so much to evidence from human beings. I do so because we know so very much more about the death of human beings than of other animals; and though I feel a professional obligation to say something about the natural history of senescence, there is no time to do so, and even if there were, there would not be much to say.

[1] Higher organisms have means for counteracting the cumulative effect of recurrent injuries. Two of the three principal reflex (i.e. response-to-stimulus) systems of the body, the immunological and the nervous, have the power of 'storing their information' for long periods. The hormone system, apparently, has not. In general, an animal is less likely to contract a particular infection on its second exposure than on its first, and this is mainly due to the fact that what immunologists call the 'secondary' response to an immunity-provoking agent is a good deal brisker than the first. An animal is also less likely to get bitten, burnt, or otherwise abused at each successive exposure to such a hazard; it will have 'remembered' the earlier and accordingly learnt better. Two exposures to infection or physical risk may therefore have a no more harmful consequence than one, and the cumulative effects of some sorts of recurrent stress may therefore be in high degree corrected by the benefactions of an immunological or nervous memory. Memory, as Professor J. Z. Young has reminded me, is also the outcome of some influence that has left a physical 'trace'.

We can be quite sure that mammals undergo a process of 'innate' senescence. But why are we so sure? The answer is vital to my later argument. It is because we keep mammals as pets, in zoos, and in domestication. If we had to rely upon information derived from truly wild animals, we should be very much indeed less certain, and it is arguable that we might never know at all. For, as Dr Chitty tells me, wild mammals of any perceptible degree of senility turn up in traps so seldom that we should always be inclined to think up causes for their enfeeblement that were not necessarily connected with their age—the wasting due to infection, maybe, or to an injury that stopped them getting food. Animals do not in fact live long enough in the wild to disclose the senile changes that can be made apparent by their domestication. Many wild birds, as Dr Lack has shown, are the victims of so savage an exaction of mortality that, beyond a few months of youth, their likelihood of dying is actually independent of their age! It is of vital importance to remember that senility is in a real and important sense an artifact of domestication; that is, something revealed and made manifest only by the most unnatural experiment of prolonging an animal's life by sheltering it from the hazards of its ordinary existence. Here is a story with a pertinent moral. An eminent naturalist was once taken tiger-hunting by a courteous Indian potentate; he got his tiger and saw at once that it was very, very old. Here then perhaps, he thought, is something that he had long vainly looked for—a truly wild animal that was very old and very decrepit, and no doubt very cunning and very wise as well. On closer inspection he found that the tiger had gold fillings in its molars; the potentate, courteous as I said, had simply 'laid it on'. So when you hear speak of the 'natural death' of animals, remember that no death is less 'natural' than that which is commonly so called.

If there are doubts about mammals and birds, which comprise the higher classes of vertebrates, how many more must there be about the members of what we are now obliged to call the underprivileged classes? There is still, it appears, no more to be said about senescence in fish than was said by my predecessor Sir Edwin Ray Lankester some eighty years ago: 'Fish are not known to get feeble as they grow old, and many are known not to get feebler.' My professional colleagues will know that Dr G. P. Bidder held some fas-

cinating and far from implausible views on the origin of senescence which turn on the belief that fish do *not* deteriorate with ageing. These I cannot delay with. But is it not a most revealing fact that there should be any doubt about the matter at all? Fish *may* be potentially immortal in the sense that they do not undergo an innate deterioration with ageing, and yet the naturalists who ought to know about it simply can't be sure! As you will see, this uncertainty is the most tell-tale evidence in favour of my later argument. Whether animals *can*, or cannot, reveal an innate deterioration with age is almost literally a domestic problem; the *fact* is that under the exactions of natural life they do not do so. They simply do not live that long.

VI

I have deliberately spent more than half my time in discussing the measurement and definition of senescence, and I now want to discuss the factors that may have played their part in its origin and evolution. As a text I shall use a quotation from the works of August Weismann.

> Death takes place because a worn-out tissue cannot for ever 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. . . . by the operation of natural selection, the life of a theoretically immortal individual would be shortened by the amount which was useless to the species.[1]

Weismann's propositions have the great merit of suggesting, for only the second time, that senescence has had a very orthodox evolutionary origin. But Weismann is arguing in what a student of mine once called a viscous circle, or more exactly a vicious figure-of-eight. He assumes that the elders of his race are worn out and decrepit—the very state of affairs whose origin he purports to be inferring—and then proceeds to argue that because these dotard animals are taking the place of the sound ones, so therefore the sound ones must by natural selection dispossess the old! This is all a great muddle, but there is certainly some truth in it, and I shall

[1] I quote from *Weismann on Heredity* (ed. E. B. Poulton, S. Schönland, and A. E. Shipley; 2nd ed., Oxford, 1891), pp. 23–42 ('The Duration of Life') and pp. 111–61 ('Life and Death').

spend the rest of my lecture in an attempt to find out what that truth may be.

My argument starts with a discussion of certain demographic properties of a population of potentially immortal individuals, and it will be illustrated by an inorganic model which I shall animate step-by-step. This choice makes it possible to avoid two common traps. The first of these is to argue that senescence in higher animals has come about *because* they have a post-reproductive period; for 'unfavourable' hereditary factors that reveal their action only in the post-reproductive period are exempt from the *direct* effects of natural selection and there is therefore little to stop them establishing themselves and gaining ground. Any such argument is wholly inadmissible. The existence of a post-reproductive period is one of the consequences of senescence; it is not its cause. The second trap, into which Weismann fell headlong, is to suppose that a population of potentially immortal individuals subject to real hazards of mortality consists in high proportion of very aged animals with a relatively small number of no doubt browbeaten youngsters running round between their feet. It will soon be clear that this idea is equally mistaken.

I want you now to consider a population of objects, living or not, which is at risk—in the sense that its members may be killed or broken—but which is potentially immortal in the sense that its members do not in any way deteriorate with ageing. Test-tubes will do, since they are clearly 'mortal', and I shall peremptorily assume that they do not become more fragile with increasing age.

Imagine now a chemical laboratory equipped on its foundation with a stock of 1000 test-tubes, and that these are accidentally and in random manner broken at the rate of 10 per cent per month. Under such an exaction of mortality, a monthly decimation, the activities of the laboratory would soon be brought to a standstill. We suppose therefore that the laboratory steward replaces the broken test-tubes monthly, and that the test-tubes newly added are mixed in at random with the pre-existing stock. The steward will obviously be obliged to buy an average of 100 test-tubes monthly, and I am going to assume that he scratches on each test-tube the date at which he bought it, so that its age-in-stock on any future occasion can be ascertained.

Now imagine that this regime of mortality and fertility, breakage and replacement, has been in progress for a number of years. What will then be the age-distribution of the test-tube population; that is, what will be the proportions of the various groups into which it may be classified by age? The answer is illustrated in Fig. 3.

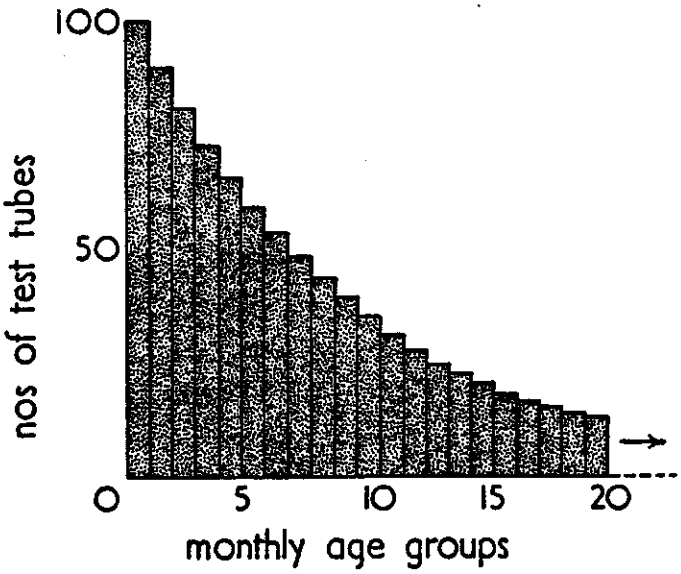

FIGURE 3

The population will have reached the stable or 'life-table' age-distribution in which there are 100 test-tubes aged 0–1 month, 90 aged 1–2 months, 81 aged 2–3 months, and so on. This pattern of age distribution is characteristic of a 'potentially immortal' population, i.e. one in which the chances of dying do not change with age. The curve it outlines is of a sort very familiar in science. Fig. 3 illustrates this very elementary truism: the older the test-tubes are, the fewer there will be of them—not because they become more vulnerable with increasing age, but simply because the older test-tubes have been exposed more often to the hazard of being broken. Do not therefore think of a potentially immortal population as being numerically overwhelmed by dotards. Young animals outnumber old, and old animals those still older.

VII

As a first step in animating this model, I want you to imagine that the test-tubes now do for themselves exactly what the steward has hitherto been doing for them, i.e. they reproduce themselves, no

matter how, at an average rate of 10 per cent per month in order to maintain their numbers. Since the population is potentially immortal, the rate of reproduction of its members will not vary with their age. It follows that each 'living' test-tube of the existing population will make the same average contribution of offspring to the test-tube population of the future. Each test-tube may lay claim to an equal share of the ancestry of future generations, and its reproductive value is invariant with its age.[1]

The next step in the argument is vital. Although each individual test-tube takes an equal share of the ancestry of the future population, each age-group most certainly does not. The older the age-group, the smaller is its overall reproductive value. The group of test-tubes 2–3 months old, for example, makes a very much greater contribution than the group 11–12 months old. This is not because the test-tubes of the senior group are individually less fertile—their fertility is *ex hypothesi* unchanged—but merely because there are fewer of them; and there are fewer of them not because they have become more fragile—their vulnerability is likewise unaltered—but simply because, being older, they have been exposed more often to the hazard of being broken. It is simply the old story of the pitcher and the well.

Some of the consequences of this decline in the reproductive value of older age-groups will be apparent when I take the next step in animating my test-tube model. The test-tubes are no longer to be thought of as immortal; on the contrary, after a certain age,

[1] The actuarial characteristics of a 'potentially immortal population' are particularly simple: the life table is defined by the relation $l_x = l_o e^{-\mu x}$, where l_o is the size of the original cohort, l_x is the number of them that survive to the age of x, and μ is the force of mortality ($\mu = -\frac{1}{l_x}\frac{dl_x}{dx}$), independent *ex hypothesi* of age. The probability p_x of surviving from birth to age x is simply $l_x/l_o = e^{-\mu x}$. If the number of offspring born to each member of the population in each unit of age remains constant, as we have supposed, at the value b, then the reproductive value remains constant throughout life at the value $R_x = \frac{1}{p_x}\int_x^\infty bp_x \,.\, dx = \frac{b}{\mu}$; and this will also be its value at birth (the net reproduction ratio R_o). If the regime of constant mortality and fertility has been in progress long enough, and numbers are not declining ($b > \mu$), then a stable age-distribution will be reached in which the fraction of the population falling within the age interval x to $x + Dx$ is given by $c_x = \int_x^{x+Dx} be^{-bx}\,dx$; the proportion of the population aged x and upwards is thus simply e^{-bx}.

as a result of some intrinsic shortcoming, they suddenly fall to pieces. For the time being we shall assume that they disintegrate without premonitory deterioration. What will be the effect of this genetically provoked disaster upon the well-being of the race of test-tubes? It must be my fault if the answer does not appear to be a truism—that it depends upon the age at which it happens. If disintegration should occur five years after birth, its consequences would be virtually negligible, for under the regime which we have envisaged less than one in five hundred of the population is lucky enough to live so long. Indeed, if we relied upon evidence derived solely from the natural population of test-tubes, we should probably never be quite certain that it really happened. We could make quite certain, as we do with animals, only by domesticating our test-tubes, shielding them from the hazards of everyday usage by keeping them in a padded box as pets.

If disintegration should occur one year after birth, an age which is reached or exceeded by about one-quarter of the population, the situation would be fairly grave but certainly not disastrous; after all, by the time test-tubes have reached the age of twelve months they have already made the greater part of their contribution of offspring to the future population. But with disintegration at only one month, obviously the consequences would be quite catastrophic.

This model shows, I hope, how it must be that the force of natural selection weakens with increasing age—even in a theoretically immortal population, provided only that it is exposed to real hazards of mortality. If a genetical disaster that amounts to breakage happens late enough in individual life, its consequences may be completely unimportant. Even in such a crude and unqualified form, this dispensation may have a real bearing on the origin of innate deterioration with increasing age. There is a constant feeble pressure to introduce new variants of hereditary factors into a natural population, for 'mutation', as it is called, is a recurrent process. Very often such factors lower the fertility or viability of the organisms in which they make their effects apparent; but it is arguable that, if only they make them apparent late enough, the force of selection will be too attenuated to oppose their establishment and spread. Such an argument may have a particular bearing on, for

example, the occurrence of spontaneous tumours and the senile degenerative diseases in mice of which Dr Gorer has made a special study, for these affections make themselves apparent at ages which wild mice seldom, perhaps virtually never, reach. We only know of their existence through domestication; small wonder if they have no effect on the well-being of mouse populations in the wild. Mice, of course, do already show evidence of deterioration in the course of ageing, but my reasoning does not presuppose it. It applies to 'potentially immortal populations' with only a quantitative loss of cogency.

It is a corollary of the foregoing argument that the postponement of the time of overt action of a harmful hereditary factor is equivalent to its elimination.[1] Indeed, postponement may sometimes be the *only* way in which elimination can be achieved; but I cannot argue this without an appeal to the phenomena of pleiotropy and linkage, which time will not allow.

VIII

It is not good enough to say that what happens to very old animals hardly matters and that what happens to youngsters matters a great deal. For the degree to which anything may matter varies in a predictable way with age, and the selective advantage or disadvantage of a hereditary factor is rather exactly weighted by the age in life at which it first becomes eligible for selection. A relatively small advantage conferred early in the life of an individual may outweigh a

[1] As an example of what I mean by the time of 'overt action' of genes, I should say that the earliest age of overt action of a 'coat colour' gene was with the growth of a coat of hair in mice, which are born naked, or with birth in animals like the guinea-pig, which are born with a pelt of hair. It is not until hairs are both formed and exposed to outward inspection that the various coat colours, as such, can influence the welfare of their possessors. But I agree with Dr Grüneberg that one must be very cautious in speaking of the time of action of genes—if for one important reason among several, because its influence on coat colour may be only one, and by no means the most important, of the manifold actions of what is only for convenience of labelling described as a 'coat colour' gene. We have furthermore only the vaguest idea of what we mean by speaking of a gene's 'acting' at all. This particular difficulty can be overcome by accurate formulation: the time of action of a gene G with respect to a character C is the age at which, in a stated genetic and environmental context, the substitution of G for its allelomorph G' transforms the character C' into the character C. In short, it doesn't matter when (or even whether) G and G' are 'acting' until they give evidence of acting in different ways.

catastrophic disadvantage withheld until later.[1] Go back to the test-tube model for a moment, and compare two competing test-tube populations. Both suffer the same average monthly mortality of 10 per cent, and one has, as hitherto, the average monthly birth rate of 10 per cent. The other population has an average monthly birth rate of 11 per cent, but the price paid for this hardly profligate increase of fecundity is the spontaneous bursting asunder of each member at age 2. Which population will increase the more rapidly in numbers—that potentially immortal, or the mortal population with a birth rate only one-tenth part higher than the other's? The simplest calculation shows that it is the latter.

A heightened juvenile rate of reproduction, achieved perhaps at the expense of recurrent stress that later leads to deterioration, is by no means the only possible realization of the phenomenon illustrated by this model. It is a general rule, for example, that the parts of the body multiply their substance at unequal rates, so that proportions change as the body grows. There is very likely to be a 'best' proportion, or a best range of proportions, from the standpoint of functional efficiency and therefore of survival. In theory these proportions could be arrived at once and for all by starting the baby or embryo off with the appropriate shape and allowing growth to proceed by symmetrical enlargement. This does not happen in practice, and it is not biologically feasible for a whole variety of reasons. In practice, as I have already said, adult proportions are achieved by the adoption of a more or less fixed regime of differential growth, i.e. of a more or less constant ratio between the multiplication rates of the several parts of the body. The danger inherent in this alternative solution is that there may well come a size, and therefore an age, at which proportions become functionally and structurally grotesque. The size of the male fiddler crab's claw increases as a power, greater than unity, of the size of the rest of its body, and Dr Huxley, who has made a special study of these differential growth phenomena, points out that a crab whose body

[1] By something that is a catastrophic disadvantage to an older animal I mean a change which is personally catastrophic, and which would certainly be catastrophic to the species as well if it made its appearance in younger animals. But in the strict sense, the verdicts 'advantageous' and 'disadvantageous' can be delivered only after trial by selection, and in this sense to speak of 'catastrophic disadvantages' which don't in fact much matter is self-contradictory.

weighed 1 kg. would carry a claw about ten times that weight. But the sense of my argument is that if the appropriate proportions are achieved at some earlier stage of life, it may not much matter that the regime of differential growth that brought them into being should *eventually* lead to mechanical ineptitude of this degree. The early advantage more than makes good the later disadvantage which it necessarily entails.

IX

The postponement of the time of overt action of 'unfavourable' hereditary factors is not just a good idea which the organism would be well advised to apply in practice; postponement may be enforced by the action of natural selection and senescence may accordingly become a self-enhancing process. Let me give you a real example in which this process appears to be happening at the present time.

Huntington's chorea is a grave and ultimately fatal nervous disability distinguished by apparently compulsive and disordered movements akin to, and perhaps identifiable with, 'St Vitus' Dance'. Its first full clinical description is in George Huntington's own memoir of 1872, though the evidence I shall appeal to comes largely from the fine treatise of Dr Julia Bell. Huntington's chorea is a hereditary affliction of a rather special sort. Its disabling and clinically important effects first become manifest, not in youth or old age, but at an intermediate period, its time of onset—later in men than in women—being most commonly in the age-group 35–39. Its age of onset does however vary, and I want you to assume (what is almost certainly true, though it would be hard to collect the evidence for it) that its age of onset, like the disease itself, is also genetically determined.

If differences in its age of onset are indeed genetically determined, then natural selection *must* so act as to postpone it; for those in whom the age of onset is relatively late will, on the average, have had a larger number of children than those afflicted by it relatively early, and so will have propagated more widely whatever hereditary factors are responsible for the delay. But as the age of onset approaches the end of the reproductive period, so the direct action of selection in postponing it will necessarily fade away.

One may now ask why, if such a thing must happen, has it not happened already, and, if it has not, what is the evidence that it is happening now? The first question amounts to asking why Huntington's chorea is not *already* one of the diseases of the post-reproductive period, since selection of the sort I have outlined must be pretty vigorous and has presumably had tens of thousands of years at its disposal. My answer to this is based on an aside of Professor Haldane's. It is only in the last century or so that selection has had a real chance to get a grip on it, for it is only within this period that the average expectation of life at birth has come to equal the average age of onset of the disease. Even so, there is indirect evidence of a postponement of its age of onset. Since the male reproductive span is longer than the female's, the force of selection must in men be less quickly attenuated with increasing age; postponement should therefore have gone farther in men than in women—and this, as I have already said, is indeed the case. Ultimately, no doubt, the age of onset will come to a standstill in both men and women at the end of their respective reproductive periods. I gratefully acknowledge the origin of this train of thought in Professor Penrose's writings on mental disease and natural selection.

With Huntington's chorea as a lucky concrete example, I can now propound the following general theorem. If hereditary factors achieve their overt expression at some intermediate age of life; if the age of overt expression is variable; and if these variations are themselves inheritable; then natural selection will so act as to enforce the postponement of the age of the expression of those factors that are unfavourable, and, correspondingly, to expedite the effects of those that are favourable—a recession and a precession, respectively, of the variable age-effects of genes. This is what I mean by saying that senescence is a self-enhancing process. The theorem in the form in which I have just put it does not depend upon the existence of a post-reproductive period; it only requires that the reproductive value of each age-group should diminish with increasing age. I have argued that this must necessarily diminish even with a population of potentially immortal and indeterminately fertile individuals, provided only that they are subject to real dangers of mortality. In such a population a younger age-group must necessarily outnumber an older, for the older represents the residue of

those who have been longer exposed to mortal hazards. If you should have, as I believe, unjustified qualms about an argument based upon combining an innate potential immortality with a contingent real mortality, I would recall to you my earlier distinction between senescence of sorts (*a*) and (*b*). Senescence of sort (*b*) is not innate or 'laid on' developmentally; it represents the outcome of the cumulative effects of recurrent physical damage, physiological stress, or faulty cellular replication. If you will admit that senescence of this sort is a means by which, irrespective of any genetical background, the reproductive value of each individual in a population is caused to diminish with increasing age, then my argument is quantitatively strengthened, because the numerical preponderance of the younger age-groups will become so much the more pronounced. And if, further, a post-reproductive period of life is already established, then indeed it becomes, as it were, a dustbin for the effects of deleterious genes. But these propositions are mere glosses or refinements. The argument must stand or fall on the case which I first proposed.

X

I have now suggested three agencies which may have played a part in the evolution of 'innate' senescence: (1) the inability of natural selection to counteract the feeble pressure of repetitive mutation when the mutant genes make their effects apparent at ages which the great majority of the members of a population do not in fact attain to; (2) the fact that the postponement of the time of action of a deleterious gene is equivalent to its elimination, and may sometimes be the only way in which elimination can be achieved; and (3) the fact that natural selection may actually enforce such a postponement, and, conversely, expedite the age of onset of the overt action of favourable genes. All these theorems derive from the hypothesis that the efficacy of natural selection deteriorates with increasing age.

I am inclined to think that the third factor, the enforced precession and recession of the ages of the overt action of genes, has the widest ambit of significance. But although I have foresworn the introduction of too many qualifying and saving clauses, one indeed is most important. Real animals, unlike imaginary test-tubes, are

neither born mature, nor do they get on with the business of self-reproduction at once. There is always a pre-reproductive period during which animals are far from exempt from the hazards of mortality, and during this period the average reproductive value of an individual must therefore rise to a maximum, irrespective of whether or not it falls later. If my reasoning is correct—there is no time to go into details—the precession of the time of action of genes comes to a standstill at the epoch when the reproductive value is at a maximum, and it is *then* that senescence should be expected to begin. Professor R. A. Fisher has pointed out that the actuarial prime of life of human beings and the age at which their reproductive value is at its maximum do in fact nearly coincide.

Even with such refinements as this, my proposals can hardly be said to add up to a self-sufficient theory. If we concede that the force of natural selection is rather exactly weighted by the ages of the animals on which it operates, it is still far from easy to see in detail how senescence has become shaped into its distinctive pattern—the early onset and slow progressive fulfilment that the curve of the force of mortality so conspicuously reveals. Some of the agencies described seem to suggest a rather precipitous onset of senescence—more like that which befell the expatriates of Shangri-La than that suffered by the inhabitants of the world at large. But even allowing this shortcoming, I think it must be clear that the origin and evolution of senescence is not an insoluble *genetical* mystery, however mysterious it may be in other ways. The geneticist can see how it might well have happened; its occurrence does not outrage his sense of the fitness of things. So perhaps I was unduly disrespectful to Weismann's memory when I poked fun at his conjectures on senescence. In very broad outline they were probably not erroneous, at least in so far as natural selection was recognized as the instrument of its origin and perpetuation. I said earlier, as you may remember, that there was *some* truth amidst a good deal of what we can now see to be nonsense, and that it would stir up his successors to think up a more polished and cogent explanation. Not much more than this can be said of any biological theory of comparable pretensions, and I shall count myself lucky if I hear an equally sympathetic criticism of my own.