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ALFRED WATSON MEMORIAL LECTURE

MORTALITY AND THE NATURE OF AGE PROCESSES

THE following is the text of the eighth Alfred Watson Memorial Lecture which was delivered on 28 April 1958 by **Dr Alex Comfort, M.A., M.B., PH.D., D.C.H.,** Nuffield Research Fellow in Gerontology at University College, London.

ACTUARIES study the pattern of the change in the force of human mortality with age to enable us to order our affairs in terms of our probable life-span: gerontologists study it to find out why the change occurs, with the ultimate object of controlling it. In doing this, they are coming to depend increasingly upon tools manufactured and sharpened by the actuary. Not all these tools were designed for the purposes or the materials to which biologists apply them, and not all biologists who find themselves under the necessity of using actuarial methods are skilled in their use. Since these methods form so important a part of our equipment, I want to describe to you tonight some of this material and some of these objectives.

Death is a single, all-or-none event, and its use as an index of continuous processes is open to objections which are as evident to biologists as to mathematicians.

Actuaries might reasonably ask the biologist to provide them with a criterion of ageing which could be measured quantitatively in individuals. But if they do come to consult him on these lines they will find him on his way to consult an actuary. We have so far no better general measure of vigour, and the changes in vigour with age, than survival and mortality. These criteria of vigour, in spite of their defects, have the unique advantages of making no direct assumption about the nature of the ageing process, or its uniformity between individuals; they are applicable to all kinds of animals in spite of differences in their physiology; and they are applicable to man from current observation without the need of special experiment. Our general criterion of ageing is therefore still the actuary's criterion—the risk of death and the probability of further survival.

The differences between actuarial and biological approaches to mortality-measurements are in the main the differences between the prospective and retrospective use of statistics. The most practically important of these differences, for the kind of problems we have in hand, is the value we attach to smoothness. For almost all prospective purposes it is convenient in the first instance to assume some degree of uniformity, to recognize as few and as gross modalities as possible, and to deal with minor modalities by smoothing. For most retrospective purposes, the main consideration is to extract as much reliable, or even suggestive, information from scanty data as the limits of significance will allow. This will require the use of methods which will exaggerate fine structure where it is present. The biologist's main requirement in using standard actuarial techniques of research on age is that he shall be able to distinguish clearly between regularities which probably exist in the material, and any regularities which may result from the methods themselves. Most animal populations are heterogeneous for life-table purposes.

Curves based on such material are averages, which are serviceable for prediction of limits, but often misleading as indications of the pattern of a biological process. Fig. 1 illustrates such an effect in human growth curves, from the study by Tanner (1955); it compares the longitudinal plots of growth velocity against age in five individual children, the smoothed average which would be obtained by combining the measurements, as they would be combined in a cross-sectional study, and the same measurements as percentage deviates. The true age-velocity curves are typically peaked. Many instances

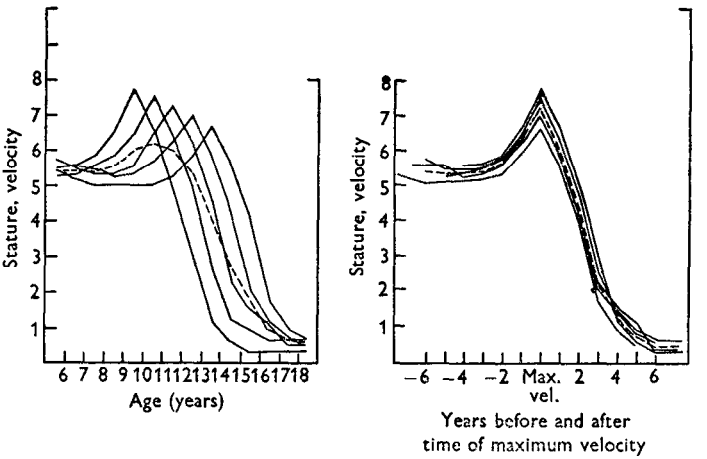

Fig. 1. Relation between individual and mean velocities during the adolescent spurt. Left, the height curves are plotted against chronological age; Right, they are plotted according to their time of maximum velocity. ——, Individual curves; – – –, mean curve.

quoted to demonstrate that 'Nature does not progress by leaps' are a direct result of this type of treatment. Where, as in this case, longitudinal as well as cross-sectional studies are made the error is evident. But unfortunately there is still no measure of the decline in individual life expectancy which we can study longitudinally, as we can study the increase in stature, and all actuarially-derived curves for the rate of ageing in heterogeneous populations will tend to show the properties of self-smoothed averages. Unlike the actuary who deals with human data, the gerontologist can sometimes overcome the difficulty where he can carry out radical actuarial experiments; but the number of animals in which he can do so is small.

Most of the problems of age research on animals arise, however, not from general statistical considerations like these, which are familiar in biometry, but from the nature of the subject and the material. The life spans of many animals are appreciable fractions of our own: old organisms are inherently variable as a result of ageing: relatively few animals can be aged accurately by inspection: and they often reach old age only in circumstances remote from the wild environment to which they are adapted. For the vast majority of animal species we have no serious vital statistics and little prospect of obtaining them.

There are three main problems about which animal vital statistics could be expected to provide information. We need initially to know whether senescence, in the sense of an increase in mortality with age, occurs comparably in all vertebrates, given certain defined conditions. We need to know what exactly takes place during this increase, in terms of anatomy, physiology, cytology—the study of cells and cell-processes—and chemistry; and we need to know what factors are responsible for the large differences in rate of ageing between related organisms.

Such evidence as we have suggests that under appropriate conditions the force of mortality rises with age in all warm-blooded animals, 'appropriate' conditions being those in which the environment is sufficiently good for the random component of mortality to be small. No increase is evident in wild populations of small birds and mammals, because the standing death-rate is extremely high; the force of mortality remains almost constant with respect to age, and may even fall, owing to selection (Haldane, 1953).

It is not certain that the force of mortality rises similarly in all vertebrates. Bidder (1932) long since pointed out that animals such as the larger fish, which have no fixed size, and in which growth does or may continue indefinitely, may have a similarly indeterminate life span. We now have some grounds for doubting this in the case of fish (Comfort, 1957*a*; Gerking, 1957), but it might still apply to large amphibia and reptiles.

There is at present no evidence to show whether, in those vertebrates which lose vigour with age, the timing mechanisms are always the same, analogous, or wholly species-specific. The processes involved are almost certainly multiple. At the same time, since the cells of animals are in many respects similar, it is quite possible that some deteriorative processes are shared by all. It is probable in particular that the life of non-dividing cells is limited in terms of molecule-operations: if so, any animal containing essential and non-renewable cells would undergo a loss of vigour from that cause at a rate depending on their metabolic turnover. Even though this is so, it does not follow that vertebrates age for this reason. They might equally well do so through progressive change in the quality of successive generations of cells. They might do so because of changes in structural materials with a low turnover rate, like the mechanical changes which cause the senescence of some trees. Only comparative studies can indicate which if any of these effects are important.

The rates of ageing differ conspicuously from species to species within a group. Man reaches his last decile survival at about 85 years, the thoroughbred horse at about 27 years (Comfort, 1958), and the laboratory mouse at $1\frac{1}{2}$–3 years, depending on genetic strain. Definition of the life-span, for purposes of comparison, is a problem in itself. The accepted figures include a mixture of guesswork, estimated averages, and maximum records. The last decile is probably the most useful single parameter in comparing survivals under a wide range of environmental conditions. Virtually nothing is known of the factors which determine interspecific differences. There are rough correlations between longevity and size, longevity and metabolic rate, and a rather better correlation between longevity and the relative size of the brain (Sacher, 1957), but little reliance can be placed on the life-spans which have been compared. Birds have much longer potential lives than mammals of comparable size and activity. Cold-blooded animals have life-spans which are usually longer still; their rate of ageing may be temperature-dependent.

There is, finally, evidence that the rate of senescence can be profoundly altered independently of some other body processes, not only by inherited characters, but by dietary procedures which retard growth and development. McCay (1943, 1952) was able to keep rats in a juvenile condition for most of their expected life-span by reducing their calorie intake: when fed, they resumed growth, and lived almost twice as long as the controls, the rise in force of mortality from all causes being delayed in step with the retardation of development. If this is so, it indicates that the rise in vulnerability with age, in this case at least, can be slowed without reducing normal body activity, since the rats were fully active throughout the experiment. Since some such dissociation in man is the object of our research, it becomes a matter of great importance to determine what developmental factors score highest in bringing about the senile decline in vigour.

If we had a comprehensive account of the relation between growth, development, mortality and chronological age in a sufficient range of vertebrates, some at least of the general theories of mammalian senescence could probably be tested by inspection. For this purpose we require a range of vertebrate vital statistics, based on animals living under conditions of captivity sufficiently good for a fair proportion of them to reach old age. These figures are lacking. So far as can be ascertained, no life table has been published for a captive population of any fish, reptile or amphibian. One incomplete life table exists for domestic poultry, and it is based on an assumed equation to cover losses from culling (Gardner & Hurst, 1933): there is no other table for birds in captivity. Apart from these, we have so far satisfactory actuarial data only for man, laboratory rats and mice, and a few other small rodents, with partial figures for culled populations of agriculturally important animals (e.g. Merino ewes, Kelley, 1939). There are thus no data to indicate how ageing is related to development, or even if it occurs, in any vertebrates other than mammals; the figures which might throw light on the evolution of mammalian senescence, those for cold-blood animals, birds and marsupials, have never been sought.

One consequence of this lack of information is that we have no experimental mammal intermediate in size between man and the small rodents whose rate of ageing is actuarially known. There are no published actuarial data for rabbits: the modal specific age for all strains is probably about 8 years, but large hybrids may reach ages as great as 15 years. Data for guinea-pigs have been collected and briefly reported (Rogers, 1949), but we have no comparison of strains. Accordingly, many physiological and other differences between young and old animals described in the literature are in fact differences between infant and young adult animals.

Over the last five years we have been engaged in collecting animal vital statistics with this object, under a project maintained by the Nuffield Foundation. This has proved particularly difficult.

For vertebrates which cannot be aged by inspection, and which live more than 2–3 years, it is evident that we can expect to obtain figures only from existing records. This material varies greatly in quality. We have been able to make very little use of the actuarial work which has already been done on the useful life and lifetime production of agricultural animals because of the very high rate of culling. Even foxhounds are commonly put down at 4–5 years of age. The useful data which we have collected have all been derived, therefore, from specially kept laboratory animals, from a few records of longevity in

various breeds of dog, from the records kept by zoological gardens, and finally from the General Stud Book of racehorses.

Nearly all these sources of information, other than figures for laboratory animals, have much the same characteristic statistical drawbacks. They were usually not kept originally for actuarial purposes, or not for the study of life-spans. They mostly consist of multiple small batches of lives, and in many of these the losses to the record, by sale, deliberate killing, or disappearance, amount to half the initial population or more. The General Stud Book of racehorses is an exception as regards sample size, because it records the life-time progeny, and in many cases the year of death, of all the fillies foaled in England from 1820 to the present time which returned to stud as brood mares. In this case the only limit on the material is the labour of following each life individually through successive volumes, but the losses to the record are large and, of the lives in sample cohorts taken from an origin at 4 years of age, only about a third end in natural death at a known age, though the remainder contribute in varying degrees to the significance of the mortalities calculated.

All the survival curves were derived from the crude mortality with no further adjustment. In spite of this, and the small sample sizes, they have been unexpectedly regular (Comfort, 1957*b*). All the curves of survival for zoo animals approach an arithmetic straight line over the adult period. There is no modal age of adult death, once the infant mortality is past. In the sample of Patagonian cavies (Fig. 2) there were no losses, and points represent individual deaths. The records extend over 25 years, and the apparent periodicity of deaths is not due to epidemics or environmental clumping. We plotted curves (Fig. 3) for two species of sheep (*Ovis musimon*, the mouflon, and *Ammotragus lervia*, the Barbary horned sheep) and a series of wolf × timber-wolf hybrids in the London Zoo: these, predators and prey, are practically identical when superimposed. The survival of wild goats followed another straight line, which declines at rather more than half the rate. The figures for sheep are of importance, because they can be compared directly with those of Merino ewes under pastoral conditions, and with a life table for wild sheep, drawn by Murie (1944), who collected the skulls of wild Dall's sheep on Mt. McKinley and determined their ages by counting the horn annuli. There are therefore three series of data for related animals under widely differing conditions.

The study we have made of thoroughbred racehorses (Comfort, 1958) provides a life table for a contrasting population, in which early mortality is low, and survival into old age is comparable with that in man. The work was undertaken originally to examine the claim of Vitt (1949) that racehorses display a large parental age effect, paternal as well as maternal, upon longevity and vigour. Vitt's paper gave no statistical details, and his findings were not borne out by our results, but horses are particularly suitable material in which to look for such an effect, because there is little or no correlation between the ages of stallion and mare at covering, and both sexes continue at stud until very high ages.

We drew life tables from 4 years for 1492 brood mares foaled in the years 1875–80, for 1250 brood mares foaled in 1860–64, and for a further 412 mares which were the lifetime progeny of three noted stallions—Hermit, Galopin and Hampton. There was good agreement between the survival curves of these groups (Fig. 4), in spite of the large number of losses to the record

through sale, disposal and shooting. We made no attempt to correct the last half of the curve to allow for animals shot by reason of age or infirmity. The oldest animal in the three samples reached 30 years—the oldest thoroughbred mare of which we have record reached 34, and the oldest stallion, Matchem, who died in 1781, was reputed to be 33.

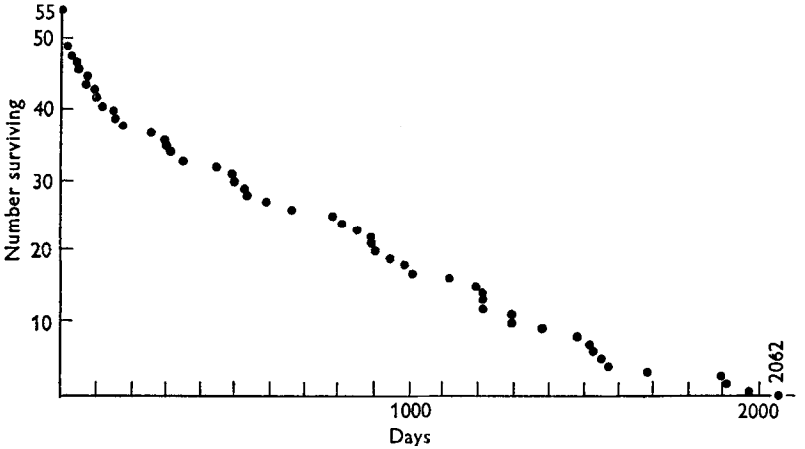

Fig. 2. Patagonian cavy (*Dolichotis patagonica*). Survival of 55 individuals—sexes combined (London Zoo).

The samples were also analysed by parental age and parental longevity. These results are summarized in Tables 1*a* and 1*b*. They are now being re-scored for coat colour, since in Rhenish horses Schiermann (1948) found correlations between colour and useful life (Fig. 5). Grey horses are known (McFadyean, 1933) to be susceptible to pigmented tumours; though these are not usually malignant they make the animal unsightly and may lead to destruction. The longevity of stallions has proved harder to examine than that of mares. Upon the basis of two cross-sectional samples it is significantly greater. There is much further work to be done upon Stud Book material. The scale of the study has been limited by the necessity of looking out each animal, and its parents, individually by name—about 5000 life histories in all. We may be able to consider a punch-card study later, particularly to obtain information about the sib-sib and half-sib correlations of longevity in horses.

We have studied dog records with an eye to a different problem, the comparison of ageing pattern in physically dissimilar strains derived from the same wild originals. Dog breeds show large heritable differences in physiology, shape and behaviour. One of the most evident is in size, from over 200 kg. in the mastiff and St Bernard to less than 2 kg. in the chihuahua. Since our first reasonably complete records were for an exceptionally large breed (Irish wolfhounds, Comfort, 1956) we are attempting initially to find out what relationships exist between longevity, body weight and cell number in several breeds, and whether the specific age of pedigree dogs has been greatly modified

by domestication compared with that of wolves and feral dogs (*Canis familiaris dingo*) under zoo conditions.

We have obtained for comparison the first eight 10-monthly intervals of a life table for pedigree Pekingese dogs from two different kennels, and enough additional data to predict the rough shape of the rest of the table. Most

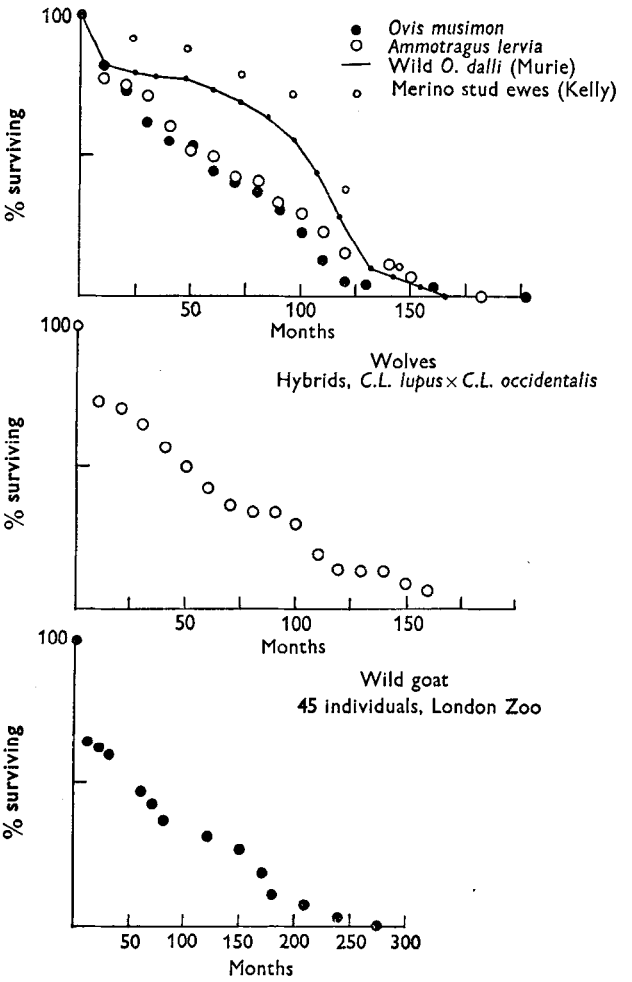

Fig. 3. Survival curves of sheep, wolves and wild goats.

breeders agree that small dogs are much longer-lived than large: this is so far borne out by the figures. About 10% of male wolfhounds and 22% of bitches which reach the end of their first year are likely to survive until the end of their eighth, compared with about 20% of mastiffs and 54% of Pekingese (combined sexes), and none of the large dogs reached 14 years, against an estimated 20–25% of Pekingese. There was a specially heavy mortality of

young male wolfhounds from miscellaneous infections. Several of the oldest animals died from malignant growths. These are apparently rarer in Pekingese, and occur at later ages (Fig. 6).

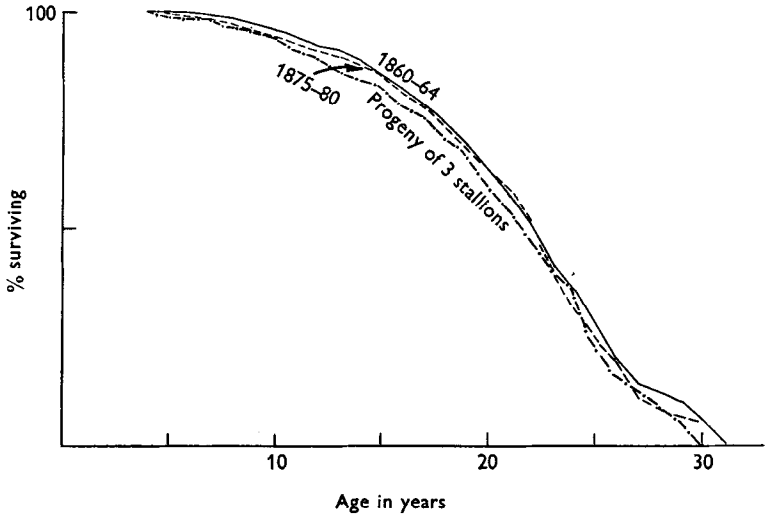

Fig. 4. Survival curves of thoroughbred mares—General Stud Book.

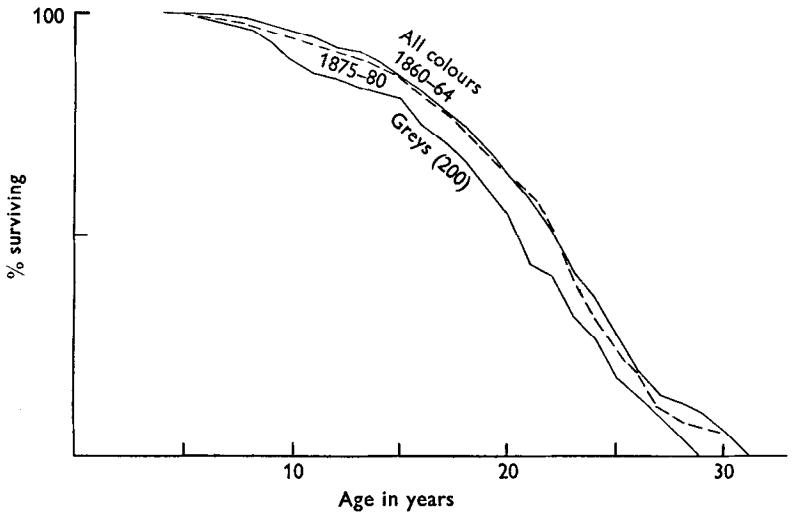

Fig. 5. Survival curves of thoroughbred mares—General Stud Book.

In spite of the observed breed differences, the median and maximum ages for all the breeds studied do not appear to differ by more than 20% from those of wolves and dingoes under zoo conditions. It seems likely that the shorter lives of large dogs may be due to their being specially vulnerable to disease in

Table 1 a. Longevity of thoroughbred mares by parental ages (sire at covering, dam at foaling)

	n	$e_{x=4}$	Variance V_e	Median
Whole sample				
Foaled 1875–80 (A)	1492	17·04	0·046	22·18
Foaled 1860–64 (B)	1250	17·31	0·044	22·07
Mares foaled 1875–80 (sample A)* and 1860–64 (sample B)*				
Dam: (sample A)				
< 8 years	297	16·90	0·12	21·07
8–12	537	16·66	0·09	21·06
13–16	303	17·29	0·17	22·21
⩾17	248	16·15	0·23	22·83
Sire: (sample A)				
< 8 years	250	16·73	0·16	22·10
8–12	537	17·11	0·10	22·35
13–16	352	17·26	0·20	21·83
17–19	151	16·87	0·28	22·08
⩾20	65	16·87	0·73	21·03
Dam and sire				
⩽9 years. Sample A	128	17·91	0·22	22·28
B	220	16·51	0·27	21·50
⩽12† A	449	17·39	0·22	22·28
B	531	17·07	0·11	21·90
A+B	980	17·33	0·07	22·10
⩾13† A	270	16·45	0·23	21·61
B	150	17·24	0·28	22·64
A+B	420	17·03	0·16	22·05
⩾16 A	70	15·71	0·69	20·41
B	44	17·26	1·10	23·17
Progeny of Hermit, Galopin and Hampton				
All mares:	412	16·60	0·15	21·73
Got in or after sire's 20th year	124	16·65	0·33	21·83
Got in or after sire's 16th year, dam ⩾16 at foaling	41	16·29	0·89	21·19
All mares (A, B and selected sires)				
By parents ⩾16 years	154	16·45	0·38	21·12

* Not all parental ages were ascertainable.
† Include extreme groups.

early life, not to different rates of ageing. The gestation period and rate of development are closely similar in all breeds of dog. The survival curve of wolfhounds is nearly linear, while that of Pekingese, and probably spaniels, is plateaued. We hope to extend this investigation when more breed data are available.

We have also obtained detailed vital statistics for a cold-blooded vertebrate, the guppy fish (*Lebistes reticulatus*), based on the longevities of several thousand specially kept individuals. The mortality of fish increases with age; we have been able to correlate it with growth pattern and reproductive rate under

Table 1b. Longevity of thoroughbred mares by longevity of parents

	n	$e_{x=4}$	Variance V_e	Median
Mares foaled in 1875–80				
Sire reached 25 years*	132	17·54	0·50	22·63
Sire died ⩽14	113	16·27	0·60	22·53
Dam reached 25 years	238	16·96	0·16	22·25
Dam died ⩽13	53	16·35	0·59	21·18
Dam and sire reached 23 years	113	18·07	0·34	23·74
Progeny of mares foaled in 1875–80				
Dam reached 25 years	168	16·33	0·31	22·54
Dam died ⩽13	58	16·67	1·25	20·02
Progeny of Hermit, Galopin and Hampton				
Dam reached 24 years	100	17·11	0·82	21·52
Dam died ⩽18 years	58	15·39	0·83	21·51

* Stallions whose date of death appears in the obituary lists: mares by Hermit, Galopin and Hampton are excluded from this figure, but included in the figure for dam and sire ⩾23 years.

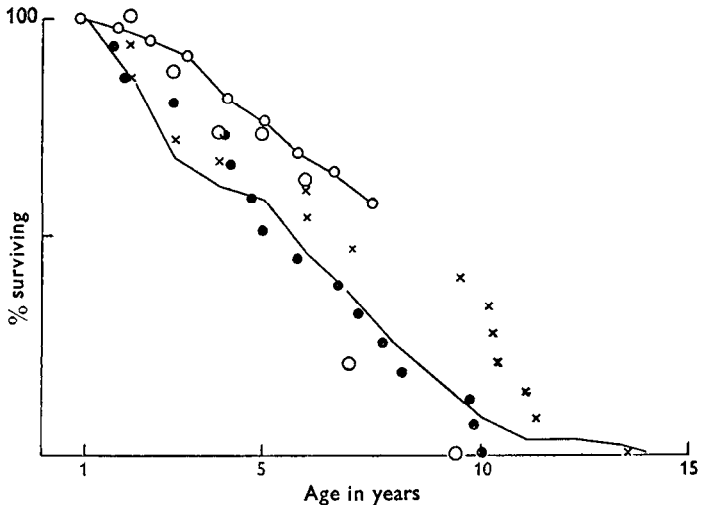

Fig. 6. Survival curves: dogs. ——, Irish wolfhounds; O—O—O, Pekingese; O O O, Mastiffs; × × ×, Spaniels; ● ● ●, Dingoes. Sexes combined.

various experimental conditions. These experiments are still in progress. Under good conditions at 23° C. less than 10% of fish in a cohort have died by 1 year of age, and less than 10% exceed 1000 days in the series so far kept. The force of mortality in this species, both in the females, whose rate of growth depends on feeding and space, and the males, which cease growing soon after sexual maturity, appears rather similar in its distribution to that of the

laboratory rat. We have parallel figures for the rate of fin regeneration at different ages and under different conditions of growth.

One use which we hope to make of animal survival curves such as these is in the analysis of heterogeneity, and it is to that problem that I wish to turn attention for the remainder of this lecture. Of the various factors which may render a population heterogeneous for actuarial purposes, the most interesting, for the understanding of ageing processes, are those which arise from polymorphism, that is to say from the presence in a single population of a large range of physical and constitutional types.

The polymorphism of life-spans probably affects both the individual ability to withstand destruction and its rate of change with time. Survival curves represent the distribution of a vitality parameter, and we might be able to obtain some indication of the distribution of this quantity in a mixed population by comparing the form of the survival curve under good and bad conditions. If we consider the individual vitalities of animals as being measured by the amount of stress they can survive, and we know that this amount declines in each individual with age, we could infer the distribution of vitalities at a given age by raising the amount of environmental stress until it causes the death of a fixed proportion of animals in successive comparable samples at successively earlier ages. This treatment is analogous to the assessment of the toxicity of drugs—the median lethal dose of environmental hardship is being measured. If the frequency distribution curve of deaths with age is an approximate measure of the distribution of vitalities, then the effect of worse conditions on samples of the same composition will be to move this distribution towards the origin. The change in slope of the survival curve will give some indication whether the vitalities of individuals remain, as it were, equally spaced throughout life, and consequently decline in parallel.

The chance of doing this is greatest in animals which have an extremely low early death-rate, and whose survival curve is of Teissier's form (1934) with a very long early plateau and a fairly sharp modal age of death thereafter. In some of these forms the effect of worsening external culture conditions, or of an internal handicap on vitality, such as that produced by inbreeding, is to move the whole curve bodily toward the origin without any change of slope. We are attempting to plan experiments on such animals in which the culture conditions impose repeatable degrees of stress, arranging the samples so that the need to allow by calculation for the effect of selection is avoided. We are able to compare in this way populations of fish which are kept individually in half-pint bottles, individually in two-pound jars, and collectively in tanks, and the survival curves for genetically comparable groups under each regime show a high degree of repeatability. In this case one can determine experimentally the effects of good and bad conditions on the survival curve, the degree to which selection or cumulative injury has taken place in fish reared to median survival under one regime and subsequently promoted to another, and the effect of an acute stress, such as exposure to cold, on the subsequent survival curve under standard conditions. There is a tendency for any acute environmental rise in mortality to be followed by a plateau in the survival curve, and the form of this plateau may also afford some information about the distribution of individual vitalities.

Perhaps the most striking feature in many vertebrate curves of this kind is the existence of a group of indestructible individuals making up the last half-decile, so that even under conditions of very high early mortality, and with

relatively small samples, one or two animals come close to the maximum record for the species. This is even more marked in birds. The mortality of wild birds, measured in marking experiments, is extremely high compared with the potential life. 77% of young robins ringed by Lack (1943) died in the first year, and the annual mortality thereafter was about 50%, but there is a reliable record of a marked robin reaching 11 years in the wild state. The total of all ringed birds recovered in Europe does not exceed 10,000 per year; the number of similar records of extreme age among them is considerably more than might be expected from the annual mortality; 17 years in the redwing, 16 in the goldfinch, 13 in the meadow pipit, and 18 years in the starling, all of which have annual mortalities in excess of 50% (Perry, 1953). Many of these old birds are likely to have been infertile for a number of years before death. If this is so, it raises an extremely interesting consideration about the evolution of the life-span in birds; natural selection can hardly have produced this effect unless long-lived birds within a strain contribute socially to the survival of its younger members.

Genetical research and the production of inbred lines make it possible to approach heterogeneity in a different way, and to undertake the synthesis, as well as the analysis, of heterogeneous populations. The differences in life span and survival curves between genetic strains of domestic animals depend on at least three factors—the occurrence of specific and heritable causes of death which have a characteristic age distribution; differences in rate of development between different strains; and, in some cases, a general depression of vigour, which results from inbreeding *per se*. We are dealing here with the complement of Karl Pearson's division of heterogeneity by age-dependent causes of death. It is possible by genetic selection to produce large numbers of individuals of closely similar constitution, and to draw life tables for them directly. Such lines differ considerably in rate of development and in longevity: some of them die from a single cause, while others die from a wide range of causes, but age at different characteristic rates. From these strains we could construct models of a natural polymorphic population, either by calculation, or if necessary by actual experiment. If the range of life-spans and ageing patterns were sufficiently wide, it would evidently be possible to make up a mixed population which would have a survival curve of almost any required form.

The investigation of strain differences in longevity is so far practically confined to mice, because of the absence of suitable breed-specific vital statistics for other mammals. Curves of survival are not a by-product of normal genetical or animal-breeding research, since this requires, as a rule, the maximum number of generations in the available time, so that old individuals are not kept. Survival curves showing age-specific and heritable disease have come into existence chiefly in connexion with cancer research, for strains susceptible to spontaneous tumours. With the growth of interest in age studies it should be possible to produce in the mouse a large number of lines in which the predominant cause of death is predictable, and in which the force of mortality rises at different rates.

On the normal assumptions made about the heritability of long life, one might expect to be able to produce long-lived lines by selecting the progeny of long-lived parents. This is logistically very difficult, even in an animal as short-lived as the mouse, because fertility declines much faster than vitality, and all the offspring must be reared until the parents actually die. But there is

also a biological limit on the extent to which longevity can be conserved, let alone increased, in the presence of close inbreeding. If we select the progeny of long-lived parents, there is normally some increase in life-span over the first few generations, followed by a decline, which reaches equilibrium in a life-span shorter than the wild type.

The life-span of inbred lines is in most, but not all, cases, inherently shorter than that of hybrids between them, and this shorter life is the result not of specifically inherited diseases but of a lower and more rapidly declining vigour. It occurs in lines which do not exhibit an overwhelming preference for one mode of death; where hybrids between two inbred lines retain an inherited disease-susceptibility, they may show it at the same or a later or earlier age than corresponding inbreds, but their mortality up to that age will usually be lower, and the individuals will commonly be much more uniform, both in size and performance. Hybrids between two inbred lines commonly display less heterogeneity within the line, for all their physiological responses, than do the closely inbred animals of either parent strain.

Actuaries generally attach weight to the longevity of parents in predicting individual performance. The general trend of work on animals is to show that while specific disease-susceptibilities are heritable, and may be predictable in mixed populations, as, for example, when they are colour-linked, the chief correlate of general vigour and of slow rate of mortality-increase is outbreeding. In nearly all cases the wild type appears to be longer-lived, after domestication, than any inbred substrain. There are no highly inbred human populations which are at all comparable with these laboratory races, produced by many generations of brother-sister mating. It would not be unreasonable to expect that long life in man should be best achieved by having genetically dissimilar parents. Haldane has pointed out that in this case one might expect a higher correlation between the life-span of sibs than between the life-spans of parents and children, and this, in fact, was what Beeton & Pearson (1901) found in their investigation of Quaker pedigrees. Here, if deaths in early life were excluded, the parent-child correlation in life-spans was only one-quarter that for stature. In the same way, we found an unexpectedly small parent-child correlation in the longevity of thoroughbred racehorses.

You will see that in working with human records the point has now been reached at which the objects of actuarial and gerontological study of life tables are becoming identified with each other. Both for predictive and for analytical purposes we need to break down the aggregate human survival curve into the modalities which compose it. This has already been done on Pearsonian lines in the case of disease-mortality curves, and all civilized countries now devote a great deal of actuarial labour to constructing mortality curves for those individuals who die from specific diseases—retrospective analysis. What we now require is to devise means of sorting the extended polymorphism which occurs in man, prospectively—by correlates of early ageing and longevity, rather than by Pearson's 'separate deaths'. This is perhaps the prime problem of medical biometry today. The gerontologist is interested in it for a specific purpose, apart from the important possibility of forestalling disease: if it is possible to identify in advance human genotypes whose rates of mortality-increase from general causes, as opposed to one specific disease, is significantly fast or slow compared with the universal, they could provide the experimental key to the factors which time the general age-decline in vigour.

From the diversity of growth patterns one would expect such genotypes to occur. There are genotypes which depart rather widely from the normal rate of development, as for example those which produce constitutional precocious puberty. In these children, menstruation begins in infancy, and growth is nearly ended by the age of 6 or 7. They are abnormally small owing to the gain in stature being outpaced by its early cessation. The condition is not a disease but a constitutional and probably familial anomaly (Jolly, 1955). In this particular instance, so far as can be judged from the very small number of cases, the life-span is normal. At least it is not grossly subnormal.

If there are human genotypes in which the rate of ageing deviates as greatly from the normal as does the rate of development in precocity, it would clearly be most important to identify them. The simplest case would be that in which the whole tempo of ageing was reduced, and with it the force of mortality, producing an extremely long-lived subgroup. There appears in most animal samples to be a group of resistant individuals who might represent such a subgroup. The possibility of a rare human genotype with similar properties is the main contemporary reason, other than mere anecdote, for interest in extreme age records. It gives added biological importance to the most intractable part of the life table, that which indicates the pattern of the rise in mortality at very high ages.

The difficulties of this work are familiar: I have been particularly impressed by the fact that estimates cannot be based with complete success on our present vital statistics, because the registered ages of death are so rarely confirmed by comparison with birth certificates. Although the errors discovered over the whole age range by sample verification are small, this extreme group is liable to concentrate errors which may not be random in direction and which are probably as large as those which William Thoms (1873) found in his investigation of centenarians. Special confirmation of records over 90 years is clearly not a task we can expect to add to the already indispensable work of the Registrar General's staff, but it may none the less prove eventually to be necessary for research purposes, as a special project.

On the analogy of precocious puberty, there may also be human subgroups in which the general force of mortality follows an atypical course without producing a large change in mean expectation of life. Such genotypes could only be detected actuarially, however consistent their pattern of behaviour, if there were linkage between that pattern and some extremely obvious character which is already a subject of study. The biological difficulty of planning work to detect such patterns is very great, and the problems which have been encountered with far simpler correlations, such as those between smoking and cancer, or between blood groups and tumour site, are small compared with the complications we could expect in relating age-mortality to body build, by any finer criteria than thinness and obesity—or to any other character which has large two-way social, occupational and pathological associations. Most of the work of this kind is concerned with the correlates of a single disease propensity, but the linked marker need not be of evident importance to health—blood groups or tissue antigen groups might well be examined in this way for correlations with age-specific mortality. I have mentioned the investigation of longevity and coat-colour in horses. So far as I know, no similar studies have ever been made of coat-colour in man, though I am sure that the idea would have appealed to Karl Pearson. It is worth ensuring, I think, that when surveys or longitudinal records are being prepared,

the information collected should be suitable, if at all possible, for analysis by traits as well as by specific disease states. It is possible, judging from animal investigations, that useful results might be obtained from samples much smaller than those which form the basis of most actuarial study.

What I have said about the heterogeneity of age processes is a partial answer to the question which is asked today, as in the past, whether the results of biological study of age processes offer, or are likely to offer, an inductive instead of an empirical basis for a law of mortality. Ageing is the name which we give to a group of processes in development which are deteriorative, in other words, which human beings dislike and wish to control. These processes appear to be different in different animal groups, and may be different between individuals of the same species. The gravest failing of the biologist who has discovered mathematics and the mathematician who has discovered biology has long been the gross abuse of mathematically-constructed curves to form hypotheses, rather than to confirm or disprove them. The curve of declining growth is similar in the rat and the pumpkin; it also resembles the curve of physical entropy, or of a monomolecular reaction, but so does the curve of growth for the population of the United States. The curves of survival are rather closely similar, as Pearl long since pointed out, for rats, cockroaches and motor cars (Griffin, 1928; Pearl & Miner, 1935). Any attempt to infer a natural law of mortality in the apparent diversity of age processes comes moreover at a time when, as Haldane says, it seems reasonable to stop talking about laws of nature and speak of regularities of behaviour.

In spite of this, regularities of behaviour still require to be accounted for, even under another name; the fact that human mortality is sufficiently predictable to make life assurance a remunerative business is in itself ground for expecting that the shape of that regularity will give information about its nature. The experience we have with animal life tables has in fact shown an unexpectedly high degree of consistency in the behaviour of very small samples.

In many other cases, a group of effects which have been arbitrarily isolated for practical purposes have proved to have a real biological unity apart from their interest to man. If the pattern of mortality is similar in very dissimilar organisms, this is likely to be analogous to the similarities of physical shape or of behaviour between unrelated organisms which are called convergence. There is a marsupial dog, related to the kangaroos and wombats, whose skeleton closely resembles that of the domestic dog, with which it is quite unconnected. It was evolved entirely separately in response to similar biological conditions and requirements. These resemblances have been determined by natural selection and fitness to a particular mode of life, and the common factor in age processes might be that they have a common evolutionary origin.

Medawar (1952) has suggested how this might come about. There are many animals which, unlike Murie's (1944) wild sheep, rarely if ever survive into old age. In a population made up of animals which did not weaken with age, but which was subject to a substantial mortality, young individuals will always greatly outnumber old. Now fitness, expressed in terms of Darwinian selection, is the power to produce the greatest number of fertile offspring. For this reason, the selection pressure, which controls the precision with which an animal is adjusted to its environment, must be expected to decline with age. Changes in an individual which contribute proportionately little to the next generation can only be selected for if the advantage they yield is large—changes in the same organism once it is infertile can only be selected for, or

against, if they affect other, fertile, individuals. From the standpoint of evolution, the postponement of an adverse change until after, or late in, the reproductive life is equivalent to its elimination; and selection would operate for, not against, a hereditary trait which yielded a large increase in progeny early in life, even if it led to a fatal disorder late in life.

There are a number of objections to this argument as applied to specific cases, but it seems beyond question that Medawar's view must, at least in some cases, represent what has happened in evolution. It also fits extremely well with the biological characters of age processes as we see them in animals. Human ageing is not, so far as can be detected, a single pathological change, but an increase with age in the number of pathological changes. Ageing organisms become increasingly erratic in their responses to their environment, their power of adjustment declines. The manifestation of this decline does not suggest the behaviour of a device with a deliberately-designed time limit so much as that of a device running out of programme, or operating on a programme with a steadily increasing noise level (Strehler, 1957; Yockey, 1957). It may be, then, that the law of mortality reflects the loosening with increasing age of the grip of natural selection, and a consequent progressive running-out of the evolved programme which maintains the animal as an organism.

This is an analogy which has only recently become popular through the joint interest of biologists and physicists in the effects of radiation on the rate of ageing, a collaboration which has already led to the useful exchange of ideas such as feedback and homoeostasis, that is to say the power of self-righting or maintaining equilibrium. It has particular interest because the actuaries have forestalled us. Attention has often been drawn to the similarity between mortality and entropy curves. So long as this concept was interpreted in terms of a single causal chemical basis for ageing, or the dissipation of life energy, it was barely descriptive. A far more promising idea is that the positive entropy of a system is a measure of its information content.

Organisms are islands of orderly structure, capable of reproducing themselves, and buffered against random change. Beginning as a rule from single cells they carry out complicated processes of development, and their power of self-adjustment changes appropriately as their structure changes. Ageing represents the failure of this power of buffering and an increase in randomness. The information which organizes development and behaviour is stored in two main sites—in the order of the chemical groupings in the chromosomes of the cell nuclei and in the patterns of electrochemical activity in the brain and nervous system. The internal information needed for the whole process of physical development in man or any other vertebrate is presumably present in the chemical structures of the fertilized egg; it is even present, in early stages, in a half-embryo, since identical twins develop normally. After birth, the main organ of physiological reaction to short-term emergencies is the brain. If there is a single predominant, pleiotropic cause of age-deterioration, that is to say a cause having effect on a number of different organs or systems, it would be reasonable to look for it in one of these two information-stores.

The loss of cells from the brain has occasionally been regarded as a key process in human ageing, and relative brain weight is more closely correlated with life-span than any other factor (Sacher, 1957). More interesting is the possibility that the copying of the information-carrying molecules in actively dividing body cells, and the function of similar molecules in non-dividing cells, deteriorate with age: that noise accumulates in the cellular information

system, with a steady loss of vigour, until failure occurs at a weak point. In the early stages of development, the organism may well be able to control not only itself, but the noise level of its control system. The running-out of programme might well be due to the deterioration of this control of control, rather than of the main effector system.

Interest has focused very much upon the use of information theory to explain age processes since it has been found that radiation, which specifically disorganizes the chromosomal information-store, appears to accelerate ageing. This does not mean that ageing is due mainly to background radiation, but it suggests, if confirmed, that the chromosomal changes produced by radiation may be similar to those which normally occur with the passage of time. The problem of discovering whether radiation actually accelerates a natural loss of vigour, or produces only a rising mortality in its own right, is one of the consequences of the actuarial definition of ageing. There is very little known as yet of the normal activities of information-containing molecules, or of the factors which make them deteriorate. It is interesting, however, that the greater vigour of hybrids is highly correlated with longevity, and with low variability in the face of stress. Hybrids are animals which contain a greater diversity of information in their chromosomes than do inbreds, and in many ways the biometric characters which distinguish young from old animals resemble those which distinguish hybrid from inbred animals.

At this point actuaries have anticipated research by at least thirty years—Perks, for example, was writing in 1932 that the inability to withstand destruction might be of the same nature as diminution of energy in entropy theory, or, more particularly, in terms of the modern statistical conception of entropy as 'the generation of the random element'. It is a sobering thought that papers making precisely this observation as a fundamentally new contribution are being published today in the United States, where physicists, like biologists, have recently discovered actuarial statistics.

I think I have indicated the extent of the debt which biological age studies owe to the actuary. It is a debt which will increase, and which we may be able to repay in part when more detailed knowledge of age processes in man make prediction of life-span and the forestalling of particular diseases more reliable on an individual basis. I will not discuss the possibility of making large changes in the human life-span. If the mainspring of human ageing is situated in the basic cellular information store, the discovery of the predominant causes of ageing may do little to render ageing itself controllable. In this case removal of successive causes of death may only tend to distribute all human lives more and more normally about an age only slightly higher than the present mode. Talk of one hundred or more as the potential age of man is clearly misleading, because it ignores the heterogeneity which I have discussed.

At the same time, it is clear that the rate at which the force of mortality rises is dependent not simply on time but on some physiological equivalent of an aircraft's life in flying hours. We may find it possible to alter that rate. Dietary manipulation and the use of drugs similar to those which protect against radiation (Harman, 1957) are only two of the possible lines of experiment. All these studies depend, among other things, upon a wider knowledge of the pattern of mortality in man and especially in animals. If we live to see these possibilities enter seriously into assurance accountancy, we shall, I think, have cause for satisfaction.

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