

GERONTOLOGY—IMPLICATIONS FOR FUTURE MORTALITY EXPERIENCE

an address by

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[Delivered to the Faculty on 16th February 1970. A synopsis will be found
on page 168.]

Science can be expected to affect human longevity favourably in two quite distinct ways. It already does so by suppressing causes of premature death, through the entire repertoire of applications which now render our lives less nasty, brutish and short than they would otherwise be. It could also affect longevity by postponing the process which causes our liability to disease and death to increase logarithmically with time.

The first of these two influences has already meant that in privileged countries more and more people reach the so-called "specific age" (75-80 years) but has not altered that age appreciably. The second, which is now in the stage of active research, would aim at postponement or slowing of aging itself.

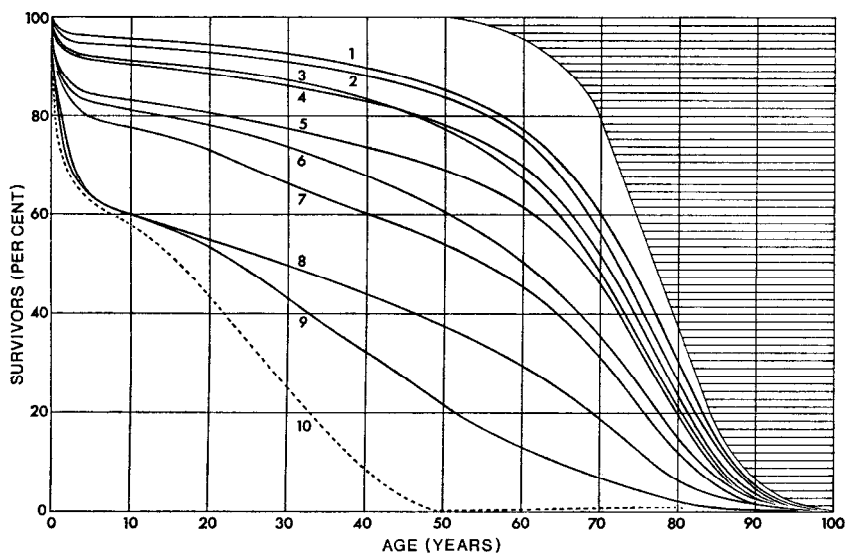
It is important to recognize the difference between this approach, based on the search for a "systems breakthrough", and the sum of all other sociomedical advances. Figure 1 illustrates what has happened to date. The large changes in the survival curve of Man over the last century represent quite simply the removal of causes of premature death: the age at which a man "becomes old", judged by the criteria of growing multiple infirmity and growing liability to die, is exactly what it was in Biblical times—three score and ten to four score years. Aging in the gerontologist's sense is a process which leads to increasing instability with time. This "loss of information" is multiform, but its rate, measured by the force of mortality, is highly stable, and its increase roughly logarithmic. The high stability of the process against nearly all environmental factors is the basis of the well-justified assurance of actuaries that all premature and accidental causes apart, an annuitant will die between the likely ages of 70 and 90, regardless of any foreseeable advance in the cure or prevention of specific diseases.

I won't trespass on actuarial mathematics, but, as Redington pointed out last year, if z is the age at which

$$\mu_x = 1,$$

then we can safely treat that age as a datum for the species.

There is, accordingly, a biological "wall" against further human life-prolongation which cannot be shifted very far by further improvements in medicine or living conditions. From Figure 1 it can also be inferred that advanced societies are just about hitting that wall, represented by an ideal near-Gaussian distribution of



- 1 New Zealand, 1934-1938; 2 U.S. (Whites), 1939-1941; 3 U.S. (Whites), 1929-1931;
4 England and Wales, 1930-1932; 5 Italy, 1930-1932; 6 U.S. (Whites), 1900-1902;
7 Japan, 1926-1930; 8 Mexico, 1930; 9 British India, 1921-1930; 10 Stone Age Man

FIGURE 1.

Life tables indicating the effects of social and general medicine on life span

deaths in which nobody dies before age 70 but all or almost all are dead by age 100. It is now computed that radical cure of the three leading present causes of death from disease in Britain or the U.S. (heart-vessel disease, malignancies, brain-vessel disease) would increase the overall life expectancy by 5 to 7 years, and the life expectancy at age 65 by 1.5 to 2 years: people would simply die soon after of other causes. The same applies to all piecemeal public-health measures. The patching-up of single age-dependent diseases is both expensive and of predictably limited use, judged by the length of further vigorous life.

At the same time, the high stability of the rate of vigour loss in every investigated species also suggests that the uniformity of the

process is not simply a statistical derivate of underlying diversity. It suggests that there is a clock or clocks, by tampering with which the timing of degenerative changes could be altered, not just piecemeal, but across the board. The conviction that such a project is worthwhile has grown steadily over the last 20 years. In many countries, investment decisions are being taken, or are about to be taken, about its future scale. Several means are already known by which the lifespan of rodents can be increased by 20% to 40%, using relatively simple dietary or chemical techniques, and one (radiation) by which it can be decreased. The exact relation of these manipulations to the rate-of-ageing clock may be debatable, but it seems highly likely that similar means would affect the human lifespan in a similar way, and the possibility is one we must all take seriously.

The reason that innocuous longevity-agents such as calorie restriction have not been long since tested in man is a byproduct of the fixity of lifespan, which affects investigators as well as subjects. So long as observed mortality is the only good measure of aging experimental gerontology must be limited to rats and mice by reason of tedium—a 20 to 30 year experiment in man, even with a manifestly nonhazardous procedure, is from the viewpoint of feasibility not on. The work of the last five years, however, has altered this, by the development—on paper at least—of possible battery tests for rate-of-ageing in the short term: the earliest models of this kind were significantly enough developed to assess possible accelerated aging in Hiroshima survivors. It would now be possible to assess the rate of change in several dozen unrelated but normally age-related parameters over 3 to 5 years in treated and untreated human samples, with a high probability that if these were all affected, so would eventual mortality be. The experiment would be of the same order of size as, say, current studies of the effects of diet on heart disease—neither bigger nor more difficult. It is a fairly safe bet that assuming only current funding, such an experiment will be begun somewhere during the next 5 or 10 years. The effect of success in applying any of the known rodent techniques to man would be that a treated subject of (say) 80 would have the values for the selected parameters, the vigour, and the disabilities, which he would have had, untreated, at age 70. The projection, if we are really influencing the clock, is that most if not all of the deteriorative changes in a given individual would be postponed roughly in step. True, one can think of likely exceptions, such as glaucoma from continued growth of the eye-lens, which might be refractory to clock-slowness and would have to be picked off singly: how many of these there

would be will depend on the number and interdependence of the "clocks" involved. But the gain, if we got it, would be wholly a gain in the duration of adult vigour. Neither infirm old age nor, ideally, pre-adult development would be lengthened.

The argument for switching a sizeable part of our medical research to rate-control rather than disease control is accordingly threefold :

- (1) longer vigorous adult life can probably not be achieved in any other way ;
- (2) the project appears on present evidence to be feasible ;
- (3) most important, it ought to be easier to affect a rate than to rewrite a programme. Accordingly, if we want to postpone death, it should be very much easier to postpone cancer or atheroma than to prevent or cure them when established.

To these can be added the fact that it is extremely likely that in view of the complexity of mammals we shall discover the nature of the effective aging "clock" or "clocks" by pinpointing manipulations which slow them down, rather than the other way round.

The nature of the manipulations worth trying changes, and their number increases, from year to year. Calorie-restriction (because it works), antioxidants (supposed to limit free-radical attack on a whole range of long-term molecules and blueprints), anti-crosslinking agents and immunological manipulations are currently fancied. Further research may remove some of these and add others. What we badly need now is experience with the assay technique, which is the same for any conceivable agent, and a "facility" devoted to getting it. At the moment nobody has one, though the germs exist in automated clinical chemistry systems like that set up by the gerontologist Leo Gitman in New York. Someone will be obliged to set up such an organization at any moment now under pressure upon the Dunlop Committee or the F.D.A. to assess an "anti-aging" pharmaceutical : it would be better to set it up more purposively, but set up it will have to be—and it could then be applied not only to aging research but also to environmental and radiation studies in man, which are now retrospective and contradictory. Even if the first three agents selected for test proved wholly inactive, the payoff in experience and in checking of the parameters chosen against age and later longevity would be scientifically well worthwhile, justifying the capital outlay while the scientific community comes to recognize the importance of rate-determining processes in public health at large.

We are now designing battery tests by which rate-of-aging could

be examined in treated and untreated people in study of feasible size. For this purpose the variables chosen must :

- (1) be sufficiently diverse and unrelated to any single assumed process for it to be highly likely that a manoeuvre which is found to stabilize all of them will also affect the rate of actuarial aging ;
- (2) correlate closely with chronological age, either directly or in a simple transformation ;
- (3) change sufficiently, and sufficiently regularly, with age for us to expect significant differences over a 3 to 5 year run at the selected age of test ; and
- (4) be measurable in volunteers without unacceptable hazard, discomfort, labour, or expense.

Age-dependent variables in man show three main patterns of change. In one large group, change is greatest between infancy and adulthood and negligible thereafter. It was this group which prompted repeated statements by twentieth-century biophilosophers that " the rate of aging is highest in infancy ". This saying indicates the limits of their usefulness as alternative indices to mortality. Others exhibit peaking (blood-cholesterol) or are suspect by reason of covert selection (blood-pressure). Of the serviceable variables, we select from those which are arith-linear with age, regardless of sign, and those which are Gompertzian or log-linear with age, paralleling the force of mortality. Mortality itself is lowest at around 12 years, but by reason of the large dispersion at low ages when the function is inverted to read off chronological age from the other variables, rather than *vice versa*, useful curves are best taken from an arbitrary origin about 40 years (i.e. from the end of the plateau of adult vigour rather than from the low point of the Gompertz curve). Other indices which are more consistently linear (e.g., collagen contractility) are therefore best adapted to the same arbitrary origin, and the test-period set between 40 and 70 years. The ideal battery accordingly measures what happens at the point of maximal change, and after the end of the period of adult vigour. The function(s) fit better with Teissier's convention than with the conventional Gompertz-Makeham function giving

$$\mu_x = e^{a(x-b)} ; x > b$$

rather than

$$\mu_x = \mu_0 e^{at} + A$$

b representing the duration of the " plateau " as seen in small population samples. The samples will in any case be small by actuarial

standards. In fact, however, the postulated origin at about 40 years corresponds roughly with the origin of the linear part of the Gompertz curve allowing for the irregularity seen in real human mortality curves at earlier ages. The study should in any case be set for choice at age 50-55 or age 60-65 where mortality will be significant and the rate of change in log mensurables large.

The battery I suggest is based on that described by Hollingsworth *et al.* which was designed to measure the rate of aging in Hiroshima survivors, from studies of about 450 Japanese. Here nine functions selected from seventeen functions examined gave a correlation with age of nearly 0.90. Compared with other attempts which lean heavily on clinical impressions, this study appears the best available starting point. It can, however, be expanded considerably in both number and variety of indices. For our objective—viz., leapfrogging dog or primate studies and testing non-hazardous procedures directly on man, the most numerous and available primate, as well as the beneficiary in view—we require a test-procedure of realistic size and duration, comparable, for example, to dietary studies or clinical trials on a single lesion. This means, in effect, a procedure giving reasonable expectation of significance for between 100 and 500 subjects including controls, with the probability of having to settle for the smaller number. The same battery could be used both for gerontological work and for environmental or radiation studies (which are now, in man, both contradictory and necessarily retrospective). Experience gained here, even if the tested agent proves inactive and both series are pooled as controls, will be invaluable in the next 10 to 20 years if reported influences on human longevity multiply.

Test Battery

For initial use, the test age should be 50 years and the sample should be confined to males to avoid further statistical breakdown and complications associated with differences in age of menopause, which affects some variables.

Available test-procedures fall into three groups—straightforward (anthropometry, clinical and chemical examination, sensory tests, psychometric tests), those requiring, for example, biopsy, and those depending on the fact that deaths will occur in the test samples. The “straightforward” groups might be modelled on the procedure used for clinical screening by Gitman, based on a flow-type centre using lay staff, and the psychometric tests should be automated, probably by means of the machine devised by Gedye and Wedgewood.

On grounds of labour, most of the more elaborate, though theoretically important tests would probably have to be limited to one-fifth or one-tenth of the sample.

Mortality would be expected in a 50-year-old sample. For U.S. or U.K. white males we would expect thirty deaths between 50 and 55, and about fifty between 60 and 65 for a sample n of 500 lives (i.e., too few for significance if the sample were any smaller, but enough to give some necropsies). A full legal-consent and pathological programme should be written in, however, to secure these. Necropsy-based measurements would include cause of death, number of lesions present, lipofuscin, collagen, cell-counts, presence of amyloid and atheroma, and organ weight.

In Hollingsworth's series of seventeen tests, the highest age-correlations were for characters (hair greying, skin elasticity) which contribute most to the "clinical impression" of age. Hair greying was excluded from the final *Hiroshima series* because of difficulty in quantification. Various ways of estimating it have been suggested: percentage of grey hairs per axilla might provide a measure and if skin biopsy were done, skin melanocyte concentration might prove an alternative. Besides the Hollingsworth-Gitman series, a number of additional tests are suggested in the table either because they are easy, even if poorly correlated with age (anthropometry), or because they are evidence of things not seen (nail calcium accumulation, which parallels aortic calcification in time) or because, though speculative, they are theoretically important (blood copper content, blood elastase, autoantibodies). These are chosen on the basis of the most accessible measure—e.g., skin elasticity rather than skin collagen properties, nail calcium rather than aortic calcium. Psychometric tests are important: several of these correlate with five-year survival as well as with chromosome-error accumulation. Others seem to correlate with the state of the heart and vessels though at a low level of significance. Psychometric changes may reflect both normal aging and subclinical disease. It would be valuable to extend our knowledge of these correlations. Automation of the Wechsler adult intelligence scale test battery should be feasible. Sensory tests (audiometry, flicker-fusion frequency, optometry) though time-consuming, are also essential.

If aging is a failure of self-adjustment it should in theory be possible to measure it directly by measuring variance but this has pitfalls arising from the aging organism's capacity for improvisation, as well as from the selection exercised at high ages by mortality itself. The Gitman battery has a statistical advantage in that it

can show not only whether the observed values are in the normal range, but also the trend of readings in the individual at re-examination. It was designed as a clinical screen, not a measure of aging, but includes a great many indices which have been independently standardized against age.

Procedure

The battery is designed, essentially, to test any non-hazardous agent or manoeuvre which might be offered as likely to affect the aging clock. The nature and diversity of some possible agents for test have been described elsewhere.

The feasible size of an aging study depends on the number of available volunteers, and on the procedure (diet, injections, or additives) required in the treated group. Recruitment of volunteers would normally be from a large employer, a closed group (monks, prisoners, pensioners), or from a profession (physicians, academics, Government employees). Administration and supervision of treatments cannot be discussed *in vacuo*. The most likely agents for trial within the next 5 to 10 years would appear to be diets, antioxidants, and possibly anticaloric or anti-crosslinking drugs. All these create problems of supervision and continuity, and English society provides few healthy closed communities from which volunteers could be recruited: some of the major difficulties of long-term diet experiments were well illustrated by a recent U.S. Veterans Administration trial on diet and heart disease. Physicians are a potential source of volunteers: they might in theory be self-policing, and they would certainly be capable of giving themselves a parenteral agent, if one such were available for trial. Choice of a 50 or 60-year baseline makes the problem of a controlled population of willing volunteers more complex by excluding students or soldiers, for example, but it must, as I said, be part of the philosophy of attempts at age-control that we should aim, initially at least, at the possibility of a late-acting agent, so as to reduce the total span of treatment required.

Pay-off

Testing of specific agents apart, the creation of an "aging assessment unit" in this country, though not cheap, is likely to be a rewarding investment. It is almost certain to be needed some time before 1980 if clinical trial of possible approaches to the slowing of the aging clock are not to be confined to rats or to patients in other countries. Tests of this kind are already in preparation in the U.S.

If the agent or procedure first chosen for test proves wholly inactive, the results will still be of prime importance as a test-run of the parameters chosen, the administrative structure, and the co-operation of physicians and volunteers. We need to find out how to do this kind of experiment, and the "know-how" obtained could well be a prime tool in the experimental medicine of the 1970's, as well as in the assessment of diets, environmental hazards, and radiation effects. It is an interesting thought that acceleration (or delay) in the process of aging, which would affect the age of onset of all diseases, not the frequency of one, is a perfectly possible side-effect of drugs or environmental factors now current. It would also be, at present, undetectable unless gross enough to influence the life-table for the whole population, and then only inferentially and in retrospect. An aging battery would bring this kind of effect within the scope of immediate detection. It would also enable doctors and actuaries to identify much more accurately which kinds of individual are likely to have long and short lives, ahead of all present indicators.

Some forecasting is already possible, regardless of the state of funding. If present research investment in the U.S. is no more than maintained (at about \$40m. per year out of a total R. & D. budget of about \$24 billion) it is fairly safe to predict

- (1) that direct experiment on the delaying of aging in man is virtually certain to be in hand somewhere by 1975, using battery techniques, and probably at more than one centre ;
- (2) if by good luck one of the currently-fancied rodent techniques proves directly applicable, some agent colorably reducing the rate of human aging is likely to be known within 15 years (it would not be fully proven until most of the untreated controls had aged) ;
- (3) the increase from such a technique could be as much as 20%, might be more, and would be worthwhile if it were less. (There is, of course, a staircase-effect here—the bigger the success, the bigger the further investment, from which the beneficiaries might in turn live to benefit: this is quite unforeseeable).

These predictions, moreover, represent the lower limit of speed in development given present investment. If, on the other hand, rodent-type procedures fail to work when started in adult life, or the postponement of age changes is patchy, the logic of the next step is very likely to have appeared already from the results. Most but not all rodent experiments have involved lifelong manipulations, but the

current view favours siting the human battery age at, say, 50, when changes in the parameters begin to be sizeable. It seems in any case logical to look first for a relatively late-acting agent in order to cut down treatment-length and increase the number of possible beneficiaries.

A purist could argue that in the absence of a universally-accepted theory of aging we should not run before we can walk. Certainly the procedures tried should be theoretically accountable, but theories of aging, judging from recent meetings, are one commodity we do not lack—what is missing is a sieve to pick those which are clinically relevant. Broadly speaking, aging probably resides in cells or long-term molecules or both. If it is a noise process, like the wear in a record, we need to cut the rate of noise injection—in other words lubricate the needle. If it is programmed, like a record which, once played, cannot be rerun, we need to run the record more slowly, though not so much so as to spoil the music. The main predictive point is that given an empirical effect on mammalian aging, we do not need initially to pinpoint its exact site of action in order to apply it, and are more likely than not to discover that site in the process of finding out what alters it. Theories are our starting points, and need to be well-chosen, but the Wassermann reaction for syphilis, that keystone of preventive medicine, was devised on a wholly false assumption, and its exact rationale is still unclear. There is a case for starting (as we have done) on shortlived rodents and working our way through the animal kingdom until we come to a second trombone, but having come so far, the need to leapfrog dog and primate studies (with a 20 to 30 year timescale) and work on man, who is the most available and numerous primate and the intended beneficiary of the research, is, for any non-hazardous procedure, overwhelming.

If we are in a mood for prediction, we could go further and guess, with reasonable probability

- (1) that given some decent human experimentation, we shall know by 1990 of at least one proven way of extending vigorous life by up to 20% ;
- (2) that the most likely agents will be simple and cheap, and will not depend e.g. on grafts or elaborate intensive-care units ;
- (3) that the direct application of such research will be at about the same rate as that of antibiotics, world-wide ;
- (4) that all existing medical services and governments will elect to apply it, or at least be unable to prevent its application.

We need to get used to the idea. My only reservation on application (other than world-wide disaster) is for the case where longevity

is shown to depend on prolonged tiresome dietary restriction. The model of cigarette smoking suggests that public concern in the West for longevity does not extend to making itself uncomfortable. If caloric restriction were to be the answer, it might have to wait for the development, e.g. of oral amylase-blocking agents (now under study as a remedy for obesity) which would leave our diet unchanged. These predictions agree reasonably well with those of the Smith, Kline and French Delphic study (a "significant extension" of lifespan by control of aging—median date 1993) and the Gordon-Helmer study (median 2023). In one of these studies one-third of the respondents considered the research unnecessary—a measure of the poor present comprehension among scientists of the limit upon conventional medicine. Judging from current extrapolations, the 10 to 20% increase mentioned here is likely slightly to predate, e.g. the immunological or chemical control of all malignancy (by the early 1990's). We might do well to start considering its psychological, political, business and demographic implications—just in case. We should also consider whether Britain ought not to be more strongly represented—ahead of the market.

Note: References to the work cited in this address are given in *The Lancet* (1970) (ii), pp. 1411-1415.

SYNOPSIS

Up to the present, medicine has successfully concentrated on the treatment of specific diseases and the successful progress has contributed notably to reductions in mortality rates in early and middle life. This progress has, however, not materially increased the total life span. Future improvements in longevity may therefore come from methods of delaying the "aging" process, rather than from specific advances in preventative medicine. Such methods are known to be effective when applied to the animal world, and the possibility of applying them to human life opens fascinating prospects. The possibilities of, and need for research into these factors are discussed.

DISCUSSION

Mr. M. D. Thornton.—I was struck by the effect of dietary control on mice. Did the mice go without food every third day from birth (or from weaning), or only from the end of their age plateau? If the former, as I gathered was the case, is it not quite likely that a similar treatment, applied to men aged 50, will fail because of the damage already done by over-eating or aging, even though it might succeed if applied from age 20 or earlier?

Dr. Alex Comfort.—It is a very complicated business. Professor Morris Ross has investigated this in rats. You can greatly postpone adolescence in mice by marked underfeeding from weaning. You can produce the effect I have shown you by underfeeding from weaning at a lower level, in this case by feeding them two days in three. If you try to change the dietary regime radically halfway through life, you may kill the mice. You have to be very careful, but it is also possible by an appropriate manoeuvre, which is quite complicated, to get quite large gains in the subsequent longevity of older mice if you start them at the mouse equivalent of age 50. So, though this particular manipulation which I showed you was life-long and would be unsuitable for man, there are methods based on the fact that Ross has measured the enzyme changes in the liver and the reaction of enzymes to different levels of feeding, which has enabled him to work out a pattern which we think could be applied to man and which could possibly work from age 50. Whether it would or not, one would not know until one had tried it, but I do not promise that it would unfur arteries already furred or reduce waistcoats already filled.

Mr. A. M. Robertson.—I should like to put a question to Dr. Comfort. I was interested in his statement that there may be one age clock or there may be several. Now, I think in years gone by a fair number of us have had the experience of putting a reconditioned engine into an old car and then discovering shortly after that the body had given out. If, particularly in the initial experiments, we actually manage to slow one of the age clocks, what might be the consequences? Suppose for example our experiments result in having a fairly large increase in population between, say, the ages of 80 and 100, a large proportion of which is blind. I wonder if Dr. Comfort would care to comment on the social implications of this, how he would deal with it in his testing and what effect such a situation would have on his subsequent research.

Dr. Comfort.—I did mention this possibility in relation to glaucoma as one of the things which might well resist it. The question of multiple clocks, of course, applies most at the moment to transplant surgery. It is the main argument against imagining that you can greatly prolong human life by renewing one organ. When planning this particular battery test, we did try to scatter our parameters, so that we might get an idea whether we were altering one group of processes only or whether we were producing an "across the board" modification. The second is possible.

What you suggest is equally possible and until we have tried it I think we shall not know. I did mention that if we found the results were clinically unacceptable, obviously we should have to think again, but there clearly is a potential for there to be more than one clock in aging. One of my colleagues computed that if you took the effects of background molecular damage on the tail tendon of the kangaroo, which he measured (I don't know why he chose that), the kangaroo's tail would fall to pieces after 250 years, but this is not what kangaroos die of. I have no doubt whatever that if we did postpone all the existing causes of death, our patients would still die, if not of similar causes at a later age, then of new ones which would appear, but it is very difficult to chart this until we have been able to divide the thing up by a multi-parametric test and work out whether we are altering all of those things which I have put up on the board just now or certain clear-cut groups of them. It is quite clear that we might easily find that we were altering everything except the rate at which the opacity, for instance, of the lens increased with age. I think you chose a very good example with an ophthalmological problem because, in fact, blindness in rats is the one thing which failed to be slowed down by the initial underfeeding experiments done by McCay many years ago. Rats commonly go blind in old age and underfeeding did not delay this, but it turned out that the blindness in this case was due to the irritant effect of ammonia produced from urine in sawdust and that if the rats were kept under different conditions this blindness did not occur. I think we might have to deal with this in the same way with people. We should have then to pinpoint, and if possible deal with separately, any special pathologies of this kind which appeared.

Mr. A. P. Limb.—I read the transcript of Dr. Comfort's remarks before his address and I am afraid there is still one major point that I am not quite clear about. You spoke, Sir, about the existence of a biological wall in the beginning of your address and it was clear from the early slides that you showed that the experiments on rodents had increased the life expectancy of the rodents, and that the curve was horizontal for a longer period, but it still hit the same wall in the end. Then, in the later part of your address, you spoke of the possibility—no more than that—of one day discovering that it was theoretically feasible at any rate to reverse the aging process altogether, which seems to me to suggest that the wall would vanish into thin air and that we might live for ever. Are you holding out to us, Sir, two distinct possibilities?—first, that by slowing up the aging process we may find that the wall still exists and that we all continue to die by the time we reach 100, but that more and more of us live to advanced stages and, on the other hand, the possibility theoretically at any rate of there being no wall at all.

Dr. Comfort.—As to the first part of that, the wall is moveable to some extent in rodents. You find that in some of those curves I showed, I did point out that the author had omitted the tail of the curve. It is sometimes very hard to see from these small experiments, and it is obviously a standing problem whether you are merely making a curve squarer or whether you are moving it to the right. In the case of the dietary experiments, it quite clearly was moving to the right on the large samples.

If this wall represents the statistical expression of a hit-or-miss process of attack on important molecules or structures, which is what it seems to be, then if we slowed this down by, for instance, giving antioxidants which

prevent pre-radical attack or by the underfeeding which may in itself affect the rate of formation of molecules and, consequently, the rate in which errors are incorporated into them, we should, in effect, be moving them all to the right. The sequence is that DNA produces RNA which produces the synthetases which produce the proteins. Whether or not we can reverse an error here will depend where the damage is. If the damage is in the DNA, then it is most unlikely that we can fill up the worm holes in the punch-card or, once the record is scratched, take the scratches off it again; in this case there would be a finite rate at which the scratches would express themselves. On the other hand, it may occur lower down the chain; there is a good deal of evidence now which I can't go into here (it would take too long). It can be shown that in the case of some fungi and some lower animals aging phenomena are transferable by cytoplasm as if they were caused by a virus, and the likelihood is that what is transferred is a faulty machine tool which makes faulty products and more of itself. This suggests a virus-like, faulty synthetase and the theory is that if this occurs you get mis-specification of cells and molecules. Some of these cells have diverged so far that they cease to be regarded as self, and all sorts of autoimmune rejection processes spring up around them and disorganize the body. This is one group of theories. The theory may be quite wrong, but on the other hand, if it is right, aging would be theoretically—though not necessarily practically—reversible. On the other hand, if the theory is of the "scratch on the negative, scratch on the record" type, like loss of teeth, then it does not seem to me to be theoretically reversible, at any rate in the foreseeable future. I did not want to over-stress the rejuvenation business or how far one could get reversibility. All I said was that it is theoretically possible, if the synthetase theory is correct, that this could be done. Whether it would be practicable is quite another matter, because nobody has yet reversed the aging of a fungal hypha let alone a mammalian cell and it would involve scrubbing out all the faulty protein and replacing it; whether this is in any sense feasible one has no means of knowing. I am merely saying that we don't need to regard rejuvenation as fundamentally impossible if this model applies. In that case, I suppose the barrier (if one could do this) would vanish but I think the result much more likely to be patchy than with the other approach. If we slow down the rate of accumulation of error, then I think that might well not be patchy: it might be uniform across all diseases. If we start to try to reverse an established error, I think the result is almost bound to be patchy.

Mr. D. G. Kellock.—I should like to take this opportunity of thanking Dr. Comfort for his address and saying how very much I have appreciated it, not only as an actuary but as one who is already a pensioner.

The first point I would like to ask is about the experiment on the mice where they were not fed every third day. It seems to me that an important aspect of this must be the level of feeding with which you started. In other words, if the normal diet of these mice was, in effect, overfeeding and you simply reduced it to just enough to maintain health, it may not tell us as much as we imagine it does.

The next thing I would like to say is that one of the advantages of an occasion like this is that it enables one to disabuse one's mind of ideas which are probably quite incorrect. One thing I have always understood is that as one gets older regular exercise helps to delay the aging process. I don't know whether there is anything in that or not: whether the body

is kept better by regular exercise than by sitting in front of the fire. And the other point that occurred to me as one way of delaying aging which Dr. Comfort has not mentioned is to take a trip to Mars. We are told that by the Theory of Relativity, of course, the clock is slowed down and if you went far enough you might come back at the same age to find the World 5,000 years older.

Dr. Comfort.—In taking those in reverse order, I don't want to embark on Einstein's paradox. It has been argued, in fact, that the process would be circular and you would lose as much coming back as you gained going out. I don't think that is, in fact, true. I think the point of this is merely that your clock would appear to move more in a shorter period. Is not that so? You might well appear younger than people who had lived in another place but your experience of time would still be the same. You would not feel younger for it. All that would happen is that you would get back and you would find that everybody else appeared to you much older, which is not quite the same.

As regards exercise, it is perfectly true. A friend of mine (he is a physician in gerontology in North Italy) used to have a whole lot of smugglers among his patients who walked miles every day dodging frontier guards and carrying 40lb. of cigarettes on their backs and they apparently had none of the diseases to which the flesh was heir. When they got bicycles they still remained healthy; finally in the last few years they got these little Vespas and motor cycles and they all started getting coronaries. But, in fact, we had a number of papers on this at a recent conference and the most recent and elaborate study which has been done on this shows that it is not actually very easy to demonstrate a correlation between continued exercise and survival. The point is, and this has been claimed for everything from sex to politics, that keeping it up is good for you, whereas, in point of fact, this is often a measure of the existing vigour of those who can keep these things up. The fact that you can ride a bicycle at 80 may be due to the fact that you are vigorous at 80; or it may be that you are vigorous at 80 because you are still able to ride a bicycle. The effects in a critical study are less than I would personally have expected them to be and I would not be prepared to exclude exercise. It certainly does you no harm.

Then, as to the overfeeding of mice. It is true that laboratory mice are grossly overfed, but, in fact, if you feed them *ad libitum* all the time, they will eat as much as they are capable of eating and if you only feed them *ad libitum* two days in three they will eat as much as they are capable of eating on those two days, but they don't, in fact, catch up on the third day. And the composition of the diet also (which I can't go into here because it gets extremely complicated) does play a considerable part in this. It is also possible to give them an *ad libitum* diet which produces the same effects merely because its composition is different, and I think one could also infer that an entirely different optional diet would be necessary for men as against rodents, which have an entirely different digestion. This is what we want to work out. At the moment we have no means of approaching it.

Mr. G. D. Gwilt.—I have not done any experiments on mice, but I have some children and I have noticed that after feeding—they may have been lethargic beforehand—after feeding they immediately have enormous

amounts of energy and they rush around the place. Whether this lengthens their lives or not, I don't know, but I just wondered whether lack of feeding would mean that their life would slow down and that perhaps these mice live longer because they are like the record which is pushed through the post with an advertisement and which, if you play it more slowly, will last longer. But, of course, you get the same amount of information off that record as if you had played it fast. Now, when you work your way through the vegetable kingdom to a second trombone, does he drop a minor third or does he play adagio? In other words, are you getting the same amount of life out of people if they live twenty years longer? Would I be speaking more slowly if I took your pill?

Dr. Comfort.—If you were a mouse, Sir, you would not. McCay measured the lifetime calorie output of his underfed mice in the original experiments and it is away above the normal total for the species. In fact, they are getting many more heartbeats per lifespan, many more gramme calories per lifespan than the normally fed ones. Their metabolic rate is not greatly reduced by underfeeding. Their tail collagen ages much more rapidly than usual, though you would expect the aging of that to be slowed. This is because they remain juvenile and they remain very active and they use their tails as a fifth hand, rather as baby mice do, and consequently their tails tend to wear out. But I think it is a mistake to think that energy, as expressed by children running about, is quantifiable against aging. If there is a process which is a taxi-meter process, it is more likely to be a transcription process of molecules rather than a straightforward output of energy. In other words, it is more likely to be the number of generations of copies which have been made of a particular molecule rather than the amount of rushing about which that particular subject does. I thought you were going to ask a different question. I thought you were going to mention the fact that whereas in children food produces energy, in me at any rate it tends to produce lethargy and I find that I am much more dangerous driving when I have been eating than when I have been drinking.

Mr. R. E. Macdonald.—I should be interested to have Dr. Comfort's comments on the alleged longevity of the inhabitants of the State of Georgia in the Soviet Union and other groups such as the Mormons in North America. If this longevity is confirmed would it not be more productive of fast results if field studies were to be conducted amongst these long-living communities rather than the trial and error application of pharmaceuticals which Dr. Comfort has outlined?

As actuaries we are uncomfortably aware of the demographic and financial implications of these studies and they are seriously unfavourable. Presumably the whole operation is justifiable if the end product were a sufficient understanding of biological molecular processes that the degenerative diseases could be eliminated. Such diseases are evil afflictions of mankind but I feel that we ought to beware of regarding death from natural causes as a similar affliction; in fact it seems that old age is quite often regarded by its sufferers as "a long time a-dying".

Dr. Comfort.—With regard to the Georgians, you all know very well that if there was a village in Ireland where everybody was 150, this would be a great local joke at the expense of everybody else. I have met some of these old gentlemen and they did not strike me as exponents of what the

Irish call codology. Field studies which have very extensively been carried out, in fact, tend to show in the case of the long-lived Georgians that few of them have any written records. Where records are available and where they have colorable memories of historic events, the extreme longevity is highly correlated with their family history. It runs very much in some families and not in others. Because of this, if it is true at all I strongly suspect it is genetic rather than environmental and I do not know that we should gain a very great deal from examining this because we cannot necessarily duplicate their hand of genes. My friend, Professor Pitsche-laouri, has done an enormous amount of field work on these Georgians and they are very old men: they may not be 150, but if they are only 100 they are still doing pretty well. The balance of probability is that these are long-lived families. I think there are some long-lived families in Scotland that have a large number of centenarians, but one cannot necessarily score this for use at any clinical level.

Now, I am aware of your worries about demography. I think you want to remember that when one worries about the population problem, for instance, one is not here assuming that extra years of life will produce one more child per year. I think that is a separate problem, but also, on a world-wide basis, supposing we did bring this off and lengthen the period of adult vigour, that addition is wholly to the years of productive life. Now, whether you become a Vietnamese farmer or an actuary, you are spending your first thirty years of life reaching your optimum knowledge of the subject, you then may have, shall we say, another thirty years of vigorous life and, after that, you again tend to become dependent either through infirmity or through conventional retirement. If we could prolong the middle period at a time when training is becoming longer in every walk of life, it seems to me this would be a gain in the World's wealth though it might lead to some other difficulties. When we talk about demography, obviously whether or not this is going to produce a transient bulge will depend on whether we get one increment or more than one increment. If we got only one we should get a transient bulge but we should get it perhaps at the time when population problems were becoming most acute, so I think it would have both gains and drawbacks. I take the, I think, humanist view here that it is an expression of concern for people to keep them with us for as long as possible, so long as the quality of life is such that they would wish to stay. It is often said that old age has its compensations. Well, I may have seen more of geriatric hospitals than you have, I don't know, but it strikes me that one asks for compensation only when one has been run over and I don't think that visits to most old people's homes gives one any very great impression of the beauty of old age—or of the desirability of so-called death from natural causes, because when that death occurs comfortably in one's sleep or after a short illness like the late Bertrand Russell's, this may be one thing, but when it is preceded by growing infirmity, particularly growing cerebro-vascular infirmity, which makes one not only "ga-ga" but aware that one is "ga-ga", this is a thing which I would like very much to see something done about. In fact, my own interest in this whole subject dates from during the war and being put in charge of a chronic ward where, because nurses were some of them then conscripts, any nurse who disgraced herself was put on a geriatric ward to get her out of the acute wards. I can remember an old man dying, and I observed that ants were walking in and out of his nose, and it struck me that this was not the way in which the old should be treated. We owe

a responsibility to these people. We could either postpone these evils or remove them altogether. I think that we should all agree that this is itself worth doing. I don't think we can probably remove them altogether ; I think we might be able to postpone them and I am certain we can mitigate them.

Mr. G. M. Murray.—I was wondering if Dr. Comfort could perhaps elaborate on the control of his human sample of 500. Dr. Comfort mentioned only death as a decrement to this group, but presumably there would also be considerable mobility of the population both within the U.K. and by emigration, and even voluntary withdrawal which may or may not be made known to the doctor. Perhaps Dr. Comfort could expand on how he hopes to obtain meaningful results from his sample group of 500. While mentioning diet as a possible means of extending the useful human lifespan Dr. Comfort did not give details of the type of diet envisaged. Now, is it not the case that, in view of the fad for dieting which already exists in the United States, there are several groups following specialized diets and would it not have been expected that some results might already have been seen from these dietary groups, if diet alone were sufficient to extend the lifespan?

Dr. Comfort.—Again, if I may, I'll take the points in the reverse order. Diet is not the highest priority, I think, in these trials. I would expect, if I had to sample tomorrow and were asked what I would try first, I would try some of the naturally occurring non-toxic antioxidants. I will explain the reason for the choice. "Naturally occurring", rather than BHT and BHA and these things, because if we use antioxidants which are widespread in groceries we run the risk of sensitizing perhaps one in our 500 patients and if we do sensitize him to these big doses, he is not going to thank us because it will mean that he can't eat any processed groceries. So one would choose an antioxidant which is not used in groceries. We have our eye on some substances which are naturally occurring and will therefore not require Dunlop Committee approval, which could be used in this way and which would be worth trying.

Now, as to diets in special groups, until we have a measure of rate of aging it is going to be rather difficult to apply. It is no good just looking and saying, "Mortality in vegetarians" or something of this kind ; though we could do this and it would be interesting. It presents very great problems in getting sensible statistics, as you know, out of volunteers and getting notice of deaths. I, for my sins, have had to chase up mammalian vital statistics and it presents great problems. When the good Lord turned us out of Eden, he not only sent the angel with the flaming sword, he also sent another angel round to mess up all the animal statistics which made it nearly impossible to find any. The only people who were incorruptible were the bookmakers, and the general stud book of racehorses does, in fact, provide us with a large mammalian body of vital statistics which have been kept up with loving accuracy over the centuries. One can get some data from that, albeit with great labour, and albeit that one was confronted with a lot of problems through a gentleman who called his horse "Ditto". This sort of thing you have. I am open to any statistics people can get from vegetarians, but the way I would propose to do it would be to get them to come up, when we have got our battery, if only for even two successive measurements arranged at an interval of one year. This might tell us something, and what it would be likely to tell us would

be whether dietary manipulations were affecting one clock group, as it were, out of a number of such groups. I don't think they will affect the whole thing right across the board.

Then, as to where we get our people from. We are going to have to plan this very carefully. I had thought of trying to get volunteers who were to some extent committed and involved. We might be able to do it by making use of one of these computer centres such as the one the Institute of Directors has, where we would get people to volunteer to add a few additional tests and we would already have a body which could be used retrospectively as a rough measure of the rate of change in parameters, but I think we might perhaps do best if we actually did draw our volunteers from, for instance, physicians and research workers who have some interest in the on-going experiment. This has worked in America where they have got better results, particularly in dietary experiments, by getting biologists and physicians to take a hand in this than by going, say, to a volunteer working population from one factory where there is a lot of turnover and where they are not very conscientious about recording results. This is the initial idea we had. I can see that it might have objections and it might be difficult in any one city to get enough people who would be within the age group. But we are now looking into this, not in relation to aging retardation, but in relation to the accumulation of people for clinical trials of drugs which palliate diseases in old age. That is an entirely separate problem, but when I have a bit more experience of clinical trials in old people I may be able to answer the question more accurately. Meanwhile, if you have any suggestions I think they would be extremely valuable. This one of the big problems, getting not only an amenable volunteer population but one which won't have too large an error introduced by inability and by opting out of the experiment. We hope to use as a carrot the giving of a full medical check-up with these tests. A lot of people would value that and would come readily for it and, although I don't think it greatly affects the detection of disease, it might collect us hypochondriacs, but hypochondriacs are a fairly long-lived group, I think.

Mr. J. M. Denholm.—I would like to revert to a point which a previous speaker raised in connection with the biological wall. Dr. Comfort mentioned in his remarks Redington's paper, in which he did some experiments on μ_z when $\mu_z = 1$. Now, without going into philosophical questions as to what you have got when you have got z and accepting it for what it appears to be, if my memory serves me correctly, z showed a secular reduction, certainly so far as the English life population was concerned, over the first half of this century. Scottish population statistics over the first half of this century show a reduction in z of something of the order of three years both for men and for women. Now this may be a statistical effect due to a different mix in the population. On the other hand it may be a real effect due to pollutants, diets, stress, etc. I would like to ask Dr. Comfort, if I may, whether he has met this effect—the gerontologist trying to sweep back the approaching tide—and, if so, what is the reason for it?

Dr. Comfort.—I think we should be able to suggest both something more about the reality of that change and the reason for it. If, instead of having to adopt what is the inevitable actuarial method of waiting until people have died and ascertaining at what ages they have died, we were

able to find some technique for measuring the rate at which they were approaching death while they are still alive, that would be a gain; and that is why I want to approach this question through battery tests, because in order to elucidate the death experience which we actually observe, we really require to be able to intercept the process at a slightly earlier biological stage than its actual expression in the death of the individual. If we could do this, it would enable us to say—not with any certainty but we would draw certain inferences—whether there are factors in our environment which are shortening or lengthening life. In the case of *z*, presumably they were acting rather selectively on the last decile, weren't they, of the population and they were cutting down extreme longevity. This is exactly what one found in horses. There, it was due not to the environment, but to the fact that as stud breeding became more and more commercial horses were being put down on attaining the age of 20 instead of being kept in stud as long as they could stand up; it may be that urban civilization is not conducive to great longevity. We do find that the extremes of old age do tend to occur in rural populations, probably perhaps because the people there remain active. One does not know. There are a number of things one could guess about. To know whether this effect is real, one would like to measure the rates at which the people are aging and if the only way we can do this is by measuring a mortality computed for a large population, then we are bound to be rather at the mercy of statistical guesses, whereas if we could measure it we would also have on the computer the trend for a given individual. My method will, in fact, I think make it possible, up to a point, to measure even the rate of progress in a single individual, because we would not have only the cross-sectional measurements for each of these parameters for each age group. We might then be able to see whether being above or below the mean for the progression over those years is associated with later or earlier mortality. We might find we had to wait, in fact, a full 40 years for the end of the curve to have developed but I think that if we do the experiment now there will be a harvest of this kind from it which would make these purely mortality-based figures much more intelligible in terms of biology. At the moment, I think it is very hard to guess quite what they mean.

Mr. G. F. Menzies.—I would be interested to know a little more of how you conduct these experiments, say, on mice and rodents. These graphs which were shown, for example—what sort of numbers are they based on in order to give you significant results? You mentioned that possibly in experiments on humans, you might hold out medical examination as a carrot to induce people to come forward. Would this not interfere with the randomness of either your control or the body on which you are experimenting in that, presumably, if the examination disclosed anything material the subject would try to do something about it? Perhaps I could just add one further point. In a sample of 500 deaths, as actuaries, before we would consider a really significant difference, we would be looking for a plus or minus of about, say, 14 deaths per annum, and to regard this as significant one would need to take the experiment over a number of years during which the rate of mortality might be changing for reasons quite different from the experiment; for example, a general raising of the standard of life.

Dr. Comfort.—I was not, in fact, thinking that we would be likely to get very significant differences in the actual deaths observed, but I think

we might well get significant differences in some of these other parameters which we measured with the whole population of 500.

Size of animal experiment, of course, varies in the slides I showed you. The average for these experiments is something like 250 mice, and I can't in my head work out what the standard deviation was for the expectation of life in a given case, but in most of these cases they have been accounted by a fairly detailed statistical analysis showing the difference to be significant. I shall have to look those figures up for you from the actual papers which I showed.

It is true that if we were to offer medical examination, as you say, we might pick up some diseases in the group and treat them. Provided this would apply to both groups, I don't see it would seriously upset the experiment and, in fact, the number of abnormalities you pick up in a healthy population at random medical examination is much less than most people seem to think. I don't know how many diseases you actually detect in insurance medicals, but I would have thought pretty few. You pick up the odd hypertension and the odd diabetic, and a few infections, but, by and large, I would have thought that few undiagnosed diseases appear at this type of examination. I don't think the type of screening test which is put forward for this purpose would really help very much to pick up anything except gross disorders which their doctors would be able to pick up in a normal medical. If we, for instance, picked up the odd case of TB in one of our samples, one would imagine that this would average out between the controls and the others, and it is no worse than the fact that some are going to drop out of the samples through developing some disease which makes it inadvisable for them to go on attending the clinic, for instance. I think we plan our experiment to get round this.

I am interested to ask you what number you think would be adequate for this type—not based on mortality, based largely on the measurement of a large number of change in parameters and correlated material?

Mr. Menzies.—We would start, I should think, by taking the standard deviation of the deaths or events as approximately the square root of the number occurring. A significant deviation in the rate under examination might be taken approximately as plus or minus twice the square root of the number occurring divided by the population which gave rise to the event.

Dr. Comfort.—That would not help us very much with the deaths we are working on. It is not very easy, in fact, to compute, until we have the data, whether our results will be significant or not. Hollingsworth with his sample of Japanese got highly significant changes between age 50 and age 55. He did not, in fact, demonstrate any accelerated aging in the Hiroshima survivors, but that is probably because man is much less radio-sensitive than mice, and your guess is as good as mine whether any of these agents which we want to try will produce any significant changes. I think we can only do the experiments and see.

The President (Mr. D. W. A. Donald).—By the way you have received Dr. Comfort, by the questions you have asked him, you have shown very clearly how much you have appreciated his coming here tonight. Sir, you have dealt with a difficult and technical subject not familiar to many of us with great clarity; you have obviously held our interest throughout

and we are grateful for the wit and humour with which you have, shall I say, gilded the pill. To us, as actuaries, this is an extremely important subject : some of our offices may have larger liabilities accruing under their annuity contracts than they do under their assurance contracts : we have a National pension scheme promised—or threatened (I am not sure which is the word)—in 1972 and, if you get going on it, Sir, it may be that 1·3 or 1·5 will be quite the wrong rates to allow for abatement. I think that this is a subject in which the actuarial profession ought to interest itself if purely in a defensive way for the sake of our own offices or the people whom we are advising. I don't know whether the research that is being carried out is hampered by lack of funds or lack of people, but, it seems to me, that in self defence it might not be a bad idea for the life insurance industry to take a hand in it if purely to get, as it were, an early warning of the disasters which your well-intentioned efforts might be bringing.

I think I need say no more except again to thank you and to ask you, Gentlemen, to show your appreciation of Dr. Comfort's presence here, his giving up his valuable time and travelling 400 miles in the depth of winter, by giving him a very hearty vote of thanks.