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RESEARCH AND THE AGEING POPULATION

A Wiley – Interscience Publication

1988

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Contents

_Symposium on Research and the Ageing Population, held at the John E. Fogarty International Center for Advanced Study in the Health Sciences, Bethesda, Maryland, USA, 28–30 April 1987_

*Editors: David Evered (Organizer) and Julie Whelan*

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Preface

The 265th Ciba Foundation Symposium (134 in the new series) on Research and the Ageing Population was held at the Stone House, National Institutes of Health, Bethesda on 28–30 April 1987 as one event to mark the centenary of the National Institutes of Health and the long-standing friendship which exists between the Ciba Foundation and many scientists at the NIH. The meeting brought together those engaged in basic biomedical research — epidemiologists, demographers, physicians, health-care planners and economists. The major objective of the symposium was to review progress in research relevant to the elderly and to consider its significance in planning for the provision of care for elderly people, taking demographic, social and economic factors into account. The meeting was chaired throughout by Dr T. Franklin Williams, Director of the National Institute on Aging.

We were pleased to have the opportunity to mark the centenary of the NIH in this way. The occasion also gave us the chance to establish many new scientific contacts and to renew existing ones. We were gratified by the enthusiastic response to the symposium and by the welcome we received at the NIH. We are particularly grateful to Dr James Wyngaarden, the Director, who first extended such a warm invitation to us, and to Dr Williams and Dr Craig K. Wallace (Director of the Fogarty International Center) for their help with the planning and organization of the meeting. We also appreciated the very considerable professional help that we received from Marcia Aaronson and Rita Singer, who both took such pride in ensuring that everything ran smoothly throughout.

David Evered

Director, The Ciba Foundation
Introduction

T. Franklin Williams

National Institute on Aging, National Institutes of Health, Building 31, Room 2C02, Bethesda, Maryland 20892, USA


The field of ageing research is much indebted to the Ciba Foundation for undertaking this symposium: I am sure the outcome will be an important contribution to our further understanding in this challenging area. The participants are all leaders from scientific arenas closely related to ageing and the common problems of older people, and it is a privilege to have so many disciplines joining in the discussion of such important issues.

Let me suggest what our priorities should be in this symposium and what we may hope to learn from it. My suggestions may be especially important for a topic as broad and multifaceted as ageing and its related disorders. I would first suggest that we try to discard our stereotypes of ageing, and recognize that new knowledge is coming along rapidly and that we must be prepared to change our views. That is a standard principle in science, but I am afraid that, because of the strength of traditional views about ageing, stereotypes still abound, and infect scientists as much as the general public. It is all too often true that most of us in ageing research have not kept up with advances in related fields, and are prone to repeat or use stereotypes in our thinking. We should be prepared to discard these stereotypes and be open to the new ideas that will be presented here by people in different disciplines from our own.

My second suggestion is that we concentrate on what seem to be the most significant new findings and ideas, and that we should—in the formal papers and the discussions—be open to speculation about where we might go in our further research.

Thirdly, and most important of all, we should try to look for potential interactions between the fields represented in the symposium, and for the implications of our own work for that of others—for example, the implications of cardiac findings for the field of dementia, and vice versa; the implications of the common presence of multiple chronic conditions (such as diabetes, chronic lung disease and arthritis) for infection in old age; and so on, across the whole range of topics. We should be looking for ways by which we can inform and stimulate each other, because of the major interactions that are inevitable as part of the complex picture of old age. As an example of this interaction, it is my
experience that diabetes and cardiovascular disease both have a very low prevalence in people with dementia of Alzheimer's type, and conversely one rarely sees this type of dementia in older people with diabetes or extensive cardiovascular disease. People with Alzheimer's disease are astonishingly healthy in many other ways; specifically, they rarely if ever have diabetes. That observation may or may not hold up on further investigation: I know of one study (unpublished) which tends to corroborate this clinical observation. All sorts of speculations could arise if this is true, and would call for further investigations.

I offer this as one observation. One of our tasks here is to look at the cross-reactions and cross-implications between our different fields of expertise, not only from one disease to another, but from basic biological approaches to the variety of both biomedical and social problems in older people. This symposium provides the opportunity, through the conjunction of able people from many fields, to contribute a combined impact to ageing research.
The health of the elderly population: results from longitudinal studies with age-cohort comparisons

Alvar Svanborg

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Abstract. In the longitudinal study of 70-year-olds in Göteborg the first age cohort (born 1901–1902) has now been followed for 15 years and the second cohort (born 1906–1907) for nine years; an intervention study has been added to the third age cohort (born 1911–1912). These longitudinal perspectives (derived from studies of samples shown to be representative of the total population) have successively improved the possibilities of distinguishing between ageing manifestations and symptoms caused by definable diseases. In addition to previously reported figures on the proportions of apparently healthy people at age 70 and 75, preliminary conclusions from the follow-up periods from age 79 indicate that at that age at least 20% do not suffer from symptoms of definable diseases. These findings have allowed detailed analyses to be made of the morphological and functional consequences of ageing as well as the calculation of clinical reference values for the age interval 70–79. The improving possibilities for distinguishing between ageing and morbidity have allowed certain conclusions to be drawn on obvious differences between age cohorts relating to the prevalence of disease and manifestations of ageing. These age-cohort differences could not be related to migration and ongoing genetic changes but there is indirect evidence for relationships to lifestyle and certain environmental factors. The reasons for these age-cohort differences in the manifestations of ageing are being analysed retrospectively through information on differences in living conditions between the cohorts and prospectively through the intervention programme (InterVention Elderly in Göteborg, IVEG).

1988 Research and the ageing population. Wiley, Chichester (Ciba Foundation Symposium 134) p 3–16

The longitudinal study of 70-year-olds in Göteborg, Sweden (Rinder et al 1975, Svanborg 1977) now includes three (Fig. 1) different age cohorts (Svanborg et al 1984, Mellström & Svanborg 1987). The first age cohort (born 1901–1902) has been followed for 15 years, up to age 85, and further yearly follow-ups are planned. The second cohort (born 1906–1907) has been followed for nine years. Because of the rather remarkable differences between these two cohorts — differences not only in the state of health, but also in the
### YEAR OF INVESTIGATION

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**FIG. 1.** The present design of the longitudinal study of 70-year-olds in Göteborg, Sweden, showing the three age cohorts. IVEG, intervention programme (InterVention Elderly in Göteborg) added to the study of the third cohort.
Longitudinal and age-cohort studies

rate and manifestations of ageing (Berg 1980, Svanborg et al 1984, 1986) — a third age-cohort sample of 70-year-olds (born 1911–1912) has been studied. In order to test certain theories about the reasons for these age-cohort differences, which were also obvious in the comparison of the second and third age cohorts, we added an intervention programme (InterVention Elderly in Göteborg, IVEG) to the study of the third cohort (Svanborg et al 1986, Eriksson et al 1987).

These longitudinal perspectives, derived from a broad and detailed investigation covering many of the basic biological, clinical, behavioural and social perspectives provided by age-related morphological, biochemical, physiological and psychological changes, have successively improved the possibility of distinguishing between the manifestations of ageing and the symptoms produced by definable diseases and disorders. We have given examples of these changes in various reports, on clinical biochemical reference values (Landahl et al 1981, Lindstedt et al 1983, Svanborg 1985a, Larsson et al 1986); on age-related changes in blood pressure (Landahl et al 1986), heart volume (Landahl et al 1984) and lung function (Sixt et al 1984); on body composition (Steen et al 1979); on striated muscle function (Aniansson et al 1983); and on cognitive function (Berg 1980). This information, from studies of groups representative of a defined and characterized population, has considerably modified previous thinking on the nature and manifestations of ageing. An awareness of the complexity of both the morphological and the functional consequences of ageing has replaced previous simplified and stereotyped ideas about human ageing (for reviews of results from our longitudinal study see Svanborg et al 1982, Svanborg 1983, 1985b, 1987).

There are certain functional measures in humans that show only a two-phase curve and start to decline almost directly after the initial phase of growth and maturity. But for many functions the relationships between functional ability and chronological age are more complicated, and a global generalization implies at least four phases (Fig. 2). The beginning of the phase of decline varies considerably over the age period from about 20 to about 75. The previously reported ‘terminal phase’ of ageing (Svanborg et al 1986) has become more and more obvious, the longer we have followed our sample. This is a period in which in some individuals vitality goes down rapidly, with no obvious medical causes for this functional decline (phase IV in Fig 2). The reasons for an accelerated functional decline might be an ultimate lack of reserve capacities within different functional components.

It has commonly been thought that different components of organ systems, such as the immune system and the cognitive system, should show similar age-related changes. The discrepancy between the rate of functional decline in psychomotor speed (perceptual speed), which starts to go down around the age of 20–30, and the other measurable parameters of intelligence and memory (well preserved at least up to age 70 in the healthy elderly), is one
FIG. 2. The relationship between functional performance and chronological age. Some functions (— — —) decline earlier than others.

example of the diversity in the rate of ageing within functionally related systems. This particular discrepancy also has clinical implications. From our experience, it is a common reason for the misdiagnosis of dementia/senility in the elderly. This is especially the case when the perceptual speed is further lowered because of sensory deprivation, such as unwanted isolation, bereavement, different forms of somatic injury and disease, or mental depression (Svanborg et al. 1984). During phase III (Fig. 2) it has also been fascinating to see longitudinally how the age-related changes over time often imply not only downhill slopes in functional performance, but also periods of levelling-off (Larsson et al. 1986) or even certain improvements, although the longer longitudinal perspective obviously must imply a functional decline.

The longer the observation period available, the more we realize that previously reported (Svanborg 1977, Landahl et al. 1977) over-diagnosis not only is real but is more common than we previously thought (see, for example, Svanborg et al. 1982, Svanborg 1983, Landahl et al. 1984, 1986, Svanborg et al. 1986). Our present experience suggests that at age 70 at least 30–40% of subjects were without symptoms that could be referred to any definable disease. The preliminary conclusion is that the proportion of 'healthy' people at the age of 79 is still at least 20%. We have therefore been able to study ageing in a group of apparently healthy older people and also to calculate
clinical reference values for the age interval 70–79. We have, we hope, therefore also improved our diagnostic criteria for these elderly subjects.

Generally, our studies have shown that under-diagnosis is very common in the elderly. One reason is that elderly people expect to have certain impairments at older ages and do not even mention certain problems to their doctors. This suggests that a more systematic interview technique is urgently needed for examining elderly patients. Another reason is that many symptoms are much more discrete and sometimes also different in the elderly. Chest pain, for example, is relatively uncommon in myocardial infarctions in the elderly, and mental depression is often manifested by symptoms that are more vague and difficult to identify than in younger age groups.

The study shows, however, that over-diagnosis seems to be even more common than under-diagnosis. The reason for this is mainly our limited knowledge of how to distinguish the manifestations of physiological ageing from symptoms of definable disease. Examples of over-diagnosis include hypertension, congestive heart failure and dementia. The studies also show an over-consumption of medical services and of drugs by those experiencing loneliness as an everyday problem in life.

We have also made a detailed investigation of the nature and prevalence of different forms of disability and handicap in the elderly. As an example, at the ages of 70, 75 and 79 years, we found 3%, 5% and 8% respectively to have such advanced handicaps that institutional care is considered to be necessary. On the other hand, at 70 years, 95% of the elderly have thus been shown to be without advanced handicap. Further measurements of functional capability for certain ‘activities of daily living’ have been made. For example, a standardized test was performed in bathrooms, where older people’s ability to look after their own hygiene was assessed. The investigation of arm and hand function included tests of coordination and strength, power capacity in opening jars and bottles, and the basic movements of the arms and hands involved in washing and dressing. We have also investigated walking ability, and have shown, for instance, that only a few 79-year-old people are able to walk at the speed needed for pedestrians to cross street intersections with traffic signals (Lundgren-Lindquist et al 1983).

The dynamics of ageing and of the state of health have been further emphasized in our comparisons of the manifestations of ageing and the prevalence of disease in the three age cohorts studied at age 70, and of the two cohorts for which results are now available for ages 70, 75 and 79. So far as we can judge, from studies of the migration in the Swedish population during this century, these rather marked age-cohort differences do not seem to be explainable by genetic changes. Indirect evidence exists for relationships to lifestyle and to certain environmental factors. A marked change in longevity and further life expectancy has occurred. In 70–79-year-old women, age-adjusted mortality during the years 1970–1979 has decreased by
no less than 19%. The age-cohort differences observed also include differences in cognitive ability, dental state, and body mass index, as well as in the occurrence of advanced handicaps in women and the prevalence of certain diseases. We also have indirect evidence for probable future negative age-cohort differences, because both smoking and alcohol abuse, which are becoming more common in female cohorts, have been found to be related to lower muscle strength, lower skeletal density, and altered gonadal function (Mellström et al 1981, 1982a, Mellström & Svanborg 1987).

One example of the dynamics of ageing — an example with practical clinical implications — is age-related changes in blood pressure (Landahl et al 1986). These changes show, first, a difference between men and women; second, a difference between systolic and diastolic pressure; and finally, a two-phase curve for systolic and diastolic pressure in women and for systolic pressure in men. We have also found a three-phase curve for diastolic pressure in men, with an increase up to age 50, a plateau between 50 and 70, and a decline between 70 and 79! The diagnostic criteria for hypertensive disease have become even more difficult to establish, now that we have shown that the heart volume increases with age, apparently for physiological reasons (Landahl et al 1984). The age-related morphological changes seen in the heart seem to be mainly a structural adaptation of the ageing heart in the direction of an increased volume. Our results from echocardiographic measurements (Lernfelt et al 1987) indicate that the ratio between the volume and thickness of the heart wall is astonishingly constant. In the ageing heart there is mainly an eccentric hypertrophy, in contrast to the concentric hypertrophy of essential hypertension.

The clinical problem is illustrated by the fact that the general doctor treating the elderly very seldom has the methodological resources available for distinguishing between these different forms of heart changes. Higher blood pressure and a greater heart volume in elderly people than in younger adults are commonly taken as evidence of hypertension with increased heart load. We know that at present no fewer than 30% of women at the age of 70 are treated because of a blood pressure level considered to be too high. At age 75, close to 40% are receiving such treatment. The percentage of males — the sex that really could be expected to have an increased risk of cardiovascular complications — is considerably lower: 13% are being treated for blood pressure at age 70 and 17% at age 75, in Sweden.

The complexity of these problems is further illustrated by our observations of ongoing age-cohort differences in blood pressure (Table 1). Clinical reference values calculated from studies of present generations might thus not be relevant for the coming generations of elderly people.

We now have both direct and indirect evidence that (1) inter-individual differences commonly increase with age, up to at least age 79; (2) sex differences vary markedly over short periods of time; (3) age-cohort differ-
TABLE 1  Arterial blood pressure in three age cohorts of 70-year-olds in Göteborg

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<td>Cohort 1</td>
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<td>Systolic blood pressure</td>
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<td>Diastolic blood pressure</td>
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Comparisons were made in subjects not receiving treatment for hypertension (β-blockers, diuretics, and/or other anti-hypertensive drugs).

...ences arise within periods as short as five years; and (4) differences exist that imply not only the occurrence of different definable disorders, but also the manifestation, and rate, of certain age-related functions. This evidence must stimulate our thinking in the direction of possible measures for postponing or preventing age-related changes. We are now tackling these problems in the intervention programme added to our longitudinal follow-up of the third age cohort of 70-year-old people (Svanborg 1985c) (see Fig. 1).

The three main aims of the intervention study (InterVention Elderly in Göteborg, IVEG) are:

(1) Early and more correct diagnosis and treatment. We know from the results of the longitudinal study that both under-diagnosis and overtreatment are common in the elderly. Some examples have been mentioned here. Early diagnosis and treatment become urgent when the reserve capacity is falling.

(2) Improved options for meaningful lives with a reasonable degree of activity. The elderly in Göteborg were found to have much greater intellectual and physical capacities than was generally thought. Their ‘trainability’ seems to persist not only up to age 75, as was previously shown for striated muscle (Aniansson et al 1983), but up to 80 years and beyond, from our present experience.

(3) Improved possibilities for preventing or postponing the influence of various risk factors. Accidents are too common in the elderly. Unwanted sudden changes of a psychological and social kind, such as bereavement, are a common cause of a rapid decline in vitality and state of health (for a review see Mellström et al 1982b). We need a better understanding of the
mechanism responsible for this decline and also systematic studies of possible preventive and supportive measures.

An intervention period of two years has now been completed. After a follow-up period of another three years we shall compare this sample, in whom interventions were made, with controls of the same cohort, as well as with the 75-year-olds of the two previously investigated, longitudinally followed age cohorts (see Fig. 1).

Indirectly we thus have many reasons to believe that preventive/postponing measures could influence not only the occurrence of certain definable disorders in the elderly, but also the rate and functional consequences of ageing. In the intervention study we want to see the extent to which such effects might be obtained when the lifestyle and environment are altered, even at such a relatively advanced age as 70 years.

Acknowledgements

The study of 70-year-old people in Göteborg was made possible by grants from the Swedish Ministry of Health and Social Affairs, the Commission for Social Research, the Swedish Medical Research Council, the Göteborg Medical Services Administration and the Göteborg Administration of Social Services.

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Longitudinal and age-cohort studies


DISCUSSION

Katzman: You mentioned the possibility of improvements with ageing during your phase III (Fig. 2) and you also suggested that joint disorders would not lead to selective mortality. Do X-ray changes improve in individuals between the ages of 70 and 79?

Svanborg: These were cross-sectional comparisons. When we started with the first age cohort we unfortunately did not include methods for comparing joint disorders in our programme. We thus simultaneously studied the third cohort at age 70, the second at age 75 and the first at age 79. In the first cohort we have followed the subgroup of probands with joint disorders longitudinally to see to what extent they had a higher mortality between 70 and 79 than those without joint disorders. Although we know that certain forms of malignant rheumatoid arthritis might have an increased mortality, there were generally no statistically proved higher mortality rates in those with joint complaints and joint morbidity than in those without joint problems. Neither did we find any correlation between the density of the skeleton and the prevalence of osteoarthritis.

Fries: We have looked at the methods of assessing radiological progression in osteoarthritis by use of longitudinal study (Altman et al 1987). We studied pairs of X-rays of the same joints taken from two to five years apart, and were unable to find any case of improvement in osteoarthritis when studied longitudinally. But we did find evidence of two populations of individuals, one group who are remarkably stable over a five-year period and a second group of subjects who show progress over this period.

Svanborg: We haven't said that we have found an improvement, longitudinally, in osteoarthritis! I said that, from these cross-sectional comparisons, we have no evidence for an increase in the occurrence of osteoarthritis with age, at ages above 70. The common observation that elderly people often suffer from pain less than younger individuals might explain a difference in current complaints between the ages. We have never claimed any evidence for longitudinal radiological improvement in osteoarthritis—for example, for a disappearance of radiologically observed spurs.

Wenger: When you examined the three cohorts, could you make any comparison of changes in lifestyle? You suggested that lifestyle can exert an important effect. What have you been able to conclude about changes in activity, diet, smoking, or levels of stress (so far as one can determine the latter)?

Svanborg: Epidemiologically the prevalence of tobacco smoking is one of the lifestyle factors that is rather easy to define. In women the first two cohorts had very similar smoking habits (12–13%); the third cohort had only a slightly higher prevalence of women smokers (15%). The real increase in smoking in older women will thus be expected in later cohorts. There were also age-cohort
differences in men in smoking (50%, 37% and 34%), but showing a decreasing trend. There were also differences in the known occurrence of alcohol abuse between the cohorts. Changes in the educational system had taken place between the first and third cohorts; exposure to television and other forms of the mass media has obviously been different for these age cohorts. There must also have been differences between the cohorts in nutrition during childhood, especially in the First World War period.

We have tried to measure and estimate most of these differences. There are clearly lifestyle differences, but they are so manifold that we need to add the results from our intervention study before we can talk about causal relationships, aside from these differences related to smoking and alcohol abuse.

Wenger: What was the pattern for alcohol abuse, and was it comparable in men and women?

Swanborg: We found differences in alcohol abuse between men and women. However, it is difficult to identify alcohol abuse in an epidemiological study. We have therefore taken a contrast group of abusers of alcohol that has also caused social problems, and compared this group with all the others. Although we knew that alcohol abuse exists in the other group also, we have found marked differences between the two contrasted groups.

We know that the density of the skeleton at age 70 is about 25% lower in tobacco smokers than in non-smokers. We have also found that muscle strength is lower in smokers. In those whom we can really define as alcohol abusers we also found more loss of skeleton at the age of 70 than in the contrast group. Let me re-emphasize that the women in Göteborg who are smokers had had their menopause two years earlier than non-smoking women. We have also measured gonadal function indirectly and showed differences between smokers and non-smokers in the balance between oestrogenic and androgenic gonadal steroids. This is one reason why we can expect certain negative age-cohort differences, especially in women, when the present age cohorts with a higher prevalence of smokers reach the age of 70.

Arie: You are finding these changes in lifestyle and health-related factors between the three cohorts. Have you any information on deliberate changes made by your subjects, late in life, in part perhaps in response to local awareness of your studies? Is there a spontaneous intervention effect, in other words?

Swanborg: It is difficult to say to what extent our longitudinal study has influenced the behaviour of the elderly, and also the way doctors treat them. We have made very thorough studies to ensure that the age-cohort differences are not due to differences in non-response. Obviously, publications from a study like this have reached not only colleagues in medicine from different specialities, psychologists, sociologists, architects and so on, but also the general public. However, I think it unlikely that the later two cohorts before the age of 70 would have been markedly influenced by our comments on the vitality and health of earlier cohorts aged 70 or more.
In the intervention study we have certainly been aware that the alterations we have suggested for a representative sample have soon been extended to many other people. When we found marked differences in vitality and state of health among those who had lost their spouse compared to those still living with a spouse, we were of course interested to understand the reason for a lower state of health and longevity among widows and widowers. We know, for example, that the mortality rate increases in widowers by 48% and in widows by 22% during the first three months of bereavement. Our interest in helping these widows and widowers has apparently filled a need for these people, and care for the elderly in this situation has therefore become the interest also of other care givers besides those in our research study.

Finally, let me emphasize that if we compare age-cohort differences at age 70, 75 and 79 in the first two cohorts, we find that the differences are approximately the same at these three ages between the first two cohorts.

Andrews: In a ten-year period, many things will change besides an individual's characteristics and behaviour. To what extent in a longitudinal study is it important to monitor changes in socioeconomic conditions in the environment—such as pollution levels or other environmental risk factors, or changes in the provision and efficacy of health services? Perhaps these extrinsic elements have significant effects on your cohorts over that period of time?

Svanborg: There are many implications of those questions. In the comparison of, say, the state of health of different professional groups exposed to different forms of pollutant, one has to consider the possibility of the selection of certain individuals to certain jobs. When we look at specific risk factors, such as the inhalation of asbestos, our study material is too limited to allow any conclusions. In comparisons between Sweden and Japan we found, astonishingly, enhanced longevity in industrial areas of Japan with considerable air pollution—but also a better economy, better schools, better nutrition, better hygienic and medical facilities, and so on. The possibilities of making correlations between state of health and air pollution factors in the Göteborg study are very limited, although we know that there is an interesting age-related difference in mortality between different professional groups.

Solomons: I'd like to speculate about the implications of your data. There is no question that you are demonstrating statistically valid trends, and many of us have been trying to identify the intermediate or proximal causes responsible for the trends. But perhaps there are inherent cycles here—like the business cycle—and you happen to be looking at the down slope, or the improvement slope, of a very long, undulating cycle that may operate over centuries, and that we know nothing about. If this study had been done 50 years earlier or were done 50 years hence, you might see similar differences across time, but in the opposite direction (with increasing systolic pressures with ageing, and so forth). There is no answer to this, but it is something always to consider when we look at longitudinal data.
Svanborg: You are talking about regression towards the mean, and when we look at different variables, such as blood pressure, we have to take that possibility into consideration. As far as we can see now, there must be a risk that the increase in longevity in Swedish women will level off, or maybe even go down, because of the fact that coming generations will have a much higher prevalence of smokers and presumably also of alcohol abusers. Also, future generations of women smokers will have started smoking on an average around the age of 18, rather than at the age of 32 in the first two age cohorts we studied.

Riggs: Going back to your Fig. 2, which showed four phases of the curve relating functional performance to age, I was specially interested in the fourth phase in which there is a rapid deterioration in function, presumably near the expected time of death. To what extent is this a true accelerating deterioration of organ function, and to what extent a gradual loss of organ function over many years, to the point that a lower threshold for the maintenance of organ function is passed? This second possibility appears to be what happens in hip (proximal femur) fracture; the incidence of hip fracture is very low in middle life, even though bone is being lost over many decades, but late in life the bone density falls below the threshold required for skeletal integrity, resulting in an exponential increase in the number of hip fractures.

Svanborg: We believe that the discrepancy between our results and some animal studies is partly due to the fact that in the human it is more difficult to measure total functional ability—most organs have such a remarkable reserve capacity. There is evidence that the dopamine content of the caudate nucleus might fall to about 20% of what it was when we were young before Parkinsonian symptoms develop. We know that we can remove one kidney and half of the other without causing obvious functional decline. This final phase might be the 'naked' or 'basic' rate of ageing, but it goes very fast in some individuals and might therefore not reflect our continuous rate of change over the years. Some of our patients have had good hearing, sight and so on, yet within 1½–2 years they might go downhill in function at a very high rate. So it seems to be difficult to explain this fourth phase solely by the idea that this part of the curve reveals the 'naked' rate of ageing.

Kirkwood: The interesting example of glomerular filtration rate, which you find to decline from the age of 50 and then to level off between 70 and 79 and decline again thereafter, seems to be a good candidate for what Dr Williams mentioned in his Introduction—the importance of interaction between different factors. You also showed that systolic blood pressure rises progressively, levels off, and then starts to fall over a somewhat similar age range. If there are interactions between different factors, quite small changes in one factor can perhaps be amplified through interaction with other factors to produce a significant change over a period of time.

Svanborg: Our data on glomerular filtration rate are longitudinal, but there are cross-sectional comparisons in the literature showing that glomerular...