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Aging: a subject that must be at the top of world agendas

The aging of populations demands major changes across society and health care

Today we join some 100 other medical journals from over 30 countries in publishing an issue devoted to aging. Our aims are to alert readers, the public, and governments to the radical changes being created across the world by the aging of populations and to contribute a substantial body of research and information on all aspects of aging. Aging emerged as the favoured subject for the global theme issue after a two stage voting process among editors of medical journals. Research has shown that readers also rank it as the top issue. One reason that aging emerged in first place is that it affects everything—cells, physiological systems, clinical medicine, society, economics, ethics. This theme issue—in the tradition of the *BMJ*—tries to reflect that broad impact.

Aging has become an important issue because of dramatic changes in life expectancy. Only one in six Britains born 150 years ago reached 75, whereas two thirds of those born today will. People over 60 currently constitute a fifth of the British population but will be a third by 2030. Those aged over 80 are the fasting growing section of the population. In 1951 Britain had 300 people aged over 100; by 2031 it will have 34 000. Other developed countries have seen the same growth in numbers of elderly people, while countries that have more recently become industrialised are going through a much more rapid transition in their age structure (p 1037). Yet—because most of the population lives there—60% of people over 60 are in the developing world, and it will be 80% by the middle of the next century (p 1082). We have much still to learn about the impact of aging on the developing world.

We are thus moving to a world where older people will outnumber children—and we are not well prepared. Our lack of preparedness is illustrated by every country in the world having well developed paediatrics but only Britain (in the words of Robert Butler, an American expert on aging (p 1082)) having well developed geriatrics. We don't want children fighting elderly people for limited resources, but our societies need to change as birth rates fall and life expectancy rises. Britain is about to begin a major process to try and achieve this change—through the Debate of the Age, which its organisers hope will involve 80% of the population (p 1034).

Basic scientists have played a central part in increasing life expectancy and are now busy trying to understand aging. David Mann describes the impact that molecular biology is having on the study of aging and makes clear that aging and the disorders of later life are not the same thing (p 1078). Richard Doll and Richard Peto explore a similar theme in an editorial (p 1030). Death is inevitable but disease is not. Aging is unlikely to be explained by one theory. It probably results from an accumulation of unrepaired damage to DNA, mitochondria, and other structures and is clearly a function of both genetic inheritance and environmental factors, including lifestyle.

The aim of science and medicine is less to lengthen life and more to reduce the number of years that people spend diseased or disabled. Kay-Tee Khaw points out that those aged 60 in Britain currently must expect to spend about a quarter of their remaining years with some disability (p 1090). Yet healthy aging is clearly possible, and those who are rich, well educated, don't smoke, and are physically active do seem to be experiencing a "compression of morbidity"—their extra years of life are largely healthy. There are wide variations in the prevalence of chronic disease in different communities, and Khaw describes important measures people can take to help maintain their health. Simple measures, such as a healthy diet and exercise, are often under-rated by doctors and patients. But healthy aging will always be difficult for the many elderly people around the world living in poverty and poor housing. Public health measures are as important for promoting the health of elderly people as for promoting the health of those of any age.

Some features of promoting health in elderly people do not, however, seem to be well understood. For instance, coronary artery disease is seen by many as a disease of middle aged men, but—as Nanette Wenger makes clear (p 1085)—it is more common in elderly women than in any other group. Women are usually 10 years older than men when they first show signs of coronary artery disease. More women than men die of coronary artery disease in the United States, and a white postmenopausal woman in the United States is 10 times more likely to die of heart disease than of breast cancer or hip fracture. Furthermore, mortality and morbidity after myocardial infarction and coronary revascularisation are greater in women than men. Another public health issue that does not receive enough emphasis is smoking. Antismoking messages are often directed at the young with the aim of trying to stop them starting to smoke, but numbers of elderly

smokers are increasing in many societies—and smoking remains the leading cause of chronic illness and premature death among elderly adults. A special issue of *Tobacco Control* (which is published by the BMJ Publishing Group) explores strategies to reduce tobacco harm among older adults.

Clinical medicine has much to offer elderly people, and doctors in most specialties find that their patients are becoming steadily older. Marco Pahor and William Applegate review recent advances in geriatric medicine and discuss the possibility that non-steroidal anti-inflammatory drugs may help prevent dementia and cancer, and that antioxidants may protect against some age related disorders, urge doctors to treat high systolic blood pressure, and show how targeted and coordinated home health care can improve the health of elderly people and reduce admissions to hospital (p 1071). A randomised controlled trial from New Zealand shows how a tailored exercise programme can reduce falls at home among elderly women (p 1065), while a study from London describes a tool to help predict which elderly inpatients are likely to fall (p 1049). Unfortunately, disorders in elderly people are commonly iatrogenic, and a Dutch study shows that two of five elderly patients admitted to a general medical ward experience adverse drug reactions (p 1057). Paula Rochon and Jerry Gurwitz alert doctors to the need to consider any new medical symptom as a possible adverse drug event (p 1096). In this way, we can avoid treating adverse drug events with further medication.

A final recurrent theme of this special issue is discrimination against elderly people. A British study confirms previous evidence—summarised by Jerry Avorn (p 1033)—showing that elderly people are regularly excluded from clinical trials (p 1059). Yet it is often difficult to extrapolate the results of trials conducted in younger people to older people. Graham Sutton argues that agism has led the British to exclude women over 65 from breast screening (p 1032), although they have the highest incidence of the disease. A British study finds that doctors rarely examine the breasts of older women even when there are strong clinical reasons for doing so (p 1058). Two other studies show that elderly people often miss out on chiropody (p 1058) and influenza vaccination (p 1060), which may in part be due to discrimination. Two personal views illustrate the way that elderly people may be patronised or neglected by health professionals (p 1100 and 1101), and the British newspaper, the *Observer*, has just begun a campaign to highlight the way that elderly people are too often badly treated in hospital.

If the world is to cope with the dramatic aging of populations, changes in attitude, organisation, and behaviour are needed. We hope that the material in this issue of the *BMJ* will contribute to that change.

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Editors, BMJ Aging issue

There is no such thing as aging

Old age is associated with disease, but does not cause it

Taking all diseases together (but ignoring deaths from accidents or violence), the total death rate in developed countries such as Britain is 500 times greater at age 80 than at age 20. For vascular disease, chronic respiratory disease, and cancers of the digestive or respiratory tract, this ratio is more than 1000 to 1. Why? What biological mechanisms account for this vast difference in mortality between old and young adults? And, since so many major diseases are much more common in old than in young adults, does this imply that there must be some common biological process called "aging" that causes all of these large differences in mortality? Our answer, particularly for cancer, is that it need not do so.[1]

What the major diseases of adult life have shared for tens of millions of years is a common set of evolutionary pressures tending to relegate them to old age, but such relegation is likely to involve many different mechanisms. Natural selection acts much more strongly against death in early adult life than against death in old age. Hence, other things being equal, all major adult diseases will tend to be much commoner in old age than in early adult life.

Before asking whether "aging itself" has any direct effects on the development of disease, it may be useful to consider whether there is any fundamental biological process that can usefully be labelled aging. If so, what is it? Is it baldness, greyness, dementia, wisdom, vascular disease, preneoplastic changes, immunological deterioration, collagen cross linking, or genetic changes in particular somatic cells? Many years ago the biologist Alex Comfort commented: "Throughout its history, the scientific study of ageing has been ruinously obscured by theory, and particularly theory of a type that begets no experimental hypotheses." Perhaps the very existence of aging itself is just such a theory. For example, if we want to understand the mechanisms by which lung cancer arises we should study these and not the mechanisms of some other age related phenomenon such as the menopause; conversely, if we want to understand the timing of the menopause, of the progressive loss of tissue elasticity due to cross linking of collagen, or of senile cataracts we should study each of them directly.

When many different age related phenomena are fully understood, some will probably have part or all of

their mechanisms of origin in common, but some may not. For now, unnecessary confusion can be avoided, at least in discussions of the biological mechanisms of particular chronic diseases, by accepting that the underlying mechanisms may be different and by avoiding careless use of such an undefined physical concept as the "aging" of a tissue or an individual.

Consider, for example, the development of carcinomas in organs that are common to both sexes (and hence not strongly influenced by age related changes in levels of sex hormones). Such carcinomas account for about two thirds of all deaths from cancer in developed countries, and the death rates from them are roughly proportional to the fifth power of age[2] (which, since the fifth power of 80 is 1024 times the fifth power of 20, yields the 1000-fold difference in mortality already noted between ages 80 and 20). Ever since the 1950s it has been recognised that such a power-law relation could be produced by a "multistage" model in which the process of changing a normal epithelial stem cell into the seed of a growing cancer involves several consecutive changes in the genetic material of that cell, with the rate of progression of a partially altered cell from one stage to another being largely unaffected by age.[3]

If, for example, there are six stages that are rate limiting (that is, improbable in the time available) then the mortality from cancer would be expected to be approximately proportional to the fifth power of age.[2 3] Roughly the same relation with age would, however, be predicted by many different biological models,[2] such as those having fewer stages but some selective advantage of partially altered cells over their unaltered neighbours[4] or more stages but susceptibility to neoplastic change varying substantially between individuals.[1] Hence, these early multistage models had little predictive power, but they did show that the 1000-fold differences in cancer rates between old and young adults do not necessarily imply any effect of "aging" on the separate cellular processes leading to cancer. This conclusion has been confirmed by animal experiments in which carcinogenic treatments were started at different ages. In some (despite a power-law relation of risk to the duration of treatment) age was of no independent relevance to the production of cancer,[1 5] and in others carcinogenic treatments elicited cancer less rapidly in older than in younger animals.[1 6 7]

But, although there may be no direct link between any one thing that can usefully be called "aging" and the rates of the separate cellular processes that culminate in cancer, there remains a strong and mechanistically unexplained relation between the life span and the rates of these processes. Consider, for example, two species such as mice and men that differ 1000-fold in body weight and 30-fold in normal lifespan (2.5 years v 75 years). Suppose that both species have a probability of a few per cent of developing cancer by the end of this life span and that in both the incidence of cancer is roughly proportional to the fifth power of age. It can then be shown that, at age t years, the probability per gram of tissue of giving rise to a new cancer tomorrow would be about $10^{-7} \times t^5$ for mice and $10^{-19} \times t^5$ for humans.[1] These differ by a factor of a trillion. Whether this factor is a billion or a trillion does not matter so much as the fact that it is very large—as it has to be, for if every mouse sized lump of tissue in the human body had a probability of a few per cent of producing cancer in a mouse sized life span, humans could not survive.

It is intriguing to consider that just a few tens of millions of years of evolution since mice and men separated have produced this trillionfold decrease in the constant of proportionality relating cancer rates to the fifth power of age. Presumably human cells have managed to defend themselves against mutation far more effectively than mouse cells, but the details remain obscure, and these vast differences have not yet been accounted for, remaining an important challenge to our understanding. For, if we could produce just a twofold further decrease in this constant in humans, we could halve the cancer problem.

Similar considerations probably also apply to a wide range of adult diseases: the fact that they tend to arise in the same part of the life span is not good evidence that they have similar underlying mechanisms, nor is it good evidence that any single, unifying change awaits discovery that could properly

Richard Doll at 85

Richard Doll and Richard Peto

Sir Richard Doll, perhaps Britain's most eminent doctor, is 85 this week. He illustrates how much can be achieved by older people: as well as writing the editorial on this page, he has played an important part in the three "big" medical papers published in Britain in the past two weeks (on hormone replacement therapy and breast cancer in the *Lancet* and on passive smoking in the *BMJ*) and written a piece on wine and heart disease for our Christmas issue. He will also be giving the keynote address at our conference next October to commemorate the 50th anniversary of the streptomycin trial, one of the first randomised controlled trials.

Sir Richard is best known for his work on smoking and health. The work led to first himself, then doctors, and then much of the general population stopping smoking. The reduction in tobacco deaths in middle age has been greater in Britain than any other country. About half of those who smoke are killed by the habit, while among those who have never smoked or who have stopped 80% survive to 70 and 33% to 85. Two thirds of the ex-smokers who have survived to 85 would have died if they'd carried on smoking. They owe their lives to Sir Richard.

Sir Richard will deliver a birthday lecture, "Nature and nurture in cancer control," at 1 pm on 28 October in the Radcliffe Infirmary, Oxford. The *BMJ* wishes Sir Richard a happy birthday and thanks him for some of the best papers we have published in the past 50 years.

Richard Smith *Editor, BMJ*

be called "aging." What the many diseases of old age chiefly share is, we suggest, not a common aetiology but a common teleology.

We acknowledge extensive use of previous work by S E Parish and R G Gray.[1]

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Will you still need me, will you still screen me, when I'm past 64?

Breast screening policy is based on ageism

Breast screening policy in Britain is based on women's age, as it should be. Age is the most important risk factor for breast cancer, and in younger women the health gain from screening is vanishingly small. A lower age limit is therefore rational. But when age related decisions are irrational or inequitable, they may reflect ageism. Is this the case with the upper limit for breast screening?

The NHS screening service follows the recommendation in the Forrest report that in view of poor response rates there is insufficient benefit from offering screening to women aged 65 and over, though it may be available on request.[1] This recommendation was based on the Utrecht study and the United Kingdom trial,[2 3] both of which apparently showed a rapid fall in acceptance of repeated screening over 65.[1] In Sweden, by contrast, uptake was 80% to age 74.[4] However, neither the Utrecht nor the British trial recruited women over 65. Forrest presumably meant the Nijmegen study, where women aged 70 and over had 34% uptake in their first screening round, falling to 21% in later rounds; women aged 60-69 had 80% uptake, falling to 54%.[5]

Implementing the Forrest recommendations required a huge effort. Therefore, initially to target the service at the age group most likely to benefit was reasonable. But women aged over 65 dropped off the agenda completely. Their uptake of screening, cancer yield, and benefit from screening were uncertain, but no research was commissioned; and in an otherwise wide ranging update on research evidence after Forrest,[6] the question of upper age limits was ignored.

Several studies indicate that screening 65-69 year olds confers benefits similar to those seen in 50-64 year olds: a 25% reduction in breast cancer mortality.[5-7] Results for women aged 70 or more are equivocal, being based on small numbers, and these results needed to be checked in the context of the NHS. But the only British studies were small, in interested centres that had spare capacity.[8-10] Thus their uptake rates may have been atypical; the studies were too small for a precise estimate of cancer yield; and their costs could not be extrapolated. Moreover, these data, although positive, provoked no reaction. This selective blindness in scientific and health policymaking circles is mirrored by the media and the public. The press regularly carries stories of breast cancer in young women, ignoring the predominance of the disease in older women.

National policy in Britain is that women over 65 are not invited but can be screened on request, but few women are aware of their rising risk of breast cancer with age, or of the value and availability of screening. Those who try to refer themselves face barriers,[11] and less than 2% of the eligible population are screened.

The policy is illogical in equating programme success with a screening uptake of 70%. By that criterion, we should invite women aged 25 and abandon screening of 50-64 year olds in central London, where uptake is low.[9] The costs of invitation are trifling compared with the costs of screening and assessment. So which is the real fear: that older women would fail to attend if invited, or that they would have the temerity to turn up?

The crux of ageism is the stereotyped negative view of older people that leads to policy decisions that disadvantage them. Ageism seems to be embedded in NHS culture.[12] This is illustrated by a mental experiment: imagine that your local screening service, aimed at 50-64 year olds, achieves a 75% uptake, 5% above target. This would be cause for pride, and any resource implications would be tackled in a positive spirit of building on success. Now imagine a 5% extra workload from self referrals of older women: cause for dismay perhaps, and resentment of an unfunded extra burden?

So while it is true that "if the healthcare system is to serve the greater good of the population then resources must be directed to where they will be most highly valued,"[13] one has to ask whose values will count. For example, when in 1986 Forrest recommended screening of 50-64 year olds, the government supplied the money and political drive to make it a reality. By contrast, in 1995, when the House of Commons Health Committee[14] advocated routine invitation of 65-69 year olds (on much stronger evidence than was available to Forrest), the response was to call for further research.

That research takes the form of demonstration projects in East Sussex, Leeds-Wakefield, (where I am an investigator), and Nottingham. These deflect the pressure for routine invitation of older women, and lool like a stalling tactic. Their value will be if they permit a well informed extension of the national programme. Whatever their results, policy judgments will still have to be made, and one wonders what set of values will influence these. Ageism in health policy is not unexpected, but in breast screening, which has a strong scientific basis, it is easier to challenge.

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Including elderly people in clinical trials

Better information could improve the effectiveness and safety of drug use

See also p 1059

Practitioners face a difficult paradox in prescribing for the elderly. Those aged over 65 comprise only about 14% of the population in most industrialised countries, yet they consume nearly a third of all drugs. Ample evidence indicates that, even in healthy elderly people, aging impairs the way the body handles drugs. In ill elderly people these changes can be exaggerated considerably.[1]

In an ideal world data from premarketing and postmarketing surveillance studies would describe how a given drug is likely to affect older patients differently from younger ones.[2] Unfortunately, rather than being oversampled in clinical trials, to reflect their distribution in the drug consuming population, elderly people are inadequately represented.[3 4] Moreover, when "old" patients are enrolled in trials, they are likely to be in their mid-60s and in quite good health. Nevertheless, we do not know to what extent "the elderly" in such studies are represented primarily by robust 66 year olds, since the oldest stratum is often simply described as "≥65," a classification which is useless to any geriatrician, primary care practitioner, or person who has watched a grandparent age over time.

Why is there such a mismatch between the routine conduct of premarketing trials and the information needs of prescribers and patients? The answers lie in economics, statistics, and politics. The "old old" are a messy lot physiologically. They are far likelier than the young to have coexisting medical problems, for which they are likely to be taking other potentially interacting drugs. They also have the distressing property of being more likely in the middle of a trial to suffer an infarct of heart or brain or simply to drop dead. They are bad news for the drug development process.

All adverse events and deaths occurring in a premarketing trial must be reported and scrutinised. One of the costliest components of drug development is the cost of the capital tied up before a product is approved. And if the voices of economics needed any reinforcement, our statistical colleagues would be quick to say that the increased variance introduced by a heterogenous population of older subjects will reduce the precision of study estimates, requiring larger samples or increased duration to achieve the same study power. Not surprisingly, therefore, trial designers are often reluctant to enrol many truly elderly patients. In the absence of a compelling countervailing force to include more older patients, the regulatory requirements remain disquietingly loose on the topic of age.[5]

After approval of a drug elderly people are penalised again. Postmarketing surveillance studies could provide a second opportunity for systematically studying the effects of a drug in populations that include many older patients.[6] However, here too most nations fail to encourage a coherent, robust response. Insights about important, even life threatening, side effects are too often left to arise from ad hoc observations by alert practitioners, rather than through any proactive method of public sector surveillance.[7]

Fortunately, these problems are soluble through a few straightforward measures. Firstly, any drug likely to be used by elderly people should be required to undergo premarketing testing in patients with an age distribution comparable to that expected when the drug is in routine use. Age stratification terms such as "≥65" should be replaced by depiction of age by decade, at least to 85. Secondly, premarketing evaluation should include assessing whether important age related differences exist in efficacy and toxicity, with such differences reported for all newly marketed drugs. Thirdly, because unexpected differences may emerge in effectiveness or side effects when a drug is used

routinely by large numbers of elderly patients, particularly those too frail to be included in trials, plans for postmarketing surveillance should be required at the time that a drug is approved. The increasing availability of computerised datasets of drug use and clinical events in large populations should make this requirement practical and affordable.

Each year, the lives of elderly patients are improved by the development of new drugs, as well as the intelligent use of existing agents. However, each year a significant (albeit smaller) number of them experience serious adverse events which could have been anticipated and prevented if better information were available to the practitioner.[8] Prudent science policy and regulatory approaches should make it possible for the former number to continue to grow while the latter number becomes ever smaller.

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The debate of the age

All doctors and medical organisations should join in

As this special issue makes clear, countries around the world are experiencing a rapid aging of their populations. This will lead to big changes in all aspects of life, and Britain is to have a debate—the Debate of the Age—on what it will mean to individuals, organisations, and society. The aim is to raise awareness of how society will change and propose policies for the next 50 years. The biggest public debate ever to happen outside government, it will in many ways be a debate about the future of Britain.

The debate, started by the charity Age Concern, follows the formula of a governmental conference on aging that happens every 10 years in the United States. The foundations for the British debate have been laid, and study groups are already researching the effects of demographic shifts on five aspects of our lives: the way we work and study; health care; economic policy; the design of cars and buildings; and, importantly, our values and attitudes towards aging.

The debate has two main elements. While the study groups compile evidence, market research will gather feedback on individuals' understanding of the issues. The results from this massive survey will launch the wider public debate in 1998. The concerns and views raised by the preliminary research will be then discussed at all levels of society through the mass media, exhibitions, conferences, competitions, and other means. Citizens' juries will gather evidence from their communities, and debate packs are being produced to encourage schools, individuals, and organisations to take part.

The debate will succeed only if every section of society participates. Many organisations and corporations have already agreed to take part, and representatives of the BMA, the General Medical Council, the royal colleges, and several specialist societies have met to discuss how the medical world can contribute. Though the projected population figures are partly a tribute to medicine, we need to make sure that as people live longer we do not simply add years to life at the expense of quality.

Professionally your practice and your specialty will see more older people. Even paediatricians need to consider how their patients will be affected by a world in which many more people are old. The disease burden associated with increased life expectations has massive implications for health policy. A multidisciplinary approach is essential for the effective management of chronic disease. The distinction between health and social care will probably blur, especially for the oldest and frailest. The economics of providing this care is a concern for all politicians and managers, and the costs involved make age a tempting criterion for healthcare rationing.

The aging of the population will also affect you individually. If you plan on working until your 60s and retiring on a comfortable pension, you may have to think again. In 25 years' time nearly 20% more people will be over retirement age than now. Supporting so many healthy but economically unproductive people may render the concept of retirement obsolete.

The organisers hope that 60% of the population will take part in the Debate of the Age and that 80% will be aware of it. The discussions and research will be collated, evaluated, and published in a policy document, *The Agenda for Age*. This will be discussed at a final conference in 2000 and presented to the government as a guide to policy for the next century.

To contribute to the debate contact the Debate of the Age office on 0171 387 7446 or knights@ace.org.uk (website: www.age2000.org.uk) or the *BMJ*, which is helping to coordinate the medical contribution.

Jessica Westall *Editor, student BMJ*