Coronary heart disease: an older woman's major health risk.

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Old age has always been with us. The ancient Egyptians and the author of the 12th chapter of Ecclesiastes were familiar with the common disabilities of later life. Survival into what we still regard as old age was not unusual in classical Greece (table). The average length of human life has increased over the centuries as living conditions have improved and childhood mortality has fallen; the maximum lifespan of our species is determined largely by our genes and will be the same as it ever was.

Doctors and philosophers of antiquity commented on age associated illness. Hippocrates noted conditions common in later life, and Aristotle offered a theory of aging based on loss of heat. Two thousand years were to pass before anything better was written on the subject. Francis Bacon proposed a scientific programme of epidemiological investigations into the longevity of people living in different places and under different conditions. He also noted that the pursuit of knowledge depended on “the fresh examination of particulars,” advice that underlaid the systematic observation of nature that complemented the active experimentation advocated by his contemporary William Harvey.

During the 18th and 19th centuries several physicians wrote specifically about the diseases of later life and their treatment. These included Cheyne and Day in Britain and Rush in the United States. Charcot’s lectures on the medicine of old age aroused scientific interest in the field and became available in English translation in 1881. The word “geriatrics” was invented by Ignatz L Nascher, a Vienna-born immigrant to the United States in 1909. (It is not clear who is to blame for the barbarous miscoining of “gerontology”—the study of old men—for “geratrolgy”—the study of old age.) Nascher’s initiative provided a stimulus for social and biological research on aging, but clinical geriatrics did not flourish in the United States. The American Geriatrics Society was founded in 1942, but as a thriving and influential medical specialty geriatric medicine was essentially a product of the British NHS.

The mother of geriatrics

If Nascher was the father of geriatrics, Marjory Warren was its mother. She worked at the Isleworth Infirmary, which in 1935 took over responsibility for an adjacent workhouse to form the West Middlesex County Hospital. During 1936 Dr Warren systematically reviewed the several hundred inmates of the old workhouse wards. Many of the patients were old and infirm, and Dr Warren matched care to their needs through a system of classification. She discharged many patients by providing rehabilitation and appropriate equipment. She initiated upgrading of the wards, thereby improving the morale of both patients and staff. In two seminal papers she advocated creating a medical specialty of geriatrics, providing special geriatric units in general hospitals, and teaching medical students about the care of elderly people, by senior doctors with specialist interest and experience in geriatrics. Many visitors from elsewhere in the United Kingdom and from overseas came to observe and learn from Dr Warren’s methods, and she gave lectures in Canada, Australia, and the United States.

The achievements of Dr Warren, and of other pioneers such as Lionel Cosin, stimulated the Ministry of Health to appoint the first consultant geriatricians within a few months of the introduction of the NHS in 1948. The Medical Society for the Care of the Elderly, later renamed the British Geriatrics Society, had already been founded with eight members in 1947. Its president was Lord Amulree, who, as medical officer at the Ministry of Health, had been among the first to appreciate the importance of Marjory Warren’s work.

Old age in classical Greece

<table>
<thead>
<tr>
<th>Name</th>
<th>Dates</th>
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</thead>
<tbody>
<tr>
<td>Sophocles</td>
<td>496-406</td>
<td>91</td>
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<tr>
<td>Euripides</td>
<td>484-406</td>
<td>78</td>
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<td>Plato</td>
<td>428-347</td>
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<td>Aristotle</td>
<td>438-338</td>
<td>98</td>
</tr>
<tr>
<td>Agisilaus II</td>
<td>444-360</td>
<td>84</td>
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</tbody>
</table>
The geriatric process

- Specify the management plan
  - Objective—To close the ecological gap between what the patient can do and what the environment requires
  - Therapeutic changes—improve the patient
  - Prosthetic changes—reduce environmental demands
- Assessments
  - Health (diagnoses, prognosis)
  - Function (physical, mental)
- Agree objectives of care
  - What does the patient want?
  - What is feasible?
- Regular review
  - Is progress as expected?
  - Does the plan need changing?

Despite the continued support of the Ministry of Health the specialty was shadowed at first by medical politics. At the birth of the NHS many consultants assumed that the bulk of their future earnings would come, as in the past, from private practice. They were therefore unwilling to see an expansion of the consultant grade but at the same time were unenthusiastic about assuming responsibility for patients of the workhouses and municipal hospitals that the NHS had taken over along with the teaching and district hospitals. The solution was to appoint geriatricians but to exclude them from the main hospitals and inhibit their access to private practice. This medical apartheid contributed to a general perception of geriatric medicine as a refuge for doctors who had failed to make their way in some more desirable specialty. Not surprisingly, relationships between general physicians and the early geriatricians were soured for some years by a sense of resentful emulation. This soon began to pass, but ill feeling flared up for a while in the mid-1970s, when the government proposed an active transfer of resources to geriatric medicine from other specialties. Papers were hastily published advocating the abolition of the specialty, and old people were accused of being cuckoos in the nest of the acute general hospital. It soon became clear that the government had no intention of fulfilling its threat, and normal relations were re-established.

Geriatricians in control

Ironically, subsequent years brought the widespread recognition that geriatric skills could help general hospitals run more efficiently. The first geriatricians, given responsibility only for patients in long stay hospitals, concentrated like Marjory Warren on upgrading the environment, improving the morale of patients and staff, and developing rehabilitation facilities. Working within what has come to be known as the “traditional” model of geriatrics, geriatricians were responsible for patients chosen by other referring doctors. Patients were sent for “long stay care,” but the geriatricians saw that some would not have needed institutional care if they had received more appropriate management earlier in their illness. Geriatricians therefore began to seek more influence over the acute as well as the rehabilitative and long term care of older people. This led in the 1970s to the emergence of two models of geriatrics—the “age defined” model, pioneered in Sunderland, and the “integrated” model, from Newcastle upon Tyne. The first is based on separate parallel hospital medical services for patients above and below an arbitrary age. In the second, consultant physicians trained in both geriatric and general medicine join medical “firms” with physicians with other specialist interests, sharing wards and the same team of junior medical staff for acute work while retaining separate specialist rehabilitation facilities.

Whatever their model of service, geriatricians were agreed on the components and principles of optimal care for older people. The principles are embodied in the four stage process outlined in the box, with its emphasis on functional goals agreed with the patient and its implications for multidisciplinary working. A quest for earlier and more effective detection and management of disability in older people produced a number of community oriented initiatives. Some of these aimed to fill gaps in primary care and have been overtaken by improvements in general practice. Other initiatives have found only local applicability. The most enduring of bridges with community care has been the geriatric day hospital, first introduced in Oxford in the 1950s but rapidly replicated elsewhere, unfortunately without adequate evaluation.

During the growth of geriatric medicine in the 1960s and 1970s specialist services were developed throughout Britain. The academic base of the specialty also became established. The first chair in geriatric medicine had been set up by private endowment in Glasgow in 1965. During the 1970s most medical schools acquired academic departments or subdepartments in the specialty, mostly using resources provided by the NHS. These units were small and focused at first on teaching and recruitment more than research, and most had responsibilities for service development.

The picture in America and elsewhere

In the United States things evolved differently. Geriatrics was initially restricted to nursing home practice, and there was resistance to its establishment as a recognised specialty. There was also uncertainty over whether it should develop in primary care or become, as in Britain, a secondary care specialty. It was in the Veterans’ Administration service, significantly the only socialised section of American medicine, that a need to respond to the aging of the patient population was first acknowledged. The publication of a major critique of the neglect of older people in the United States stimulated the public concern that led to the creation of the National Institute on Aging with a multimillion dollar research budget. Experimental hospital based units, using the type of multidisciplinary geriatric evaluation that had been developed empirically in Britain, were set up and compared in randomised controlled trials with standard care. Unfortunately, given the American way of medicine, units created with research funds had no guarantee of being continued as a service even when shown, as several were, to be cost effective. Comprehensive geriatric services on the British pattern are still rare in the United States, especially in teaching centres. Medical schools, however, have members of faculty with responsibility for ensuring that students learn at least the rudiments of modern geriatric care.
The contrast between the United Kingdom and the United States has its ironies. The British developed and provide services that have been adequately evaluated only in the United States, where they are rarely implemented. But the advantages of geriatric care over conventional care in the United States may reflect not so much the excellence of geriatrics as the poor service provided to older people in other settings. In the United Kingdom the aim from the early days of the specialty has been to spread geriatric skills as widely as possible. Standards of good care that were at first restricted to geriatric departments are now normal practice throughout the NHS. Now in the age of evidence based medicine and threatened resources, British geriatricians can only invoke American studies in self justification. Our defence has to be that although irrelevant in a direct sense to what British geriatric medicine does, American research and experience warn of the consequences for the United Kingdom if the specialty had not existed or were to disappear.

In most other countries geriatric medicine has yet to develop, for example in Japan, or to evolve beyond the “traditional” model now obsolescent in England and Wales. After the recent expansion of the European Union geriatrics has qualified as an official European specialty, although it is still not recognised in several Union countries. There is wide variation in teaching facilities, and the recently founded European Academy of Medicine of Ageing is dedicated to recruiting and training a nucleus of young geriatricians to strengthen the academic departments of the future. The role of the specialty also differs between nations in Europe. In the Netherlands, geriatrics is squeezed between other hospital based specialties and a large specialty of nursing home medicine which undertakes most of the rehabilitation work of British geriatricians. Geriatrics is not a formal specialty in Italy, but there are many accomplished academic departments committed to teaching and research in the topic. The specialty has no official status in France, but several departments of medicine have a major interest in the care of older people. French patients have a right of self referral to doctors of their choice so there is resistance to recognition of the specialty from general practitioners who fear loss of custom if elderly patients have the option of specialist geriatric services.

The future

In terms of comprehensiveness of services, and more nebulous considerations of status and influence, British geriatrics at the age of 50 is still ahead of the rest of the world, but its research base remains poorly developed. On the clinical side, given the continued aging of the population and increasing technical demands on physicians in organ based specialties, doctors trained in geriatric and general medicine may come to staff much of the front line of acute medical services in hospitals of the future. Research may remain a problem. There is a tension between the generalist nature of clinical practice among older people and the need for clinical and basic research to be intensely focused if it is to be of the highest standard. There is also now a gerontological agenda in molecular biology and genetics. How to ensure both clinical and research excellence without threatening the essential link between them is now perhaps the single most important issue for geriatrics.

3 Day GE. A practical treatise on the domestic management and most important diseases of advanced life. With an appendix containing a series of cases illustrative of a new and successful mode of treating lumbago and other forms of rheumatism, sciatica and other neuralgic affections, and certain forms of paralysis. London: T and W Boone, 1849.
4 Rush B. Medical inquiries and observations. Philadelphia: Johnson and Warner, 1815.
14 Cosin L. The place of the day hospital in the geriatric unit. The Practitioner 1981;212:312-5.
Molecular biology's impact on our understanding of aging

David M A Mann

Powerful molecular biological tools have begun to open up the very fabric of life—the human genome—and have allowed us to glimpse inside this Pandora’s box. We now see that many common disorders of later life—for example, cancer, dementia, and vascular disease—are related to genetic variations that dictate an individual’s likelihood of developing illnesses like these. These genetic variations differ from those that determine longevity, though both act synergistically to dictate how long and how well we might live. Control of gene expression will be needed to counteract the adverse actions of these to promote a healthy and productive old age.

Aging and disease—separate entities or continuum of change?

Common disorders such as cardiovascular disease, cancer, stroke, dementia, and diabetes become increasingly prevalent in later life. It is tempting to ascribe these to the body “wearing out”—a viewpoint supported by the frequent finding in many old, but otherwise healthy, people of low levels of the same kind of tissue changes generally associated with certain diseases when present in higher amounts. These diseases have been popularly equated with “normal aging,” and the idea that in diseased individuals this normal process of aging may have become “exaggerated” or have “accelerated” out of control has often been put forward.

Health and disease might in this way be thought of as occupying a sliding scale of age determined tissue damage, with the one merging into the other at some point in life. Yet the argument is fallacious. Many disorders—for example, dementia—clearly become more common in later life; their incidence peaks in people in their eighties but then declines.1 Furthermore, like humans, other animals (including the higher primates) age and die, yet they do not spontaneously develop these common disorders of humans. Hence, although growing older is a biological certitude, disease in old age may represent an additional burden of tissue damage superimposed on other ongoing alterations common perhaps to all cell types in the body and applicable, to a greater or lesser extent, to all individuals. These basic changes set the stage on which the disorders of old age can be played out. So what is aging, and what is disease? How important is each of these in determining how each of us will fare in later life? What causes aging and disease, and to what extent are they interdependent?

Molecular revolution

The recent molecular biological revolution has begun to make startling inroads into these areas of uncertainty, particularly in molecular genetics. Variations in the structure or stability of the human genome are now seen to be responsible for an ever growing list of common and not so common disorders by determining not only the probability of whether sufficient tissue damage causing disease will occur but also at what time in life this can be expected and for how long it will last. Moreover, these techniques are now providing the quantitative data necessary to clarify ideas on aging and disease that have been around for many years, and the boundaries are thus being established between which tissue damage might be thought of as being caused by the passage of time alone and which is a reflection of degenerative disease in later life.

This revolution was sparked by the advent of the polymerase chain reaction2—a means of replicating “in the test tube” a small number of copies, or even a single copy, of a segment of DNA (gene) to produce multiple, identical versions whose nucleotide sequence can be determined. This forms the base of many complex molecular analyses that, for example, assign biological characteristics, such as disease trait, to chromosomes or parts thereof (by linkage analysis) or permit the “narrowing down” of genes within that region to the one causing disease (by positional cloning). Once identified, screening techniques based on polymerase chain reaction can quickly and efficiently determine how many individuals with the disease share that particular genetic change, and DNA sequencing can show whether other disease-causing base changes or rearrangements of the DNA are present (fig 1).

In this way different types of mutation have been identified in all kinds of tissues and in many clinical situations (including aging), ranging from “simple” exchanges of nucleotide bases that alter the coding sequence for one or more amino acids (missense mutations) through to complex additions or expansions (insertions) or subtractions (deletions) of genetic material. Such changes, when transcribed into RNA and subsequently translated, produce a protein of abnormal sequence which creates structural or functional changes that render it defective at its normal task (dysfunctional) or confer a new function (gain of dysfuction) away from normality. These altered proteins may compromise the structural integrity or the metabolic or replicative capabilities of the cell in such a way as to trigger...
alleles of the apolipoprotein E gene, have been associated with Alzheimer’s disease. These polymorphic variations do not absolutely dictate whether disease will occur but cause a metabolic deficiency that increases the likelihood that the tissue damage of Alzheimer’s disease will occur and thereby raise the level of susceptibility to clinical disease. Possession of one gene copy of the e4 allele doubles the risk of developing Alzheimer’s disease; two copies increase the risk eight times (to about 90% certainty). These same genetic factors are, however, associated with other disorders that share many of the tissue characteristics of Alzheimer’s disease yet produce quite different and distinctive clinical syndromes. For example, in Down’s syndrome the pathology is that of Alzheimer’s disease, but it is an extra (normal) copy of the amyloid precursor protein gene on the duplicated chromosome 21 that is causative. In hereditary cerebral haemorrhage with amyloidosis other mutations in this gene are to blame. Cortical Lewy body disease shares the same change in the apolipoprotein E e4 allele as Alzheimer’s disease. Hence, genetic changes like these confer metabolic alterations that in turn prescribe a particular pathology—β amyloid cascades that can eventually be recognised under the microscope as a tissue abnormality.

The nervous system as ideal model
The nervous system has been a traditional target for studies on aging as its principal cells, the neurones, do not divide nor are replaced routinely during adult life, as happens with cells of other tissues. They must thus endure a lifelong catalogue of insults to secure continued survival of both themselves and the individual. The nervous system therefore makes an ideal model in which to study aging and to differentiate from this the changes that relate to the common diseases of old age. Perhaps the best illustration of this conflict is Alzheimer’s disease. For years the argument has raged as to whether Alzheimer’s disease is a disease or represents the ultimate, or untimely, exaggerated effects of the process of aging.

Genetics of Alzheimer’s disease
In the past decade the perception of Alzheimer’s disease as a single entity with a characteristic clinical and pathological profile has changed into a realisation that this represents a broad neurodegenerative cascade to which entry can be gained through various routes (fig 2). Some cases of Alzheimer’s disease involve the inheritance of mutations in particular genes (amyloid precursor protein gene and the presenilin genes) in a classic mendelian manner; these mutations are so lethal that disease will virtually always occur at some time, usually well before old age. Yet such mutational events account for only about 70% of all instances where inherited Alzheimer’s disease occurs before the age of 60 and contribute nothing towards that greater mass of cases where onset is after this age or to those cases in earlier life where no clear pattern of inheritance is seen. Hence, other and more common genetic events known as polymorphisms or “natural” genetic variations, particularly the possession of the e4

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**Fig 1** Molecular approaches to gene identification

**Fig 2** Pathogenesis of Alzheimer’s disease. Mutations in amyloid precursor protein (APP) gene and presenilin genes increase production of soluble amyloid β protein. This deposits as insoluble plaques when concentration of amyloid in extracellular fluid is high. Apolipoprotein E E4 protein favours deposition by lowering the concentration threshold to plaque formation. Plaques are infiltrated by microglial cells, which secrete interleukin-1, increasing production of amyloid β protein and soluble amyloid and stimulating astrocytosis. Reaction oxygen species from microglia and astrocytes damage nerve endings, causing neuritic changes in plaques and the formation of neurofibrillary tangles in nerve cell cytoplasm. Damaged neurones die, causing clinical disability—dementia. Loss of normal secretion of APP (due to breakdown into amyloid) may also stimulate neuritic changes and hasten nerve cell death.
deposition in this instance. It is the extent and distribution of this pathology that will dictate the clinical profile that will ultimately emerge. Tissue changes associated with particular disorders are likely to be the biological products of adverse genetic variations. Modelling these genetic changes of Alzheimer's disease in animals (transgenic mice) or in cell lines has produced the same cellular metabolic changes and tissue alterations that characterise the human condition.

Thus Alzheimer's disease is a complex, multifactorial process that is essentially under genetic control and represents an interplay between various adverse genetic changes that have an impact on the pathological process in different ways. The nature and balance of these factors determine whether disease will occur, and if so, at what time of life and how rapidly progression will be. Most people will possess one or more of these factors and can thus expect to accumulate some of the pathology of Alzheimer's disease in their brains given time—this risk is unlikely to be sufficient in most individuals to ensure progress into clinical disease, but it is none the less probable for many. Other pathologies seen in the brain in old age, such as Lewy bodies, can be equated with Parkinson's disease (clinical or subclinical) and indeed the entire spectrum of neurodegenerative disorders is likely to be genetically determined. Pathologies such as plaques, tangles, and Lewy bodies should be taken as indicating nervous system disease whenever or wherever they might occur and are quite distinct from the changes of "normal aging."

Genetic changes in normal aging

So what is normal aging? Does this represent the good face of genes whose obverse side promotes pathology and disease in later life? For example, in contrast to the e4 allele, the apolipoprotein E e2 allele promotes longevity in both normal individuals and those with Down's syndrome; it delays the age of onset of Alzheimer's disease. Although this is possible in some specific instances it is in general terms unlikely. Health promoting genes will fulfil housekeeping roles, maintaining the faithful production of proteins that sustain cell viability and resistance to damage; they may form part of a genetic cluster that specifies longevity in a programmed manner. Gradual failures in these cell maintenance systems may act as a springboard on which adverse genetic changes promoting pathology might gain momentum and take their toll in later life. But what are these basic changes that potentially affect all of us, whose actions progressively build up, thereby rendering the system so vulnerable in old age?

The core physiological process supporting the life of all cells is the oxidative metabolism of glucose in the mitochondrion to provide transducible energy. Unfortunately, undesirable byproducts (oxidants or reactive oxygen species) continuously result from this process, and these damage biomolecules (DNA, lipid, protein, carbohydrate) and impair their function (fig 3). Not surprisingly therefore cells are equipped with antioxidant defences, which prevent or at least restrict these untoward effects. It is a widely held view of cellular aging that it is this unchecked damage by reactive oxygen species that leads to an acquired decline in cellular function with time. Of particular importance is damage caused to the nuclear genes responsible for producing proteins vital for these defences and the mitochondrial genes critical for bioenergy maintenance. Mitochondrial DNA is at particular risk as it is located on the inner membrane, next to the sites of cellular respiration where reactive oxygen species are produced. Furthermore, it lacks the protective histone coat of nuclear DNA and is deficient in those repair enzymes that correct much of the nuclear damage. Moreover, this nuclear and mitochondrial genetic damage cannot be diluted out by cell division and selection in post-mitotically stable tissues, thereby leaving the cell poorly guarded to deal with further oxidative change. Changes in cytokines, growth factors, or hormonal regulators, which influence gene expression, may compound the situation at transcriptional level. A downward spiral thus sets in, leading eventually to metabolic collapse and apoptotic (programmed) cell death, particularly in times of physical, chemical, or biological stress (fig 4). Individuals who inherit a robust (mitochondrial) genotype may sustain adequate energy capacity into old age, despite these damages. However, other less genetically well blessed individuals may find their energy capacity eroded over time to produce a bioenergetic weakening that in some individuals may act synergistically with inherited gene defects to produce, at an early age, overt clinical disorders such as Parkinson's disease, type II diabetes, and mitochondrial myopathies.

Hence, paradoxically, the very giver of life is also that which limits life span. The replicative potential (of dividing cells) may become progressively reduced through other DNA damage (telomere loss), and the stable daughter cells produced may, in the absence of their replacement by genetically more favoured cells, promulgate the chromosomal damage and dysfunc- tion borne by their progenitors. Oxidative or other stochastic damage to DNA may also underpin certain cancers, resulting in the loss of...
function of tumour suppressor genes and the activation of tumour promoting genes (oncogenes), with subsequent malignancy.29 Oxidative damage to low density lipoproteins may contribute significantly to atherogenesis and cardiovascular disease.29

**Conclusion**

The recent molecular revolution argues that aging and the common diseases associated with age are fundamentally determined by an individual's own genetic make up, this being partly a function of the inherited genome and the modifications to this that occur over a lifetime. How well and how long a person lives depends on the net balance of this “genetic miaisma”—what the Victorians used to call “constitution.” None the less, lifestyle can have an important role.

Clearly, diet and hygiene, excessive alcohol consumption, cigarette smoking, drug misuse, sexual promiscuity, and occupational hazards can damage even the most perfect of cells and compromise life expectancy. At greater risk are cells and tissues already weakened by aging or disease. Avoiding these risks may increase an individual's likelihood of reaching old age but not necessarily lead to a high quality of life. The goal of future research will be to find how the effects of these adverse genetic changes can be minimised, by for example, gene therapy,18 and the functioning of health promoting genes maximised, while social risks to health are avoided or controlled along the way.

This present review can only hint at the power that molecular biology has to explain why we age or become ill in late life. How we should respond to its outcome in terms of health care and preventable medicine in late life will be a major challenge for research and society alike.

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**Fig 4** Relation between aging and dementia (Alzheimer's disease). Changes associated with aging (reactive oxygen species) increase as we get older. Genetic factors leading to the pathology of Alzheimer's disease can act at any time after age 40 but have a less powerful effect later in life (the larger the arrow the more powerful the effect). At age 50 dementia is due nearly entirely to the genetic influences of Alzheimer’s disease. At 100 the development of dementia is uncommon—when it occurs it is mostly due to pathologic changes of aging.
Population aging and health

Robert N Butler

Trends in population aging

People in industrialised nations are living longer than ever before. In this century alone, average life expectancy from birth has increased by more than 25 years, and nearly five of those 25 years has been added to average life expectancy from base age 65. Indeed, the most rapidly growing age group comprises those aged 80 and above, and in some countries people over the age of 100 are leading the way in the rate of population growth by age. In most parts of the world women tend to live longer than men—nearly seven years longer in industrialised nations. In addition, reports from Japan, the United States, and Europe show that people are living not only longer but more healthily. In the United States, for example, the rate of disability has decreased noticeably despite population aging (fig 1). Unfortunately, the developing world has not enjoyed the same revolutionary increase in longevity. None the less, 60% of people aged 60 and older live in developing countries—which have huge populations—and this percentage is expected to rise to 80% towards the middle of the next century. The marked inequalities in life expectancy between the developed and developing worlds, as well as discrepancies in life expectancies within particular nations, correlate with inequalities of wealth and income, and these in turn are associated with how much or how little education and access to health care the populations have. Many countries already have at least 10% of their populations aged 65 and older (table ). Figure 2 shows the rapidity of the projected percentage increase in the population aged 65 and older in the developing world. Figure 3 details the dramatic growth of the population aged 80 and over. As it is in this population that disabilities and dementias increase markedly, this figure illustrates the dramatic impact of population aging on health care.

Western societies with declining birth rates are approaching the point where older people will soon outnumber children. This unprecedented trend in population aging has profound effects on society and its institutions, including health care.

Biomedical research and better healthcare measures, as well as other factors, have enabled people to live longer and reduced disability rates

Increased life expectancy, however, brings new challenges, including longer lifetime exposure to toxic agents and greater demands on healthcare systems and social entitlements.

Individuals, society, government, and the research community all have a responsibility to meet these challenges and improve the quality of life.

Summary points

People in all parts of the world, and particularly in industrialised nations, are living longer than ever before

This unprecedented population aging trend has profound effects on society and its institutions, including health care

Biomedical research and better healthcare measures, as well as other factors, have enabled people to live longer and reduced disability rates

Countries with at least 10% of population aged 65 and over in 1994 (adapted from Hobbs F et al2)

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<th>Country</th>
<th>Total population (000s)</th>
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<tr>
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<tr>
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Impact of health on population aging

The age structure of any society's population depends on birth rates, death rates, and net migration in or out of the society. Population aging was first the result of declining birth rates and was first noticed in France in the 1830s. But by the 20th century population aging was widespread in industrialised nations because of both lower death rates and lower birth rates. Lower death rates were due in part to an increase in people's consumption of calories. It has been estimated, for example, that in preindustrial France as many as one third of the population had inadequate caloric intake. One of the consequences of the industrial revolution was the increased availability of food, followed by increased stature and greater longevity. In addition, there is synergy between inadequate nutrition and higher susceptibility to infection. With higher caloric consumption, the incidence of infection declined. Infectious diseases were reduced still further with modern sanitation and the increased availability of immunisations, antitoxins, immune sera, and, later, antibiotics.

Gradually the early cruelties of industrial factory life, such as overcrowded living conditions and the resulting spread of infectious diseases, began to decline. Material existence began to improve with the growth of the middle class in Europe, North America, and Japan. The availability of pension funds, access to health care, and medical research further increased average life expectancy. By the 1970s the earlier marked reductions in maternal, childhood, and infant mortality were joined by reductions of up to 50% of deaths from heart disease and stroke. Both disease driven and basic biomedical research, including the biology of aging, continue to reduce disability and mortality. Hip replacements, angiotensin converting enzyme inhibitors, and intraocular implants illustrate the practical applications of such research. Moreover, the decline in disability rates along with the availability of social entitlements have improved the quality of life. None the less the extent of frailty and dementia accompanying population aging continues to prompt concern over quality of life issues and healthcare expenditures associated with late life.

Impact of population aging on health

Clearly, advances in health have promoted population aging. However, the reverse—the impact of population aging on health—is more difficult to describe. With population aging came the possibility of a longer lifetime exposure to various potential toxic agents, either recognised or unrecognised. This is particularly true of tobacco and food substances such as fats. Tobacco contributes to heart disease and stroke as well as cancer of the lung and chronic pulmonary disease. The modern high fat diet has been associated with heart disease and certain cancers, such as colon cancer and possibly breast cancer. Other aspects of lifestyle, too, over time, have an impact on health. Lack of exercise leading to physical deconditioning contributes to the chronic diseases of late life. Osteoporosis or bone thinning, sarcopenia or muscle thinning, and inadequate cardiac conditioning, for example, all follow from a lifetime of inadequate physical fitness. Indirectly, population aging could also have adverse effects on the health of populations in general if society does not allocate resources effectively and fairly along the life span, to ensure that children and older people receive the resources they need. Surprisingly, there is not a propor-
changed in response to modern conditions such as the capacities to be caregivers to older people have made. While families are the primary caregivers, their two pillars of comprehensive geriatrics—need to be residents—are recognised in most industrial countries the only available public funding is part of public assist-
as being necessary adaptations to population aging. Different nations have tackled the financing of long term care in different ways. In Germany public long term care insurance predominates, whereas in Britain commercial long term care insurance has burgeoned. In Australia, long term care is provided mostly by the private sector (profit and non-profit organisations), and includes retirement villages, hostels, and nursing homes operated by voluntary agencies and private cor-
ventions. Services. In contrast, in 1990 the Japanese government announced a 10 year “golden plan” for the welfare of elderly people and in 1997 legislated on a public long term care insurance plan modelled on Germany’s.

Taking responsibility for population aging
Sustaining a growing older population is the responsibility of everyone—from the government, to the private sector, to individuals themselves. As people are living longer they clearly must plan to take better care of themselves throughout life. They must prepare financially by saving and investing more and working longer. They must also take some responsibility for their health by adopting healthy habits early in life and maintaining them throughout life. Strong relations seem to exist between having goals and structure in life and a person’s health, longevity, and higher quality of life. Societies will be able to sustain longer life expectancies and population aging better if people not only prepare for their old age but are encouraged by society to remain productive through paid work or voluntary activities.

Government and the private sector should assume more responsibility in assuring less disability in late life by making greater investments in medical research. The benefits of medical research for older age groups will derive principally from efforts to reduce frailty and dementia, which today are people’s greatest fears about old age. Once Alzheimer’s disease and the other dementias are preventable or treatable, the negative imagery associated with individual and population aging will be dramatically reduced. For countries to respond effectively to population aging, they must make further investments in geriatrics and biomedical research. This necessitates systematic reforms in healthcare delivery as well as disease prevention and health promotion efforts and a reversal in the current trend of cutting research budgets.

Coronary heart disease: an older woman’s major health risk

Nanette K Wenger

Coronary heart disease has traditionally been considered a problem which predominantly affects men—its extent and poor prognosis in women have only recently been identified. As shown in the Framingham study, women are more likely than men to die after myocardial infarction; this is now also evident after coronary artery bypass graft surgery and coronary angioplasty. However, the prognosis is currently also influenced by access to coronary diagnostic procedures and treatments, which may in turn be affected by factors such as women’s and their doctors’ decisions about diagnostic procedures and treatments, by the allocation of health care resources, and by society’s perceptions of the importance of coronary heart disease in women.

Epidemiology

Coronary heart disease is more dependent on age in women than in men: women are usually 10 years older than men when any coronary manifestations first appear, and myocardial infarction occurs as much as 20 years later. One in 8 or 9 American women aged 45-64 years has clinical evidence of coronary heart disease and this increases to 1 in 3 in women older than 65 years (fig 1). Coronary heart disease is the leading cause of death in women in the United States; it is responsible for over 250 000 deaths annually (fig 2). With the aging of the population, more women than men now die of coronary heart disease each year in the United States.

A white postmenopausal woman in the United States is 10 times more likely to die of heart disease than of breast cancer. But most women do not understand the coronary threat. Studies show that women do not usually list heart disease among the health problems they consider most important. Morbidity from coronary heart disease in older women is also considerable; 36% of American women aged 55-64 years and 55% of those over 75 years with coronary disease are disabled by symptoms of their illness.

Mortality from coronary heart disease in women varies considerably between countries but generally parallels the mortality for men in any one country (fig 3). In many industrialised nations, it is now the major cause of death in postmenopausal women and a principal contributor to hospital admissions and consultations with doctors.

Coronary risk factors and their modification in older women

Coronary heart disease will probably become epidemic in older women as the population ages unless women take preventive measures throughout their lives. The prevalence of risk factors is high in women of all racial and ethnic groups in the United States—only a third of all American women do not have at least one major coronary risk factor, and this proportion decreases in older women. American women aged over 65 pay less attention to exercise and diet and use fewer other preventive health services than younger women. Risk factors are more prevalent in socioeconomically and educationally disadvantaged women; in the United States almost twice as many women as men aged 65 years or older are at the poverty level. Data for American women aged 20-74 years in 1991 showed that more than a third had hypertension; more than a quarter each had hypercholesterolaemia, were cigarette smokers, or were overweight; and two thirds had a sedentary lifestyle. The only risk factor less pronounced in older than younger women was smoking. Some risk factors for men and women cross over with aging. Hypertension and hypercholesterolaemia are more prevalent in younger men than women, but at older ages they become more prevalent in women than men.

Cholesterol

Cholesterol concentrations continue to predict coronary risk in older women. Lowering cholesterol after myocardial infarction in the Scandinavian simvastatin survival study (4S) reduced major coronary events by a third in women and men, and the benefit was...
maintained at older ages. In the cholesterol and recurrent events (CARE) trial, lowering cholesterol after myocardial infarction in patients with average cholesterol values reduced death or subsequent infarction by 46% in women and 26% in men.

All the women in the heart and estrogen/progestin replacement study (HERS) had coronary heart disease, and almost half were taking a lipid lowering drug at enrolment; however, most had concentrations of low density lipoprotein cholesterol that exceeded the treatment goals of the national cholesterol education program.

**Hypertension**

In people aged 60 or more in the systolic hypertension in the elderly program (SHEP), control of isolated systolic hypertension reduced strokes, deaths from cardiovascular events, and the number of non-fatal cardiovascular events in both women and men.

**Smoking**

Cigarette smoking triples the risk for myocardial infarction, with the greatest risk in women with other coronary risk factors and older age women. Nevertheless, within two years of stopping smoking, middle aged women in the nurses' health study (NHS) lowered their risk of cardiovascular mortality by 24%, regardless of the amount or duration of cigarette smoking or the age at which they stopped smoking. Data from the coronary artery surgery study (CASS) registry suggest that the benefit of stopping smoking does not lessen with older age.

**Diabetes mellitus**

Diabetes is a far greater risk factor for women than men. Women over 45 years are twice as likely as men to develop diabetes. Diabetes has an adverse effect on the in-hospital and long term prognoses after myocardial infarction, and this is much worse for women than men. More women than men who undergo myocardial revascularisation procedures are diabetic, which probably contributes to the less favourable outcomes in women.

**Physical inactivity**

Physical inactivity is a highly prevalent and independent risk factor in women, although data are limited for elderly women. In epidemiological studies, exercise reduced coronary risk, even at older ages. Moderate leisuretime activity (30-45 minutes' walking three times weekly) reduced the risk of myocardial infarction by half. Despite these benefits, fewer women, and particularly elderly women, are referred for exercise rehabilitation after a coronary event.

**Postmenopausal hormone therapy**

Interest in postmenopausal hormone treatment to reduce coronary heart disease is encouraged by the benefits suggested for oestrogen, which include favourable effects on the lipid profile and on fibrinogen concentrations. Oestrogen also favourably affects coronary vasodilation. Data from many observational studies suggest consistently that the coronary risk is
35-50% lower in women who take oral oestrogen. In the nurses’ health study, mortality was reduced in women at high coronary risk who were currently taking hormone treatment. The benefit fell with longer term treatment, however, because of an increase in mortality from breast cancer.

The likelihood of selection bias is an inherent weakness of these observational data, in that oestrogen is typically prescribed in healthy women. However, postmenopausal hormone use by elderly women was associated with both a more favourable cardiovascular risk profile and more favourable preclinical cardiovascular characteristics. Oestrogen alone and several combinations of oestrogen and progestin improved the coronary risk profile of subjects in the postmenopausal estrogen/progestin interventions (PEPI) trial. However, a third of the women who had not had a hysterectomy and who took oestrogen unopposed, developed adenomatous or atypical endometrial hyperplasia within three years, which placed them at risk for endometrial cancer. Oestrogen plus a progestin is indicated for these women, while unopposed oestrogen remains appropriate for women after hysterectomy.

Decisions about postmenopausal hormone therapy are also influenced by the fact that it reduces osteoporosis and menopausal symptoms and may lessen the risk of Alzheimer’s disease. Adverse effects include the increased risks of breast cancer and of venous thromboembolism. In the nurses’ health study, the relative risks for breast cancer were greatest in women more than 60 years (1.71 at age 60-64) and in women who had used hormone therapy for more than five years (1.45)—features characteristic of women who use hormone treatment to prevent coronary heart disease and osteoporosis. Data from randomised clinical trials which are in progress may clarify the relative benefits and risks of postmenopausal hormone treatment and give better information to guide this treatment in older women.

Aspirin
Randomised controlled trial data are also needed to define in women the risks and benefits of taking aspirin as a preventive measure. The increased risk of haemorrhagic stroke associated with taking aspirin is of concern. In women this risk is potentially greater than the benefit from a reduction in the risk of myocardial infarction.

Clinical characteristics of coronary heart disease: sex differences

Angina pectoris
Angina pectoris is the main initial and subsequent presenting symptom of coronary heart disease in women, while myocardial infarction and sudden death are the predominant presentations in men. Women with angina are likely to be older than men and to have hypertension, diabetes, and heart failure more commonly. They are also less likely than men to have had either a prior myocardial infarction or a myocardial revascularisation procedure.

Investigating chest pain in older women
The best non-invasive method of evaluating chest pain to identify coronary heart disease is uncertain in women. Because coronary heart disease is a more likely reason for chest pain in older than in younger women, they have fewer false positive results for exercise tests than at younger ages. However, because of poor physical condition or other illnesses, older women are less likely to perform an exercise test of sufficient intensity and usually require pharmacological radionuclide or echocardiographic imaging. The newer diagnostic procedures—positron emission tomography, magnetic resonance imaging and angiography, and electron beam computed tomography—have not been adequately explored in women of all ages and fewer data are available for elderly women.

Risk stratification
More women than men have stable angina before their first myocardial infarction. It must be determined whether early risk stratification procedures for women with stable angina might identify a high risk group who could be treated more aggressively, and this might prevent subsequent myocardial infarction. In people aged over 65 with chest pain on exertion the risk of coronary death is not affected by gender (relative risk 2.7 for men and 2.4 for women), and the association is independent of other coronary risk factors.

Invasive testing after non-invasive testing
In the past decade, knowledge of the adverse outcomes of coronary heart disease in women has increased, and doctors in the United States now carry out objective testing in women with chest pain more promptly than they used to. However, specific information is lacking for elderly women. In one study of non-invasive testing, the benefit of subsequent myocardial revascularisation was comparable in women and men, but in patients who had not undergone revascularisation procedures, the outcome was poorer in women. A recent evaluation of emergency department care of patients with new onset chest pain showed that in women and men with similar symptoms, women were diagnosed and treated less aggressively.

Coronary arteriography seems to be the most important determinant of access to myocardial revascularisation procedures. Differences in performing myocardial revascularisation procedures in men and women in the United States were related only to the underlying severity of coronary obstruction seen at arteriography, which is typically less severe in women. Where coronary angiography showed similar obstruction, revascularisation rates were comparable in women and men, and no sex differences were seen in the rates of coronary events during follow up.

Myocardial infarction
Hospital mortality from myocardial infarction is higher in women than in men. A recent study showed hospital mortality of 16% for women and 11% for men. Although the presentations of myocardial infarction were indistinguishable in women and men, women were not treated as aggressively; they were half as likely to receive acute catheterisation, coronary angioplasty, thrombolysis, or coronary artery bypass surgery. Women who survived had earlier and more frequent recurrence of myocardial infarction, and their mortality at one year was also greater. Although sex differences lessen when older age and comorbidity in women are
controlled for, they do not disappear. Women who present with myocardial infarction are more likely to have a higher Killip class, tachycardia, atrioventricular block, pulmonary rales, shock, heart failure, recurrent chest pain, and cardiac rupture than are men.44 45

**Coronary thrombolysis**

In the GUSTO I trial, the survival benefit from thrombolytic treatment for acute myocardial infarction was similar in women and men, even though women had more bleeding as a complication of thrombolytic treatment, particularly intracerebral bleeding and resultant stroke.46 Nonetheless, the mortality difference between sexes persisted—unadjusted mortality at 30 days was 13% for women and 4.8% for men. The risk of non-fatal complications including shock, heart failure, and reinfarction was also greater in women.44 45

Women (and particularly older women) commonly present with atypical symptoms of myocardial infarction, and this may partly explain why they receive coronary thrombolysis less often. A more important explanation is that after myocardial infarction they tend to arrive at hospital too late to benefit from thrombolysis. Patients who have had thrombolytic treatment seem more likely to undergo risk stratification subsequently than those who have not. The underutilisation of coronary thrombolysis in women may therefore have a cascade effect.

**Primary angioplasty**

Because women have an increased risk of intracranial bleeding with coronary thrombolysis, primary angioplasty is an exciting alternative. In one trial this was associated with less intracranial bleeding and better survival than was coronary thrombolysis.47 Furthermore, the hospital outcomes of primary coronary angioplasty were equally good in women and men.

**Drug treatment**

A recent study of drug treatment for suspected acute myocardial infarction also showed consistently lower use of thrombolytic agents, β blocking drugs, and aspirin in women than men, and in elderly patients than younger ones.50 Although treatment with β blocking drugs seems to provide comparable if not better survival after myocardial infarction in women than in men, specific data in elderly women are not available.

**Risk stratification**

Whether the current lower rate of risk stratification after myocardial infarction in women is appropriate or not is uncertain. This is particularly so in elderly women, since comorbidity and other features not documented in the available datasets may make them less suitable candidates for myocardial revascularisation. Nor do we know whether more women than men, and particularly more elderly women, refuse these procedures when they are recommended. The thrombolysis in myocardial ischaemia (TIMI) III registry study showed that elderly patients of both sexes had more severe disease shown by angiography, were more likely to be treated medically, and had substantially worse outcomes; the representation of women in an elderly population is disproportionately high. Women had less severe coronary disease than the men and were treated less intensively, but their outcome was comparable; with less severe disease, women should have been expected to have a better outcome.51

**Psychosocial complications**

Psychosocial complications of myocardial infarction, particularly anxiety, depression, and guilt about illness, are more common in women.52 Although women resume moderate to heavy housework early in their recovery, they are less likely than men to return to paid work and those who return to work take longer to do so.

**Myocardial revascularisation procedures**

Women who have coronary artery bypass graft surgery are generally older than their male counterparts, describe greater impairment of function, are more likely to have severe and unstable angina, and thus are more likely to have urgent or emergency surgery.50 51 The mortality for this procedure is twice as high in women.52 Women also have lower rates of graft patency, are less likely to receive an internal mammary artery graft, obtain less relief of symptoms from coronary artery bypass graft surgery, more commonly have infarction and heart failure perioperatively, and are more likely to require reoperation within five years of the initial surgery.53 As with myocardial infarction, women are more likely to have adverse psychosocial outcomes; however, 15 years after coronary bypass surgery, survival is comparable in women and men.54

Women referred for percutaneous transluminal coronary angioplasty are older, more often have a history of heart failure and unstable angina, and are more likely to have associated hypertension, hypercholesterolaemia, and diabetes.55 56 However, the success and safety of the procedure are comparable in women and men.57 58 Despite the initial good results, relief of symptoms and long term survival are poorer in women, but the latter finding mostly reflects their
older age. The newer transcatheter revascularisation procedures have lower success rates and higher complication rates in women, mainly because the devices used are large in relation to the size of the coronary arteries in women. Whether there are sex differences in the rates of restenosis after coronary intra-vascular procedures is unknown.

During the past decade the rates of coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, and other transcatheter revascularisation procedures in women have increased in the United States. This is partly related to the doubling of coronary arteriography in women and partly to the greater use of revascularisation procedures in elderly people.

Conclusion

Whether the current more intensive and aggressive evaluation of chest pain syndromes in women in the United States will improve their long term outcomes is unknown. In addition, current assessment of the role of postmenopausal hormone treatment, a risk intervention unique to women, will probably help to guide the management of half of all coronary patients in clinical practice—women—most of whom are elderly.

Only as prospectively derived, contemporary information specific to women becomes available can we discover which components of the traditional middle aged male model of coronary disease apply to older women. We can then identify the diagnostic procedures, treatments, and prognoses that apply to their coronary care, which should allow us to improve the outcome for coronary disease in older women.

40 Weaver WD, White HD, Wilcox RG, Aybeward PE, Morris D, Guerci A et al, for the GUSTO-I Investigators. Comparisons of characteristics and
Healthy aging

Kay-Tee Khaw

A major challenge facing society is how we can maintain health and quality of life in an aging population. Maximum life expectancy has not changed substantially, but average life expectancy has increased greatly in the past century. This reflects profound improvements in mortality in infancy and young adulthood, resulting in a much greater proportion of people surviving to older ages (tables 1, 2, and 3).

Aging and disability

The rise in numbers and proportion of older people has led to much concern about societal consequences, not least health consequences. Increasing age is associated with increasing disability and loss of independence, with functional impairments such as loss of mobility, sight, and hearing. In Britain in 1984-5, the estimated prevalence of those with severe disability was less than 1% in those aged 50-59 years but 13% in those aged over 80 years. Mobility, sight, and hearing are among the four main conditions identified by Murray and Lopez as the leading causes of disability. A substantially higher proportion of people aged over 85 years have severe disability than people aged 85-90 years, and this difference is even more marked in those aged 90-94 years. A further substantial proportion of these chronic disabling conditions can be prevented or postponed if appropriate health interventions and health maintenance—much is already known about the impact of modifiable influences such as diet, physical activity, smoking, infection, pollution, and housing—are implemented.

The social framework and policies that enable individuals to fulfill their potential and attain optimal health are crucial.

According to Fries, the age of onset of ill health might, however, rise more quickly than our life span increases, resulting in “compression of morbidity” (a shorter period of disability and ill health before death). So how far can we reduce, or postpone the onset of, disability that is associated with age?

Summary points

Healthy life expectancy is influenced by a relatively limited number of chronic disabling conditions

A substantial proportion of these chronic disabling conditions can be prevented or postponed

A greater focus is needed on prevention and health maintenance—much is already known about the impact of modifiable influences such as diet, physical activity, smoking, infection, pollution, and housing

The social framework and policies that enable individuals to fulfill their potential and attain optimal health are crucial

Table 1 Percentage of people surviving to, and further expectation of life from, age 55 and age 75, by year of birth, 1841-1981

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(Accepted 10 September 1997)
Can we prevent age related disability?

Fries has suggested that people of high socioeconomic status, with more education, or with particular lifestyles (such as those who are physically active) seem to experience compression of morbidity. Indeed, even in Britain, there is evidence of secular improvement. The proportion of men unable to perform four activities of daily living at any specified age has halved between 1976 and 1994 (fig 1).

Variation in rates of chronic disease

Healthy life expectancy is determined by a relatively limited number of chronic conditions that become more common with increasing age. Their exact contributions vary according to definitions of disability, but all estimates include cardiovascular disease, such as coronary heart disease and stroke; musculoskeletal diseases, such as arthritis and osteoporosis leading to fractures; neurodegenerative disorders, such as memory loss and dementia; neuropsychiatric orders, such as depression; cancers, including lung, breast, prostate and colorectal cancers; and other degenerative conditions, such as visual loss from cataracts, macular degeneration and glaucoma, and hearing loss. Reduction or postponement of these conditions may not only reduce premature death and increase longevity but, more importantly, may also decrease the period of illnesses so that people can remain healthy until near death.

The great variation in rates of chronic diseases in different communities shows that a substantial proportion of the chronic diseases associated with aging can be prevented, or at least postponed. Figure 2 gives examples of the relation between age and rates of some chronic disabling conditions in different countries; mortality has been used as a surrogate for incident morbidity data, which are often not available. Japanese men and women show much less increase with age for these conditions than men and women in Britain, with Spain having rates in between. Similar age related patterns can be seen for many other conditions, including other cancers, heart disease, cataracts and glaucoma. Secular trends and changes with migration show that these large differences are likely to be due to environmental rather than genetic factors. Over the past 30 years, age specific rates for cardiovascular disease have halved in Japan and the United States but doubled in Hungary. Rates for hip fracture have doubled in several countries, including Britain (fig 3), Hong Kong, and Sweden. These trends have a huge impact. In Britain, for example, about 50 000 hip fractures occur annually. This number is projected to increase to 120 000 by 2020, but if age specific rates could return to those of 1950, most of this epidemic could be averted. In Britain wide regional and social

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class variations exist for total mortality, which is often used as an indicator of overall health status; throughout adult life, men in social class V have about twice the mortality of men in social class I.\textsuperscript{13}

### Variation in age related physiological decline

The rate at which many physiological functions change with age, and hence the occurrence of their clinical consequences, varies greatly in people in different circumstances. In communities worldwide, blood pressure or concentrations of cholesterol or blood glucose do not increase markedly with age; thus, rises in these factors are not necessary concomitants of the aging process. These communities also have low rates of cardiovascular disease even among elderly people. Migration studies show that the primary determinants are environmental not genetic. Members of the Luo tribe in Kenya had low blood pressures when living in a rural environment but higher blood pressures that increased with age when they moved to urban Nairobi.\textsuperscript{14} Japanese people have much lower blood cholesterol concentrations and lower coronary heart disease rates than white Americans, but Japanese migrants in the United States have much higher cholesterol concentrations and rates of heart disease.\textsuperscript{15} White people with diets of Buddhist monks had low blood cholesterol concentrations similar to those of Japanese people living in Japan, but Japanese people in the United States army with an American diet had high cholesterol concentrations resembling those of white people in the army.\textsuperscript{16} Dutch women living in the Netherlands have much lower blood cholesterol concentrations than Dutch women of the same age in the United States army with an American diet.\textsuperscript{17} Their theory predicts that, rather than any single mechanism for aging, the mechanisms responsible are those types of damage for which maintenance and repair are metabolically costly, such as damage to and mutations of DNA, defective mitochondria, oxidative damage by free radicals, and accumulation of aberrant proteins. Whatever the possible mechanisms, these seem to result in a progressive generalised impairment of functions and loss of adaptive response to stress, a growing risk of chronic diseases, and an increase in the probability of dying. The biological process of aging and its clinical manifestations reflect the interaction between our genetic inheritance and the environment. Indeed, we know that the maximum life span is probably genetically determined, the likelihood of reaching that life span in good health seems to be largely determined by environmental and lifestyle factors.

### Model for intervention strategies

Evidence confirms that throughout life our chances of aging successfully can be increased in various ways. In early life the intrauterine and early postnatal environment may programme basic metabolic processes and hence susceptibility to various conditions such as cardiovascular disease and diabetes in later life, and Barker has suggested that maternal nutrition plays a critical role.\textsuperscript{18} Growth and development of vital organs such as brain, muscles, bone, and blood vessels during childhood and early adulthood build reserves that may affect later capacity. For example, pattern of fatty acid intake, or cognitive exposures in infancy influence brain development, and calcium intake and physical activity influence bone mass in youth, the consequences of which may extend well into old age. In later life, strategies may be to reduce damage (for example, from infections or toxins), to increase protection against damage (for example, by increasing antioxidant defences or strengthening immune func-

### Potential health interventions at different stages of life

| Period                  | Process                        | Maternal interventions 
|-------------------------|--------------------------------|-----------------------------
| Intrauterine            | Metabolic programming          | Maternal nutrition          |
| Childhood and adolescence| Growth and development; building reserves | Nutrition, physical activity, cognitive stimulation |
|                         | Reduce damage                  | No smoking, reduce exposure to pollution and infection |
| Adult                   | Increase protection            | Nutrition                    |
|                         | Prevent disuse                 | Physical and mental activity |
tion), or to prevent loss through lack of use (for example, by remaining physically and mentally active) (box).

The “free radical” and “immune function” theories of aging both give clues as to possible interventions. Free radicals are reactive molecules produced as byproducts of cell metabolism that cause oxidative damage to cell components, including proteins, nucleic acids, and membranes. Damage by free radicals in different tissues has been postulated to be responsible for conditions as diverse as cancers, respiratory disease, dementia, cardiovascular disease, and eye diseases including macular degeneration and cataracts. Many exposures such as infection, toxins, smoking, or high dietary saturated fat load are associated with increased production of and damage by free radicals; antioxidants such as vitamin C, carotenoids, vitamin E, or selenium may mitigate such damage.

The immune theory suggests that functional capacity of the immune system declines throughout life, with involution of the thymus gland and deterioration of stem cells; this is associated with an increased incidence of infections, cancer, and other immune-complex type diseases. Exercise, smoking, and nutrition such as zinc, vitamin A, or pyridoxine and riboflavin can affect immune function.26

### Preventing cardiovascular disease and osteoporosis

**Cardiovascular disease**

Risk of cardiovascular disease rises incrementally with increasing level of blood pressure and cholesterol concentration.21-23 Intervention trials have shown that reduction of blood pressure by 6 mm Hg reduces risk of stroke by 40% and of heart attack by 15% and that a 10% reduction in blood cholesterol concentrations will reduce risk of coronary heart disease by 30%.24 25 Reducing blood pressure and cholesterol concentrations in older people could have a substantial effect on reducing the burden of cardiovascular disease. The exact blood pressure or cholesterol concentration at which drug treatment is considered warranted is still debated. Observational studies and trials, however, have implicated high dietary saturated fat as a cause of high cholesterol concentration and rates of coronary heart disease, and high dietary sodium intake in the aetiology of the age related rise in blood pressure and stroke, and have shown that relatively modest reductions in saturated fat and salt intake may greatly affect cardiovascular disease.26-28 The feasibility and achievability of such changes in diet and cardiovascular disease are well supported by the existing large international and secular variations. Dietary changes seem to affect risk factor levels throughout life and may have even more impact in elderly people. For example, reducing dietary sodium lowers blood pressure more in elderly people than in younger people. Many other dietary and other factors such as cigarette smoking, physical activity, infection, and psychosocial stress also seem to influence cardiovascular risk throughout life through various mechanisms, such as haemostatic tendency, inflammatory processes, or homocysteine metabolism, not all of them well understood or tested in trials. Again, the available evidence shows that the potential impact may be substantial: increasing fruit and vegetables by 1-2 servings daily may decrease cardiovascular risk by 30%.29 Fruit and vegetables may

<table>
<thead>
<tr>
<th>Interventions to improve health in later life</th>
<th>Potential effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet</strong></td>
<td></td>
</tr>
<tr>
<td>High fruit and vegetable intake</td>
<td>Protective for cardiovascular disease; respiratory function; macular degeneration and cataracts; cancers including breast, prostate, colorectal and stomach; diverticular disease; diabetes</td>
</tr>
<tr>
<td>(5 or more servings daily)</td>
<td></td>
</tr>
<tr>
<td>High complex carbohydrates, non-starch polysaccharides (eg potatoes, bread, pulses, pasta)</td>
<td>Protective for cardiovascular disease; cancers including colorectal, prostate, and breast; large bowel disease; osteoarthritis</td>
</tr>
<tr>
<td>Reduced saturated fat (&lt; 15% food energy intake) and total fat (&lt; 35% food energy intake)</td>
<td></td>
</tr>
<tr>
<td>Reduced sodium</td>
<td>High sodium intake increases risk of stroke, stomach cancer, osteoporosis, respiratory disease</td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Protective for cardiovascular disease; diabetes; osteoporosis; cancers including colorectal and breast; depression</td>
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</tbody>
</table>
act through various mechanisms including increasing folic acid and lowering homocysteine levels, increasing vitamin C and flavonoids and thus antioxidant defences, and increasing minerals such as potassium and magnesium, possibly reducing blood pressure. Secondary prevention trials may be more generalisable to elderly people, many of whom may have established diseases. A secondary prevention trial of advice to eat fatty fish twice a week reduced cardiovascular death by 30%; another secondary prevention trial of Mediterranean diet (essentially substituting foods rich in α-linolenic acid for dairy and animal fats and increasing intake of bread, fruit, and vegetables) reduced mortality by 70% after four years.

Osteoporosis
Low bone mass increases risk of fracture, but bone loss and subsequent risk of fractures including vertebral and hip fractures in elderly women or in those with existing fractures can be reduced by 30-50% by various treatments including vitamin D and calcium supplementation or bisphosphonates. As with cardiovascular disease, preventive drug treatment in the whole older population is debatable because of risk-benefit issues, but risk of fracture can be reduced by ensuring that older people have adequate dietary intake of calcium and vitamin D.

Interventions to improve health in later life
Cardiovascular disease and osteoporosis are examples of conditions for which substantial trial evidence exists of the effectiveness and magnitude of impact of preventive interventions in later life; however, since many conditions coexist in elderly people, the impact of interventions on overall health is also crucial.

For most other chronic diseases, a wealth of evidence implicates the substantial role of environmental (including lifestyle) factors, though for most, data from trials are not available. The box summarises some of these factors. Tobacco smoking must be the single most preventable cause of ill health and disability; the benefits of not smoking in terms of respiratory function and cardiovascular disease are apparent even at older ages.

Nutrition clearly has a key role in health throughout life—from maternal nutrition and fetal metabolic programming, to childhood nutrition affecting growth and development, to diet in later life influencing maintenance of health. Caloric restriction is often believed to delay aging, because of experiments reporting that severe food restriction increased longevity in surviving rats. However, findings from studies of rats in strictly controlled and protected experimental conditions are not easily generalisable to humans, and prospective population studies have shown an inverse relation between mortality and caloric intake. Higher caloric intake associated with better health outcome in humans may reflect higher levels of physical activity (which may be beneficial) or higher intake of protective nutrients. Indeed, aging may be associated with less efficient processing of essential nutrients—for example, poorer ability to synthesise vitamin D in the skin, and poorer ability of the gut to absorb nutrients—so older people may need higher intakes of particular nutrients.

Numerous other nutrients have been the focus of interest, including the B vitamins such as B-12 and pyridoxine (which have been implicated in neurological function) and folate and possibly riboflavin (involved in homocysteine metabolism). Unfortunately, trials of antioxidant vitamin supplementation have been largely discouraging; several α-carotene supplementation trials show no effect or adverse effects on cardiovascular disease, cancer, or total mortality; and a trial of vitamin E in secondary prevention of coronary heart disease which reduced non-fatal events by 70% had no, or possibly, an adverse, effect on mortality. Nevertheless, high fruit and vegetable intakes have been most consistently associated with protective benefits in several conditions, including macular degeneration, visual loss, cataracts, respiratory disease, and cancers such as breast, stomach, and colorectal. The discrepancy between foods and isolated supplementation may be that many other

Resolutions when I come to be old

Not to marry a young Woman.
Not to keep young Company, unless they really desire it.
Not to be peevish, or morose, or suspicious.
Not to scorn present Ways, or Wits, or Fashions, or Men, or War, &c.
Not to be fond of Children.
Not to tell the same Story over and over to the same People.
Not to be covetous.
Not to neglect decency, or cleanliness, for fear of falling into Nastiness.
Not to be over severe with young People, but give allowances for their youthful follies and weaknesses.
Not to be influenced by, or give ear to knavish tattling servants, or others.
Not to be too free of advice, nor trouble any but those that desire it.
To desire some good Friends to inform me which of these Resolutions I break, or neglect, &c, in order, and reform accordingly.
Not to talk much, nor of myself.
Not to boast of my former beauty, or strength, or favour with ladies, &c.
Not to hearken to Flatteries, nor conceive I can be beloved by a young woman, et eos qui hereditatem captant, odisse ac vitae.
Not to be positive or opinionate.
Not to set up for observing all these Rules, for fear I should observe none.

Jonathan Swift, 1667-1745
nutrients in food or their interactions are responsible for the clinical effects. Although we may not know precisely which nutrients are responsible for which particular actions, the evidence is overwhelming that particular dietary patterns do seem to relate to good health.64 The 1994 recommendations of the Committee on Medical Aspects of Food Policy emphasize the importance of adequate intake of nutrients such as vitamins and minerals and of -3 fatty acids, which can be achieved by diets high in fruit, vegetables, and complex carbohydrates or plant polysaccharides such as rice, bread, and pulses. Conversely, reduction in dietary sodium and saturated fat or trans fatty acid intake can be achieved by reductions in intakes of certain processed foods (their major source in Western diets) or replacement with low fat foods or oils rich in unsaturated fatty acids. These are diets characteristic of Japan and Crete, which now have greatest average life expectancies.

Obesity is a risk factor for many chronic diseases. Although studies give varying values for ideal weights in older people, extremes of weight (very high (>30) or very low (<18) body mass indices (kg/m²) are adversely associated with health in most populations; to maintain adequate nutrition while keeping body mass index within the (wide) desirable range implies regular physical activity. Indeed, physical activity seems to protect against many diseases, such as cardiovascular disease, osteoporosis and fractures, diabetes, and breast and colon cancer.6 11 Exactly how much and what sort of physical activity at different ages has particular effects is still unclear, but even moderate activities such as walking, gardening, and keeping generally mobile seem to promote physical and mental functioning and wellbeing.

Prevention of cognitive loss or dementia poses a particular challenge in elderly people. Some deterioration can be attributed to atherosclerotic disease, and thus interventions such as aspirin or particular dietary patterns that reduce cardiovascular risk may also prevent dementia. High educational status early in life and, intriguingly, continued mental stimulation, also seem protective.

Many other extraneous factors offer future possibilities for interventions. For example, chronic infections such as chlamydia and helicobacter have been implicated as risk factors for cardiovascular disease and cancer of the stomach, and air pollution is now believed to affect cardiovascular health. Thus, general public health measures in other, not hitherto directly related, areas may have additional benefits for age-related chronic diseases.

**Conclusion**

For many diseases we do not yet have sufficient evidence to make highly specific recommendations for prevention, but we know the general environmental and lifestyle patterns that can help. However, individuals' ability to make changes to improve their health is determined by the societal and cultural context and circumstances including choice, access, availability, information, and income. Environmental determinants such as adequate housing and clean air and water, fundamentals for health, cannot always be taken for granted. The large inequalities in health experienced by social class and region in Britain reflect these varying circumstances.

Successful aging of course encompasses social as well as physical and psychological wellbeing. The social framework and policies that may enable individuals to fulfill their potential and attain optimal health are crucial.
The most frequent medical intervention performed by a doctor is the writing of a prescription. Because chronic illness increases with advancing age, older people are more likely to have conditions that require drug treatment. Advanced age, frailty, and increased use of drugs are all factors that contribute to a patient’s risk of developing a drug related problem. As many as 28% of hospital admissions in the United States of older people are as a result of drug related problems,1 up to 70% of which are attributed to adverse reactions to drugs.1 Creating optimal drug regimens that meet the complex needs of elderly people requires thought and careful planning.

Inappropriate prescribing is expensive. In a recent study the costs of preventable adverse drug events—namely, injury resulting from a drug related medical intervention—occurring during a stay in hospital were estimated to be £2.8bn ($4.1bn) annually in two large American teaching hospitals. The national cost of managing the consequences of inappropriate prescribing remains uncertain. One estimate has put the annual cost of drug related morbidity and mortality in outpatient clinics at £76.6bn.1 Drug related morbidity and mortality is an important area to target both to improve the quality of medical care for elderly people and to reduce the costs of health care for this population.

A prescriber can do little to modify age related physiological changes in trying to minimise the likelihood that an older person will develop an adverse drug reaction. However, when assessing a patient who is already taking drugs, a doctor should always consider the development of any new signs and symptoms as a possible consequence of the patient’s drug treatment. This article will focus on an under-recognised, and largely preventable drug related problem that we have termed the “prescribing cascade.” The prescribing cascade begins when an adverse drug reaction is misinterpreted as a new medical condition.

Another drug is then prescribed, and the patient is placed at risk of developing additional adverse effects relating to this potentially unnecessary treatment.

To prevent the prescribing cascade, doctors should always consider any new signs and symptoms as a possible consequence of current drug treatment.

Before any new drug treatment is started, the need for the drug should be re-evaluated and a non-drug treatment should be considered.

If drug treatment is necessary the lowest feasible dose of the drug should be used and alternative drugs with fewer adverse effects considered.
occurrence of preventable adverse drug events associated with suboptimal prescribing decisions.

### Non-steroidal anti-inflammatory drugs and starting antihypertensive treatment

Non-steroidal anti-inflammatory drugs are among the most frequently prescribed drugs to elderly patients. An estimated 10-15% of people aged 65 years or older are prescribed such drugs. Their anti-inflammatory properties seem to result from their ability to inhibit cyclo-oxygenase, a critical enzyme in the biosynthesis of prostaglandins. Good evidence exists to suggest that prostaglandins have an important role in the modulation of two major determinants of blood pressure: vasoconstriction of arteriolar smooth muscle and control of extracellular fluid volume. The effects of non-steroidal anti-inflammatory drugs are most prominent in patients with existing hypertension.

The high prevalence of use of non-steroidal anti-inflammatory drugs among older people emphasises the importance of studying the clinical impact of these drugs on blood pressure in elderly people. To determine whether there is an increased risk associated with starting antihypertensive treatment in older people prescribed non-steroidal anti-inflammatory drugs (table), a case-control study was performed involving patients enrolled in the New Jersey Medicaid programme who were aged 65 years or older. Over 9000 patients who were newly started on an antihypertensive drug were compared with a similar number of randomly selected control patients. The adjusted odds ratio for starting antihypertensive treatment for recent users of non-steroidal anti-inflammatory drugs compared with non-users was 1.66 (95% confidence interval, 1.54 to 1.80). The odds ratio increased with increasing daily dose of the anti-inflammatory drug: for low average daily doses was 1.55 (1.38 to 1.74), for medium dose users was 1.64 (1.44 to 1.87), and for high dose users was 1.82 (1.62 to 2.05). The conclusion was that the use of non-steroidal anti-inflammatory drugs may increase the risk associated with starting antihypertensive treatment in older people. Given the high prevalence of use of non-steroidal anti-inflammatory drugs by elderly people, this association could have important public health implications for the care of older patients.

This relation also shows a clear sequence of events where the use of one treatment leads to the start of a second that might have been avoided. Based on the findings of numerous epidemiological and clinical studies that have characterised the adverse consequences of use of non-steroidal anti-inflammatory drugs in older people, recommendations have been made to avoid using these agents when clinically feasible. As with other drugs prescribed to elderly patients, the most prudent approach is to limit prescribing non-steroidal anti-inflammatory drugs to situations in which benefits clearly outweigh risks and to use them only after potentially safer alternatives have been tried. Because of the multiple adverse effects attributable to these drugs, for some indications (such as osteoarthritis) treatments such as acetaminophen, gentle exercise, and weight reduction may be effective alternatives. When treatment with non-steroidal anti-inflammatory drugs is necessary, the lowest feasible dose should be used for the shortest time required to achieve the desired effect.

Furthermore, if patients require extended treatment with non-steroidal anti-inflammatory drugs, periodic monitoring of blood pressure is warranted, as such treatment may contribute to newly detected rises in pressure. With recognition of this association between non-steroidal anti-inflammatory drugs and rises in blood pressure, the starting or intensifying of antihypertensive treatment may be avoided.

### Thiazide diuretics and starting treatment for gout

The development of some degree of hyperuricaemia is a well documented side effect of treatment with thiazide diuretics. Population based studies have shown an association between hyperuricaemia and the development of gout. For example, data from the Framingham study document a cumulative incidence of gout of 36% over 12 years in patients with serum uric acid concentrations > 476 μmol/l, compared with less than 3% in those with lower concentrations. The occurrence of hyperuricaemia that has been induced by thiazide diuretics raises some important issues about the use of these diuretics in elderly people. Ample data show the efficacy of these agents in treating hypertension in elderly patients and in preventing major sequelae such as stroke—data that are absent for many other commonly used antihypertensive drugs. The impact of thiazide diuretics on serum uric acid concentrations, however, raises questions about whether this treatment may precipitate the use of additional drugs.

This question was recently examined in a retrospective cohort study of 9249 patients enrolled in the New Jersey Medicaid programme aged 65 or older who had been started on a variety of antihypertensive agents. None of the patients in the cohort had previously used treatment for gout (allopurinol, colchicine, or uricosuric agent). Follow up extended for up to

### Examples of prescribing cascade

<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>Adverse effect</th>
<th>Subsequent treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>Rise in blood pressure</td>
<td>Antihypertensive treatment</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Hyperuricaemia</td>
<td>Treatment for gout</td>
</tr>
<tr>
<td>Metoclopramide treatment</td>
<td>Parkinsonian symptoms</td>
<td>Treatment with levodopa</td>
</tr>
</tbody>
</table>

**Fig 1** Prescribing cascade
two years, and exposure to antihypertensive drugs was characterised over this period according to the following categories: thiazide diuretics alone; non-thiazide antihypertensive drugs alone; thiazide diuretics combined with any non-thiazide antihypertensive drug; and no use of antihypertensive drugs. The relative risk for starting treatment for gout was 1.00 (0.65 to 1.53) for non-thiazide antihypertensive drugs alone, 1.99 (1.21 to 3.26) for thiazide diuretics alone, and 2.29 (1.55 to 3.37) for thiazide diuretics combined with any non-thiazide drug. Risk for starting treatment for gout was significantly increased for thiazide doses of ≥25 mg/day (in hydrochlorothiazide equivalents) or more; no significant increase in risk was seen for lower doses. It was concluded that the use of thiazide diuretics in doses of ≥25 mg/day was associated with a significantly increased risk for starting treatment for gout, relative to antihypertensive regimens that did not include the use of a thiazide diuretic.

Considerable evidence supports the efficacy of low doses of thiazide diuretics in the treatment of hypertension in elderly people.13-15 The dose-response relations found in this study support the use of lower doses of thiazide diuretics when treatment is indicated. Although the recommendations of the United States’s joint national committee on detection, evaluation and treatment of high blood pressure suggest starting antihypertensive treatment at low doses in all patients,17 thiazide diuretics are commonly started at doses that extend well beyond the low dose range. Low doses of thiazide diuretics—for example, 12.5 mg of hydrochlorothiazide—often produce as large an antihypertensive effect as larger doses, with a reduced risk of metabolic abnormalities. In fact, evidence exists that a dose of hydrochlorothiazide as low as 6.25 mg can be as efficacious in treating hypertension in many older patients, when combined with a low dose of another antihypertensive drug.23-25 When hyperuricaemia does occur during treatment with a thiazide diuretic, clinicians should bear in mind that asymptomatic hyperuricaemia alone does not warrant treatment.

Use of metoclopramide when starting levodopa treatment

Metoclopramide hydrochloride is widely used in the treatment of gastro-oesophageal reflux, in the management of disorders of gastric emptying including diabetic gastroparesis, and as an antiemetic after chemotherapy. Its antidopaminergic adverse effects, including unwanted extrapyramidal signs and symptoms, have long been recognised. Such drug induced symptoms in older people can be misinterpreted as indicating a new disease or be attributed to the aging process itself. This misinterpretation is particularly likely when the symptoms are indistinguishable from an illness that is seen more often in older people, such as Parkinson’s disease.26 27

A case-control study, again involving patients enrolled in the New Jersey Medicaid programme aged 65 years or older, showed that patients taking metoclopramide were three times more likely to begin using a drug containing levodopa than patients not taking metoclopramide (odds ratio 3.09 (2.25 to 4.26).32 The risk increased with increasing daily metoclopramide dose: the odds ratio was 1.19 (0.50 to 2.81) for ≤10 mg/day, 3.33 (1.98 to 5.58) for > 10 mg/day to 20 mg/day, and 5.25 (1.16 to 8.50) for > 20 mg/day (fig 2). In summary, metoclopramide confers an increased risk of starting treatment generally reserved for managing idiopathic Parkinson’s disease. Such multiple prescribing may represent the misdiagnosis of Parkinson’s disease in patients with drug induced parkinsonian symptoms.

Conclusion

The prescribing cascade, whereby additional drug treatment is started after a patient develops an adverse reaction to a drug, is largely preventable by carefully considering whether any new medical condition might be the result of an existing drug treatment. The prescription of a new drug specifically to treat an adverse drug effect should be considered the choice of last resort in the care of older patients. More prudent strategies include:
Tales from retirement

A senior’s lecture tour

Like others in academic medicine I have been in many places as a visiting lecturer. Latterly, however, I found these visits were unsatisfactory on two counts. Firstly, the places I visited tended to be rather privileged. Secondly, the visits were too short to have much impact. Since retirement I have made several visits designed to lessen these disadvantages. I would like to encourage other retired doctors to try similar ventures.

As a general rule I have avoided very rich and very poor countries because for different, but obvious, reasons they don’t need me. I prefer a middle income country; one in which they may have the books and some equipment but lack experience and perspective. And, very important if selfish, the whole trip means.

By shopping around we can always find something within our means. All of this requires good local organisation. These visits are of a modern, which have appealed to the reader.

I have found that the visit is obviously flexible but we find that six to eight weeks is a reasonable limit. I hope that is enough to contribute something which will last; after eight weeks we are tired. We welcome filler articles up to 600 words on topics such as A memorable patient, A paper that changed my practice, My most unfortunate mistake, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for “Endpieces,” consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.

Education and debate

Carefully re-evaluating the absolute need for the offending agent;

Using non-pharmacological treatment for managing a patient’s medical condition;

Reducing the dosage of the implicated drug to the lowest feasible dose that is effective in treating a patient’s medical condition; and

Considering alternative drugs that might be safer in terms of the risk of adverse effects in older people.