Healthy ageing: ageing safely

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The population of the developed world is steadily ageing. In the European Union, approximately 22% of persons are over 60 years of age and this is projected to increase to more than 27% by the year 2020. This has major implications for health care resources and the productive workforce. Ageing is accompanied by a decline in the physiological reserve of all organ systems, compromising homeostasis and resistance to disease. Thus, when disease develops in the elderly it has an increased impact on organ systems not directly involved. This places older people at risk for multiple simultaneous pathologies. Treatment often requires polypharmacy, which often is accompanied by drug interactions and adverse reactions. The pattern of sequential and comorbid disease often means that the later years of life are associated with an accumulating toll of disability, which in turn consumes a high proportion of health-care resources. The major goal of health care in the elderly should be to compress morbidity into the end of the normal lifespan. To achieve this, it will be necessary to redefine our approaches to treatment in the elderly and to develop an evidence base to inform this process.

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Introduction

From the beginning of time until about a century ago, few of the world’s population survived to more than 50 years of age. Whereas this situation persists in undeveloped countries, most industrialized societies have experienced a progressive increase in the proportion of elderly people (Fig. 1)[1]. Recent statistics show that 22% of people were older than 60 years in the year 2000[2]. This proportion is projected to increase to 27% by the year 2020. Data from five different industrialized countries (France, Canada, Japan, U.S.A. and U.K.) clearly show that survival until 60 years of age is associated with a very high probability of surviving to 80 years[3]. Among women from France, Canada, U.S.A. and U.K., those who are 60 years old have a greater than 50% chance of reaching 80 years, and for Japanese women the probability is 70%. Male survival to 80 years (38–48%) is lower than that for women, in part because of their higher incidence of atherosclerosis. Worldwide, approximately 10% of the population are currently aged 60 years or more. This proportion is expected to double during the next 50 years, and in 150 years time it will have increased even further to one in three[1]. As a dramatic illustration of this trend, half of all those who ever lived to 65 years or more are alive at present.

People aged 80 years or older constitute the fastest growing segment of the elderly population, and account for 11% of those older than 60 years worldwide. It is predicted that in 50 years time one in five people will be 80 years old or older, and that there will be a 15-fold increase in those who are 100 years old or older, from 0.145 million in 1999 to 2.2 million by 2050[1]. Thus, within the ageing population, the elderly population is itself ageing. This emphasizes our need to understand better the interaction between ageing, physiology and disease, and must provide an impetus for challenging the traditional prejudices that have often minimized constructive therapeutic intervention in the elderly.

Impact of disease in old age

In general terms, the principal diseases of old age (vascular disorders, cancer, and respiratory and infectious disease) are the same as those that afflict the middle aged. As age
advances, however, there is a gradual decline in the physiological reserve of all organ systems that maintains homeostasis in the healthy state. This is exemplified by the gradual rise in plasma creatinine concentration that occurs beyond middle age and that reflects diminishing renal function in the absence of renal disease. Other examples of age-related...
functional decline include the decrease in bone density that ultimately results in loss of mechanical strength and fracture resistance, and the decline in cardiovascular reserve. Cardiologists, for instance, are familiar with the need to adjust the Bruce protocol for age.

When a disorder occurs in any organ system, the reduction in homeostatic reserve caused by ageing increases the impact of that disorder on all other organs. This makes the elderly susceptible to multiple pathologies simultaneously and may cause a ‘domino effect’ if one destabilizing event occurs. For example, a woman of 80 years with ocular cataracts and macular degeneration is at risk for sustaining a fall because of failure to see an object that can trip her up. Her underlying osteoporosis means that a fall is likely to result in a fracture, requiring hospital admission. Her coexisting atherosclerosis, and diminished cardiovascular and respiratory reserves place her at increased risk for fatal or disabling myocardial infarction while undergoing surgery to repair the fracture. Although this is an everyday situation, examination of most of the disorders that place her at risk shows that they are amenable to prior constructive medical intervention. Failure to manage actively her comorbid conditions maximizes the impact of any adverse event and reflects a fundamental failure to tackle the burden of old age.

**Polypharmacy**

The down side of effective management of coexisting diseases in the elderly is the requirement to employ multiple medications. Such polypharmacy increases the probability of adverse drug interactions, especially in the context of diminishing renal reserve. It has been estimated that serious adverse drug reactions are between the fourth and sixth leading causes of death in the U.S.A. A meta-analysis of 39 prospective studies showed that 2.2 million hospitalized patients of all ages had suffered serious adverse drug reactions in 1994, and that 106,000 (95% confidence interval 76,000–137,000) patients had died as a consequence[4]. It is likely that the incidence of serious adverse drug reactions is higher than this in the elderly because of the effects of polypharmacy and of diminished renal reserve. A typical elderly female patient may, for example, be receiving diclofenac for arthritis, warfarin for atrial fibrillation, and diltiazem and aspirin for ischaemic heart disease. Antibiotics will occasionally be added to these core medications to combat infection, and the patient is also likely to be prescribed omeprazole for intermittent bouts of indigestion. She may also be receiving statin therapy. It is easy to appreciate that most of these drugs interact pharmacokinetically in mutually influencing their free plasma concentrations, and there is potential for serious adverse interactions, particularly in terms of bleeding. This extent of polypharmacy is fairly typical, as evidenced by the finding that participants in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) were each receiving an average of six medications[5].

In order to overcome the potential for drug treatment in the elderly to do more harm than good, particular care must be taken to minimize interactions when adding medication to an existing regimen. A counsel of perfection is that drugs should be used as much as possible that do not require prior metabolism for activation, that are not metabolized through the cytochrome P450 system, that do not mutually interact at plasma protein binding, and that do not risk further impairment of renal function. Drugs should be selected on the basis of a well established safety record. Selection of drugs for an older person using these criteria is not in fact as difficult as it may seem. For instance, the use of aspirin often requires coadministration of a proton pump inhibitor or H₂ receptor antagonist. From the large number of compounds available from these classes, it is not difficult to select one (e.g. pantoprazole, rabeprazole and ranitidine) that has a low potential for interaction.

The long-term safety of statins is based on experience from more than 150,000 patient-years of experience in randomized controlled trials, as well as on that from a decade of routine use. Among this class of drugs, pravastatin is by far the most widely studied (Fig. 2). Data summarizing 100,000 patient-years of treatment in placebo-controlled trials in patients aged 30–65 years indicate that the incidence of adverse effects with pravastatin is comparable to that with placebo[6–8]. Pravastatin, in contrast to other available statins, has a low potential for drug–drug interactions, because it is not significantly metabolized through the cytochrome P450 system. This factor must take precedence over other considerations when selecting a statin as part of a complex drug regimen in older patients.

**Impact of old age on disease**

The overall impact of disease in old age is defined not only by the coexisting problems of reduced homeostatic reserve, comorbidity and polypharmacy, but often also by the associated societal issues of social deprivation, economic dependence and devaluation of the aged. Unfortunately, our traditional mindset links old age with disease, disability and deteriorating quality of life. As a consequence, the tendency has been to view the elderly as existing in a waiting room for death and thus to consider them as less deserving of effort by society.

A widespread attitude within Western societies is that the young have ‘potential’, the middle aged are ‘productive’ and the elderly are ‘superfluous’.

Disease and disability are not inevitable in old age, however. The Leiden 85-Plus study found that 40% of people over the age of 85 years have optimal cognitive function[9]. A study of centenarians identified 43 individuals (prevalence approximately 1 in 10,000) in a census of a population of 460,000 inhabitants of the towns surrounding the city of Boston, Massachusetts[10]. The 37 persons who were included in the study had a mean age of 102 years (range 100–109 years). They were receiving an average of 3-4 medications and, including hearing loss, had on average four concomitant diseases. The results in Fig. 3 show the
The benefits of delaying the onset of illness are highlighted by recent U.S. National Institutes of Health estimates[11]. These indicate that if the onset of Alzheimer’s disease can be offset by 5 years then the prevalence of the condition in the U.S.A. would be halved from approximately 4 million to 2 million, and the associated costs would be almost halved from US$81 billion to US$43 billion (Fig. 4)[11]. The challenge for the future is to delay the onset of disease so that morbidity can be ‘compressed’ into a short period of time.

We have very little evidence on which to base our approach to maintenance of health in the elderly. Clinical trials typically investigate outcomes in patients in the 35–65 years age range, and there are only a handful of major clinical trials in the elderly (e.g. Systolic Hypertension in the Elderly Program [SHEP][12] and Systolic Hypertension in Europe [SYST-EUR][13]). There is a clear need to conduct large studies in the elderly in the realistic context of comorbidity and polypharmacy so that this great gap in the evidence base for treatment is remedied.

Subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) has shown that simvastatin significantly reduces the risk for secondary coronary events in persons over 60 years of age[14]. It was also found to reduce significantly the risk for stroke and transient ischaemic attack in the population as a whole[15]. This is an important finding because it was estimated in one report that approximately one in three patients with coronary artery disease who were older 62 years of age had suffered an atherothrombotic brain infarction[16]. There is also evidence that treatment with lovastatin in patients at mean age 62 years was associated with a slowing of the progression of bypass graft atherosclerosis[17].

PROSPER is the first study specifically designed to investigate the benefits of secondary intervention with a statin in a large (n = 5804) elderly population aged between 70 and 82 years[5]. The objectives of this multinational, double-blind, placebo-controlled study are to assess whether long-term treatment with pravastatin reduces the risk for subsequent major vascular events in patients with pre-existing vascular disease or in those who are at significant risk for developing this condition. The study began in 1998 and the data will be available for analysis after a mean 3·5-year intervention period. That study will provide much needed data to

**Figure 2** Clinical experience with different members of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins).

**Figure 3** Percentage of centenarians functioning independently over the previous 10 years of their lives. (Data from Hitt et al.[10].)

**Figure 4** Economic effect of a 5-year delay in the onset of Alzheimer’s disease. (Data from the U.S. National Institutes of Health[11].)
determine whether it is possible to lower the risk of coronary heart disease events and stroke in the elderly to the same degree as has been demonstrated in younger populations receiving statin therapy (e.g. Cholesterol and Recurrent Events [CARE][6] and Long-term Intervention with Pravastatin in Ischaemic Disease [LIPID][7] and 4S[14]). It will also examine the effect of intervention on cognitive function and will demonstrate whether pravastatin treatment influences overall levels of disability. Pravastatin was chosen as the study medication because of its minimal interaction potential, and the study will allow the safety profile of pravastatin to be assessed in the context of polypharmacy in an elderly population. Measurement of the economic impact of intervention is an important aspect of the study, because of its major implications for resource utilization.

Conclusion

The United Nations has set out a series of principles for older persons based on independent participation, care, self-fulfilment and dignity. These principles state that older persons should have access to health care to help them maintain or regain the optimum levels of physical, mental and emotional well-being, and to prevent or delay the onset of illness.

There are needs to reassess attitudes to intervention in the elderly so that comorbid conditions are treated actively, to use multiple medications more rationally so that interactions and adverse effects are minimized, and to develop a realistic evidence base for treatments specifically in elderly populations. Maintenance of good health, prevention of disease and effective treatment of illness are entitlements of the elderly, which will increasingly be required to maintain a functioning society as the proportion of people over 65 years old steadily increases.

References


