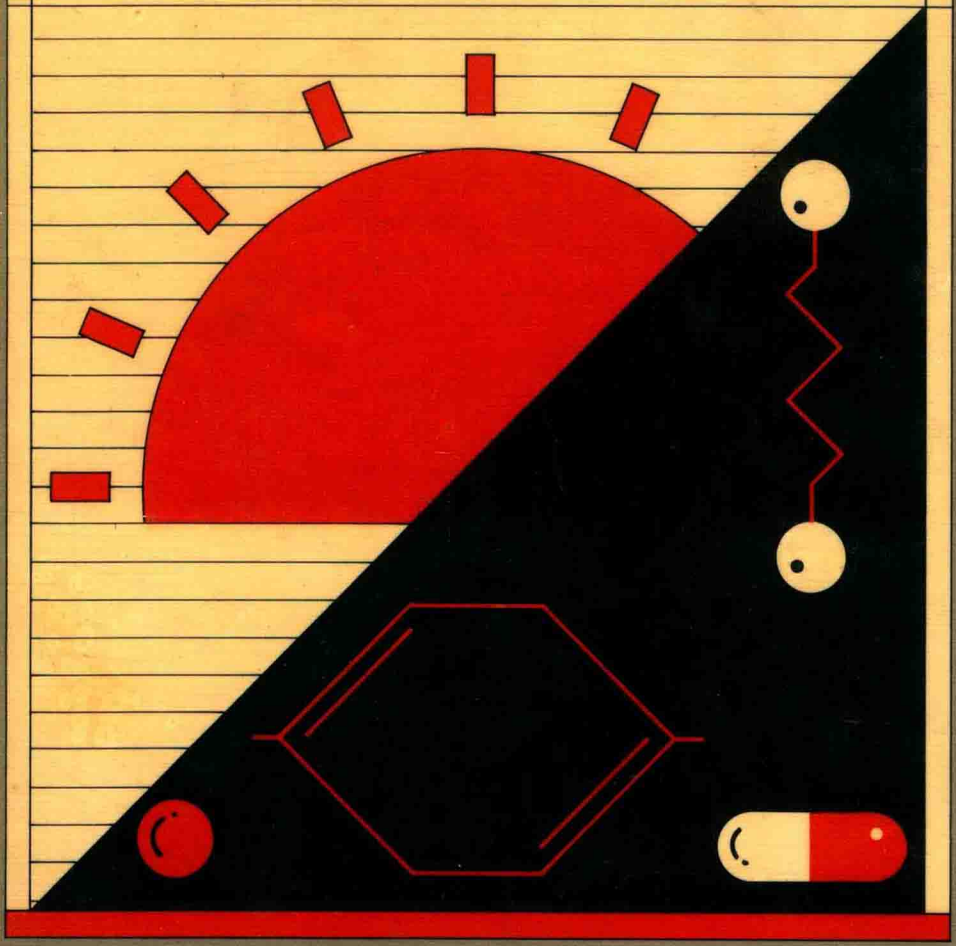
GERIATRIC PHARMACOLOGY AND THERAPEUTICS

EDITED BY J C BROCKLEHURST



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Preface

It is now well recognized that medicine in old age, while sharing most of the problems which arise in the practice of medicine in younger people, has a whole additional range of problems of its own. These arise because of the background of aging, the accumulation of pathology and the altered drug effects that occur in old people. The combination of all these factors affects not only the presentation of many diseases in the elderly but also the way in which old people react to a therapeutic regimen.

While this book does not attempt to rewrite the whole field of pharmacology and therapeutics, it does aim to deal with all those aspects of medical treatment in old people which have their own special problems and which differ in their nature and presentation from treatment at younger ages. In highlighting the differences in pharmacology and therapeutics in old age a necessary preliminary is to consider something of the processes of aging itself and how they affect pharmacodynamics and pharmacokinetics. Subsequently we consider the implications of an aging society: both as to its effect on the prescribing habits of physicians (and the nation's drug bill) and also regarding the problems that old people have in personally managing their own medications.

Geriatric Pharmacology and Therapeutics is written by a group of authors, most of whom are also involved in teaching geriatric medicine to medical students. The book has been written primarily for family practitioners but it will also be of use and interest to geriatricians and internists.

This book is intended for an international readership and a small number of drugs discussed are not available in North America. In each chapter the drugs discussed are listed in tables and any not available in North America are indicated.

J.C. Brocklehurst
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Chapter One
A General Introduction to Aging

W. DAVISON

Old and young, we are all on our last cruise
Robert Louis Stevenson (1850–94)

OVERVIEW

Aging is an essential characteristic of living things setting a limit to the potential life span of the species, even under best conditions. Some possible basic biological mechanisms and the functional consequences of aging in the human are outlined. The key role of an intact central nervous system in the fight for survival is emphasized. Attention is drawn to the possibility that much morbidity and mortality (more especially in the male) is due to an unhealthy life style.

Some social characteristics of the elderly are looked at and the changing demography is considered, especially the impact on health and welfare agencies. Lastly, there is a look at the elderly at home, their life satisfaction and health. It is hoped that this chapter will help the family practitioner view his ailing elderly patient in perspective, both biologically and sociologically.

AGING: A FUNDAMENTAL BIOLOGICAL PROCESS

What is aging?

Aging comprises those fundamental changes not due to disease occurring in individuals after maturity, which are more or less common to all members of the species and which increase the probability of death. The relative uniformity of the process of senescence and the consequent inevitability of death, is an unpalatable fact that each man's philosophy of life must embrace. Aging inevitably results in death and the increasing probability of imminent death with advancing years after puberty was expressed mathematically more than 150 years ago by Benjamin Gompertz. He showed that this probability doubles every 8 years over the age of 35. In the developed world people are least liable to die in the years just before puberty, thereafter the risk of imminent death increases exponentially (Finch & Hayflick 1977, p. 513). Aging is the increasing inability to resist death.

Aging as an evolutionary adaptation

Death by aging is essential for the vigour and the survival of the species. It helps to keep down total population size and those who die make way for youth. Without death, life as we know it would be impossible. With these processes of death and birth comes the possibility of change in the species by genetic mutation. The more favoured mutants are more likely to survive and procreate; the less favoured mutants more likely to succumb. Presumably the different species-specific life spans have evolved to confer on each species the maximum vigour and survival potential for living in its own environment in a particular epoch; for example, in *homo sapiens* the long postmenopause may have evolved to allow more intellectual development (which provides the hallmark for our species). The long postmenopause allowed the longer-lived members to act (before books and computers) as vital repositories of knowledge, i.e. as data banks. Thus older people earned their postreproductive lives by conferring considerable survival advantage on the young. This crucial role has been eroded in modern society.

Table 1.1 Possible molecular mechanisms of aging.

Biological clock
Error hypothesis
Hayflick limit
Accumulation of waste
Cross-linkage of proteins

The biological clock

The predictable rate of aging in each species suggests some kind of biological clock mechanism programmed genetically to run for a set time before allowing death to occur. A mechanism of this sort seems essential to allow natural growth and development; for example, the early death of tissues between the digits on the hands and feet of the human fetus (morpho-genetic death), and (in another species) the death of the tail and gills of the tadpole to allow the normal metamorphosis to a frog to take place (phylogenetic death). Controlled death and regeneration is as important within individuals as it is for the development and survival of the species as a whole.

The error hypothesis

It has been suggested that aging may be due to an accumulation of errors in the molecular content of the cells of the body. DNA and RNA provide the key control mechanisms for protein synthesis but they can be damaged

by mutagens such as radiation, free radicals (e.g. superoxide) and drugs. There is a continuous turnover of enzymes, hormones and neurotransmitters and at each stage in the biochemical processes there is the possibility of error. If errors accumulate beyond a certain level, the cells or tissues will become incompetent and may die; for example, if the brain cells deteriorate chemically then even if the cells themselves survive, ultimately the brain as a whole would cease to function satisfactorily, homeostatic controls would fail and death would ensue. If dysfunctioning cells in any tissue are allowed to survive and proliferate, death of the whole organism will eventually occur as in many malignant diseases.

The rate at which errors accumulate depends partly on the rate of error production and partly on the rate of error removal and this applies at both the molecular and the cellular level. In cell division normally the replication of DNA is a highly accurate and reliable process so that the daughter cells have all the proper constituents, viz. chromosomes, RNA and proteins. However, damage to the genetic material may produce coding errors and result in faulty cell proteins.

The Hayflick limit

In the first half of this century it was commonly believed that certain vertebrate cell types such as the fibroblast could grow in culture indefinitely. The work of Carrel and later Ebling suggested this. However, in the mid 1960s Hayflick and others observed that some 40–50 doublings was the upper limit for cells grown from human fetal tissue. This 'Hayflick limit', as it has come to be called, is now generally accepted as the ultimate life span of genetically normal human fibroblasts in culture.

Accumulation of intra- and extra-cellular waste

Some cells are actively dividing and replacing themselves throughout life. These cells are all 'young' even though the whole organism is 'old'. This is true of the cells of the blood, gastrointestinal mucosa and outer layers of the skin. Other cells have to last literally for a lifetime. If they die before death of the whole organism, they are not replaced. Examples of these postmitotic cells are heart muscle cells and neurones. Throughout life they gradually accumulate lipids, lysosomes and lipofuscin. Opinion is divided as to whether these accumulations are deleterious with respect to normal aging.

One of the most constant biological features of aging is the increasing quantity of lipofuscin or 'wear and tear pigment' found in many tissues. Its origin and effects are not known but production from lysosomes is a probability. Formation of lipofuscin can be inhibited by antioxidants and its removal from neurones can be achieved by centrophenoxine in the

experimental animal. The benefits which might accrue from preventing the formation or affecting the removal of lipofuscin from the human brain are none too clear but some clinical reports are encouraging. There is also extracellular accumulation of other substances, such as amyloid which may have adverse effects on cell or organ function.

Aging of connective tissue

Connective tissue aging may contribute to the failure of the more metabolically active tissues as well as causing many of the other manifestations of old age, including thinning and fragility of the skin, loss of elasticity of blood vessels and stiffening of heart muscles and joints. Collagen is the main connective tissue protein. Its stiffening with age is due to chemical cross-linkage of adjacent parts of macromolecules with resultant altered physical properties. Similar changes occur in elastin and other proteins of the interstitial tissues. Lathyrogens such as beta-aminopropionitrile (BAPN) and penicillamine have been shown to inhibit cross-linkage in collagen.

Immune system failure

The immune system (IS) functions less effectively in older animals than in the young, and some parts of it (e.g. thymus) atrophy comparatively early in life. Normally the IS protects the body against invasion by bacteria, viruses and fungi and also prevents accumulation of the body's own unwanted cells. Cells which are not acceptable because they are effete, foreign to the host or malignant are identified and destroyed. If the IS fails in this task, it may allow alien cells to invade, or may fail to recognize 'self' cells and proceed to destroy them as if they too were alien (autoimmunity).

General failure of the IS would help to explain the susceptibility to infection and the increased incidence of autoimmune diseases and some malignancies with age. There is an inverse relationship between the overall incidence of cancer and the activity of the IS and this is seen most clearly in the aged. Experimental attempts to combat these problems have used immunosuppressive drugs to prevent or suppress autoimmune reactions. In some cases, immune cells are infused from a healthy young donor to counteract the immunodeficiency of the elderly recipient. The results are not encouraging. Existing immunosuppressants (e.g. azathioprine and cyclophosphamide) are much too toxic and non-specific in their effects to use as general life-extending agents. Also the use of IS cell homografts is beset by formidable technical problems of immunological match and mismatch. One suggestion is to use IS cell autografts which were removed in the full bloom of youth and stored in a tissue bank, as is done with sperms, for use when required in old age!

WHAT DOES BIOLOGICAL RESEARCH TELL US?

Despite the mass of research into biological and especially molecular aspects of aging there is no evidence yet to suggest that we can influence the rate of human aging. We can, however, affect the incidence of disease and thus maximize activity and prolong life. Medical practice must focus on the promotion of good health and the identification and effective treatment of disease. The retardation of aging is not yet on the medical agenda despite many claims to the contrary (Finch & Hayflick 1977).

Functional consequences of aging

Age changes comprise a decline in efficiency, a loss of homeostasis, a weakening or damage to structure and an eventual breakdown in health. Death is the outcome. Primary aging, although an inherent process, is also influenced to a greater or lesser degree by the social and physical environment. It must be distinguished from secondary aging which refers to the effects of trauma and disease.

The general appearance and behaviour of an individual will give a good indication of his age. Careful camouflage by clothes, cosmetics (even cosmetic surgery) and 'acting young' may for a time give an impression of extended youth but soon the truth will out! Greying of the hair, frontal balding, wrinkling of the skin and puffiness under the eyes are all manifestations of middle-age. By the age of 50 years half the population have at least half their body hair grey, irrespective of their sex or early hair colour. Also over 60% of this age group have bitemporal recession and some vertical thinning. Failing vision (presbyopia), slowing of dark adaptation and decline in hearing (presbycusis) also develop. There is need for improved illumination to allow adequate vision and also need to provide good contrasts in the environment to give clear visual signals. Taste and smell sensitivity also decline.

Even in the absence of disease, changes take place which affect pharmacokinetics (Finch & Hayflick 1977, Chapter 8). The lean body mass (LBM) consisting of brain, heart, lungs, liver, kidney and other organs together with the voluntary muscle mass (which is maximal at age 20–30 years) decreases and body fat increases. By age 80 years about half of the striated muscle cells have been lost and replaced in this way. This reduction in LBM can be demonstrated by the 15–20% drop in exchangeable potassium per kilogram body weight between age 20 and 75 years. Thus despite continued physical exercise there is a decline in both strength and stamina. The loss of stamina is noticeable in both work and leisure by the age of 40 years and is well established by 60. It is more marked in sedentary males than in manual workers and females. Total respiratory capacity (including arterial oxygen saturation), glomerular filtration rate and tubular functions are all

reduced. There is loss of one-third of the nephrons and the mean value of glomerular filtration rate in healthy 80-year-olds is only half of that of young people. Even in the presence of a normal blood urea a big drop in renal function must be assumed. The importance of this lies in the liability to overt renal failure during illness and the reduced ability to excrete drugs via the kidney, even in the absence of disease known to affect renal function.

Basal metabolism is very high in childhood, drops rapidly from before puberty to the mid-twenties and continues to decline, albeit more slowly, for the rest of life. To avoid obesity it is necessary to reduce calorie intake in keeping with these changes—say by 5% in each decade from 40 to 60 years and by 10% in each decade from 60 to 80 years (Trémolières & Geissler-Brun 1975). That is to say the 60-year-old needs 10% less energy from food than at 40. The 'ideal' body weight (i.e. that which confers the lowest mortality in statistical studies) is 15% below the average weight in the USA. If the body weight is 30–50% above the mean in middle age the mortality risk doubles.

Table 1.2 Some functional consequences of aging.

Loss of vigour and mobility
Altered pharmacokinetics
Failing special senses
Liability to fall and fracture
Failing thermoregulation
Failing intellect

Aging of the nervous system

Differential aging occurs in all body systems. Nevertheless in terms of self-care the role of the central nervous system (CNS) is paramount. Evidence of this abounds in everyday medical practice; when the intellect goes, self-care is no longer feasible.

Brain weight decreases with age, more especially very late in life, so that the brain weight of the 80-year-old is found to be some 10% less than that of the 30-year-old. Progressive neuronal fallout has long been accepted as the most plausible explanation of loss of both brain volume and intellect. Certainly some neuronal loss occurs but it is less general than previously believed, being much more marked in certain areas of the brain than in others (Birren & Sloane 1980, p. 75). Some brain shrinkage may be due to loss of stroma rather than neurons. Characteristic histopathological and neurochemical changes also occur with aging but will not be detailed here. However, let it be noted that malfunction of brain cells rather than simply

neuronal fallout may be the main problem affecting the aging brain; for example, defects occur in central neurotransmitter synthesis of acetylcholine, dopamine and other catecholamines as well as γ-aminobutyric acid. Aging brings increased forgetfulness, difficulty in acquiring and assessing new information and concepts, as well as slowing of sensorimotor responses. Psychic energy or drive (conation) is lost so that the speed and agility of the mind diminishes with increasing years. There is a narrowing of interest and although 'crystallized' intellect performs well enough into great age (which is adequate for high court judges and clergymen!), 'fluid' intellect falls off markedly; most elderly people do not exhibit a quick grasp of complex new data, nor can they analyse it rapidly. Thus they are less adept in newly developing mathematical sciences. Despite these changes, high level intellect can be maintained by various adaptive strategies, including the use of experience, a slower pace and a smaller volume of work.

Sleep requirements change throughout life and older people sleep less well. Older women spend more time in bed and sleep longer and wake less often in the night than do men. Men take longer to go to sleep and their sleep is more broken. Most older people adjust satisfactorily to these changes but the more neurotic individuals with unresolved anxiety, characteristically complain of broken sleep and many find difficulty in coping without sleeping tablets. As a result there is an age-related increase in the consumption of hypnotics.

There are well-established, age-related declines in thermoregulatory functions; for example, elderly people often show reduced ability to discriminate between skin temperature differences as wide apart as 5 °C—there is diminished sweat response to heating and impaired shivering response to cooling. These changes, together with intellectual failure and impaired mobility, put elderly patients at risk of hypothermia in cold weather. Thus in a survey of over 1000 elderly people living at home in the first quarter of 1972 in England it was found that 10% had borderline hypothermia with a deep body temperature of less than 35.5 °C. Also in 75% of the homes in this survey the ambient temperature was at or below the minimum generally accepted housing standard temperature (18.3 °C). Impaired thermoregulatory responses were found to be very common. Detailed tests, on a subsample of the survey showed impaired thermoregulation of some degree in 50% of subjects. Further tests a few years later showed that the disorder was progressive (Exton-Smith & Evans 1977, p. 41). Coping with a very warm or a very cold environment becomes more difficult with increasing age. Rapid temperature swings are particularly stressful and produce a sharp increase in morbidity and mortality.

Loss of postural stability is another decline in CNS function. Women are twice as liable to fall as men. The risk of falling increases linearly with age; in one study, 30% of women in the 65–69 years age group reported

falls, compared with more than 50% of the women aged 85 and over. In the very old (aged 75 years and over) tripping, giddiness and drop attacks are all important causes followed by loss of balance. Tests of control of sway in the upright posture show a progressive decline with age after maturity (age 30–40 years) and again the phenomenon is much more marked in women at all ages (Exton-Smith & Evans 1977, p. 47). Visual failure and inadequate illumination and lack of colour contrasts in the environment increase the chance of falling.

Falls are incapacitating in themselves but also they put the victim at risk of additional hazards, especially hypothermia and fractures. Not surprisingly there is an age-related increase in fractures. After the age of 60 years the incidence of femoral neck fracture doubles every 5 years in women and every 7 years in men. Thus for the female population the cumulative risk of sustaining a fractured upper femur is 25% by the age of 90 years. Apart from a liability to fall, the other major causative factor in the occurrence of fractures is the age-related decrease in quantity and quality of bone (Exton-Smith & Evans 1977, p. 51). Much evidence exists to show that loss of bone with age is a universal phenomenon but postmenopausal oestrogen deficiency causes accelerated loss and puts the female especially at risk (Stevenson & Whitehead 1982). Poor nutrition, inferior skeletal status in earlier years, lack of physical exercise and the effects of disease, including osteomalacia, are all implicated in addition to aging *per se*.

From what has been said it is clear that health in old age is determined by a multiplicity of factors of which aging is but one. Inheritance, early growth and development, education, life style, environment and the impact of disease are also important in the crucible of life. An understanding of the relative contributions of these multiple factors offers hope of a greatly enhanced quality of life for old people, even without being able to comprehend, let alone modify the aging process itself.

Demographic and social trends

How old can you become?

It is well known that people are living longer and there are more old people now than ever before. However, there are no well-documented cases of people in the USA or UK living to age 120 years or more, suggesting that age 120 or thereabouts is the theoretical maximum life expectancy for human beings. The few who approach this maximum represent the biological elite. Nowadays people are achieving a bigger tranche of the theoretical maximum life span, and the average life expectancy at birth has risen by 20 years this century.

However, people are not living all that much longer from the standpoint of the middle-aged and elderly. Thus the life expectancy for an infant born

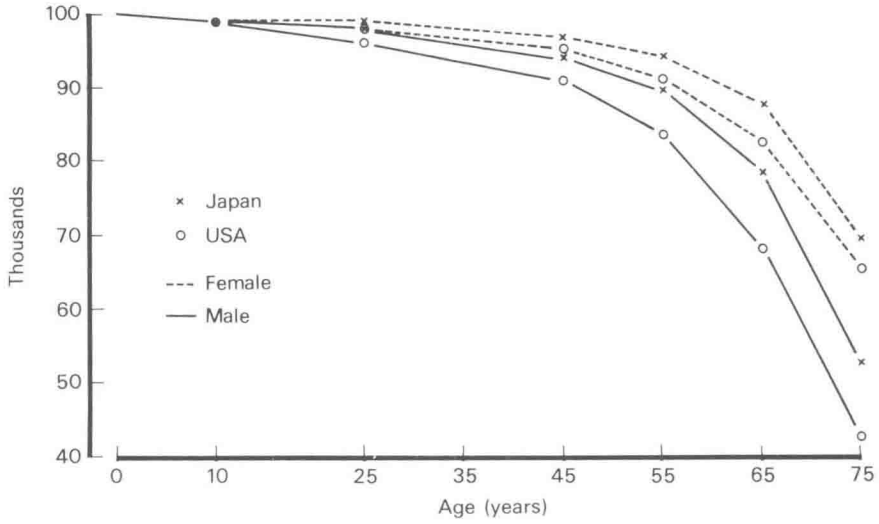

Fig. 1.1 Numbers surviving out of 100 000 born alive (WHO 1978).

in the USA today is very much better than for one born in 1900 but the life expectancy for the average 40-year-old male has improved little over the same period, certainly not by more than 3 or 4 years. Middle-aged females have done rather better by gaining an extra 8 or 9 years since 1900. In 1975 the average expectation of life of white females was over 77 years and for white males almost 70 years. For non-whites, male and female, the expectancy was 6 or 7 years less.

Males die earlier

Contemporary male mortality rates in middle age in the USA are 60% higher than those for women. Why should this be? The longer life span of the female is seen in species other than man and so the possibility exists that this is a fundamental biological phenomenon not responsive to external influences. However, there is evidence that human male behaviour patterns largely determine this excess mortality in middle age. More than half the excess male deaths in middle age are attributable to ischaemic heart disease with its possible aetiological factors including diet, lack of exercise, cigarette smoking and a persistently intense aggressive competitive life style. About a third of the excess is due to deaths from road traffic accidents, cirrhosis of the liver, respiratory tract cancer, bronchitis and emphysema. Virtually no heavy drinkers (i.e. consuming more than 100 g alcohol per 24 h) survive into old age (Trémolières & Geissler-Brun 1975).

An overall improvement in these mortality rates must come from a change of life style and there is evidence in western countries that this

message is being accepted and acted upon, more especially in the middle (professional) classes. The dramatic fall in cigarette smoking amongst the middle classes, and physicians in particular, and the worldwide interest in regular and strenuous physical exercise to promote positive health are examples of this. Mortality rates are still declining in the middle-aged and in the elderly. The current life expectancy of the average 65-year-old American is 16 years or more. If cancer and cardiovascular deaths were eliminated, it would add about 10 years to the average total life expectancy.

The elderly

The elderly are usually regarded as those aged 65 and over, to provide a social and legislative frame of reference. Different countries have different statutory retirement ages. In the USA for retirement and state-facilitated pension purposes the age of 65 is used for both sexes, whereas in the UK the retirement ages for men and women differ, being 65 and 60 respectively. In France the retirement age is 60 years for both sexes and in Norway 70 years. However, those so defined do not constitute a homogeneous group and in addition to frailities attributable to aging, many have multiple chronic disabling conditions and often social problems. Despite this the majority can cope at home even when living alone, although the ability to do so falls off rapidly in extreme old age.

These somewhat arbitrary cut-off points represent thresholds beyond which most people will engage in little or no paid employment. Thus income levels drop dramatically but this loss is abated by pensions and possibly a lump cash payment on retirement. There are no dependant children, and for the relatively affluent the house mortgage is paid off and of course there is a drop in income tax and many other factors. Furthermore those fortunate and prudent people in work prior to the official retirement age will have provided for their own retirement by moving to a more convenient house with less expensive overheads. Consumer durables and clothes will have been renewed and so forth.

However, the relative prosperity of many of the newly retired is a far cry from the penury of some of those who have been retired for many years and whose resources have so dwindled that they have insufficient income to make ends meet. Special attention must be given to the needs of these extremely old, frail and economically impoverished people.

Utilization of health and welfare resources

The proportion of elderly people with severe dependency increases markedly with age, yet less than 5% of the elderly are in institutional care on a long-term basis (mainly nursing homes in the USA and in the UK divided almost equally between Local Authority residential care homes and