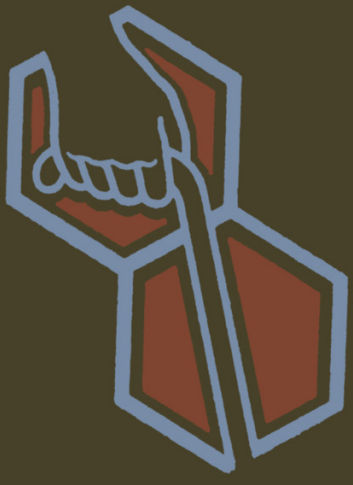
DRUGS AND THE ELDERLY

Perspectives in Geriatric Clinical Pharmacology



Edited by
J. Crooks and
I. H. Stevenson

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Perspectives in Geriatric Clinical Pharmacology

Proceedings of a symposium held in Ninewells Hospital, University of Dundee, on 13 and 14 September 1977

Edited by

J. CROOKS and I. H. STEVENSON

Department of Pharmacology and Therapeutics, Ninewells Hospital, Dundee, United Kingdom

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Symposium contributors

Professor Sir W. F. Anderson,
Department of Geriatric Medicine,
Southern General Hospital,
Glasgow, UK

Dr A. D. Bender,
Smith Kline and French Laboratories,
Philadelphia,
Pennsylvania, USA

Professor F. Bourlière,
Unité de Recherches Gerontologiques Inserm,
F. 75016,
Paris,
France

Dr R. A. Braithwaite,
Poisons Unit,
New Cross Hospital,
London, UK

Dr O. T. Brown,
Department of Geriatric Medicine,
Royal Victoria Hospital,
Dundee, UK

Dr F. I. Caird,
Department of Geriatric Medicine,
Southern General Hospital,
Glasgow, UK

Professor R. D. T. Cape,
Department of Geriatric Medicine,
Parkwood Hospital,
London,
Ontario,
Canada

Dr C. M. Castleden,
Area Department of Geriatric Medicine,
Leicester General Hospital,
Leicester, UK

Dr. L. J. Christopher,
Medicines Evaluation and Monitoring Group,
Department of Pharmacology and Therapeutics,
Ninewells Hospital,
Dundee, UK

Professor J. Crooks,
Department of Pharmacology and Therapeutics,
Ninewells Hospital,
Dundee, UK

Professor J. W. Dundee,
Department of Anaesthetics,
Queen's University of Belfast,
Belfast, N.I.

Dr A. Elithorn,
Royal Free Hospital,
Hampstead,
London, UK

Professor J. A. Forbes,
Primary Medical Care,
University of Southampton,
Southampton General Hospital,
Southampton, UK

Dr G. K. Freeman,
Primary Medical Care,
University of Southampton,
Southampton General Hospital,
Southampton, UK

Professor C. G. Gottfries,
Department of Psychiatry,
University of Umea,
90185 Umea,
Sweden

Dr D. A. Hall,
Department of Medicine,
University of Leeds,
General Infirmary,
Leeds, UK

Dr D. S. Hewick,
Department of Pharmacology and Therapeutics,
Ninewells Hospital,
Dundee, UK

Foreword

Professor Sir W. Ferguson Anderson

In the so-called developed countries there is an ageing population, and in the next 30 years there will be a massive increase in very old people, for example those aged 85 and over. In the United Kingdom between 1971 and the year 2011 there will be a 62 per cent increase in that age group, and in France and Canada to the the year 2000, increases of 122 and 156 per cent, respectively. In this country, among these old people, there will be three women to one man, and there is every likelihood that the older people reaching 85 will be frailer and feebler than the people of that age-group today. The élite is being diluted. If geriatric medicine has contributed anything it has laid emphasis on the essential need for a correct diagnosis, or more accurately, a list of diagnoses. Unfortunately, this has, on occasion, lead the doctor to try and treat all the diseases that his elderly patient suffers from at one and the same time.

The ageing processes themselves produce profound effects in terms of the pharmacological action of therapeutic substances, and in recent years potent drugs, often with complicated actions, have become available to the doctor. When it is remembered that in many cases, even when an order of priority of treatment has been established, an older patient may be on two or more drugs, the need for further understanding of drug metabolism can be clearly seen. This book covers the field admirably. It deals with the ageing process in animals and man and with the influence of nutrition. It covers drug handling in general with specific examples, and metabolism and excretion of drugs with reference to computer techniques and to dementia, are included. The wide range of drugs prescribed for the elderly, the problem of the treatment of high blood pressure and of drug compliance, are all dealt with. This is a truly impressive list. I am certain that the work detailed here will represent a memorable milestone in the progress of our understanding of the therapeutics of old age, and I congratulate Professor James Crooks, Dr Ian Stevenson and their colleagues on the recording of this impressive symposium.

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The ageing process

CHAIRMAN: Professor F. Bourliere (France)

1
The biochemical background to current theories of ageing

D. A. Hall (Department of Medicine, University of Leeds, General Infirmary, Leeds, UK)

INTRODUCTION

Theories devised to explain the ageing process were originally based entirely on studies of particular aspects of human ageing. The various protagonists of one theory or another, therefore, sought first to explain those changes which occurred with increasing age in the outward appearance of the elderly—changes such as the loss or greying of hair, wrinkled or dry skin, the appearance of bruising due to bleeding into the skin, decreases in stature and marked kyphosis. Studies of these latter changes inevitably led to theories which were aimed at an explanation of the more fundamental aspects of ageing as they affect the skeletal and muscular systems, the cardiovascular and gastrointestinal tissues and those neurological changes which can be correlated either directly or indirectly with alterations in the special senses, with loss of memory and with the behavioural response of the individual to his surroundings. As knowledge of the underlying physiology and biochemistry of the life processes developed, theories advanced to explain the phenomena of ageing became more specialised in outlook. During the early 1960s attempts were made to devise theories which could explain ageing on the basis of the failure of single organ systems or individual biochemical processes in an attempt to identify a prime lesion, the eradication of which could reverse, arrest or slow down the ageing process. It was not until nearly ten years later that gerontologists as a whole appreciated that ageing was in all probability a multifaceted condition which could not necessarily be modified by the alteration of a single basic process. This realisation changed the whole pattern of age research and paved the way for the present holistic approach. Concurrently, with the development of these studies of the ageing process, a variety of more broadly based theories were being developed. As early as 1920 Pearl had suggested that age changes could be due to the depletion of irreplaceable material within the body, whereas other workers (for example, Brody, 1923) had invoked an ill-defined factor 'vitality', the progressive depletion of which resulted in the symptoms of senescence. A progressive decrease in the numbers of viable cells in many organs was early estab-

lished (Ellis, 1920; Gardner, 1940) and confirmed as a possible factor in senescence by Andrew (1938) and Hayflick (1965). Progressive failure in coordination due to decreased rates of information transfer was also studied at the neural (Still, 1956) and hormonal levels (Voronoff, 1920; Niehans, 1954), leading to a generalised cybernetic theory of ageing (Hirsch, 1955). The most pronounced division of opinion in the realm of ageing theory has, however, arisen between those who have supported a programmed or genetic basis for age changes and those who believe that random damage to a variety of fundamental aspects of the body's metabolic pathways can account for age-induced reductions in the functional activity of organ systems and inevitably for the death of the organism as a whole.

Over the past decade many studies have been carried out which provide evidence in support of one or other of these theories based on an examination of the age changes which can be observed in a variety of biochemical parameters.

ENZYME CHANGES WITH INCREASING AGE

The age changes which can be most clearly defined by biochemical studies are those relating to enzyme activity.

Age changes in the enzyme content of tissues

Since age changes are usually deleterious to the organism (Strehler, 1962), it is to be expected that the concentration of those enzymes which are involved in the synthesis of tissue components or the provision of energy will be reduced, whereas the concentrations of catabolic enzymes may be enhanced. It is therefore of considerable interest that the patterns of enzyme change with age only meet these requirements in a limited number of instances.

Rubinson *et al.* (1976) examined seven enzymes in human erythrocytes: pyruvate kinase, glucose 6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, phosphoglucose isomerase, lactate dehydrogenase, mannosidase and β-glucuronidase. A continuous fall was observed in only one of these—the lysosomal enzyme mannosidase. Two others—lactate dehydrogenase and the lysosomal enzyme β-glucuronidase—pass through peak activity in young adulthood, whereas the remaining four pass through a trough at this age. These patterns of enzymic ageing are very similar to those observed by Kirk (1959*a*,*b*; 1960; 1961*a*,*b*; 1962; 1965; 1966), Kirk and Ritz (1967), Kirk, Wang and Brandstrup (1959), Hall (1968), Loeven and Baldwin (1971), Wilson (1972, 1973) and Wilson and Franks (1971) for a variety of enzymes. For instance, of the 52 sets of results reported by Wilson (1972) for 13 enzymes isolated from 2 tissues of male and female mice (strain C57), 13 per cent rise with increasing age, 42 per cent reach a peak at between 6 and 18 months of age, 19 per cent pass through a trough and the remaining quarter either remain roughly constant or demonstrate a variable response which does not fit any of the previous three patterns.

If it is accepted that enzyme activity should suffer a progressive decay with age, it is difficult at first sight to see how patterns which entail continuous increases, rises followed by falls, or initial falls followed by late elevations, can be explained. One possible answer to this question may lie in the methods used for these studies. When enzymes are estimated in intact tissue or in plasma, the measurement is often

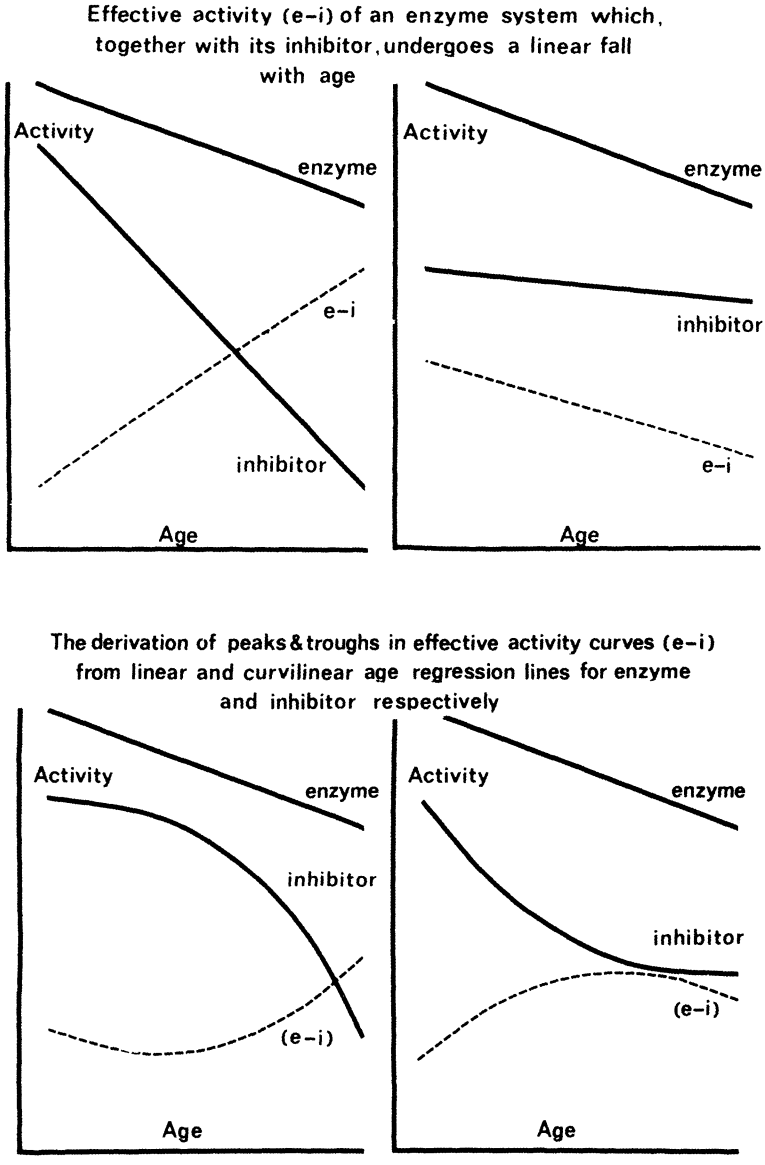

Figure 1.1 Theoretical curves relating the effective activity of an enzyme in the presence of its inhibitor to the age of the organism: (a) both enzyme and inhibitor decrease linearly with age, the latter at a faster rate than the former; (b) the linear age regression of the inhibitor in this case is lower than that of the enzyme; (c) a linear regression of enzyme concentration is combined with a convex regression of inhibitor activity, resulting in a trough in the curve for effective activity; (d) in this case the concave inhibitor curve combined with the linear enzyme curve results in a peaked curve for effective activity.

rendered less than optimal by the simultaneous presence of inhibitory material. A very relevant case in point is the pancreatic enzyme elastase, which cannot be measured by normal means in plasma or serum (Hall, 1966) because of the presence of either a specific inhibitor for elastase circulating with the α_2-globulin fraction or a trypsin inhibitor which is partially effective against elastase in the α_1-globulin fraction. El-Ridi and Hall (1976), however, have demonstrated that the fractionation of human serum by the technique of electrofocusing results in the separation of the enzyme from its accompanying inhibitor, thus permitting measurements of full enzymic activity to be made. Inhibitory materials in other tissues and tissue fluids may not be so complete in their degree of inhibition, but the net effect in each case will be the measurement of an *effective* enzyme activity representing the difference between the *true* activity and the proportion by which the activity is reduced by the presence of the inhibitor.

All enzymes and many inhibitors are protein in nature and may be expected to be synthesised at decreasing rates with increasing age. However, there are numerous ways in which this decrease can be related to age. The relationship may be linear, concave or convex. The effective activity at any given age will be dependent on the difference between the curves relating enzymic and inhibitory activity to age with the consequent results indicated in figure 1.1, to take the simplest case where both the enzymic and inhibitory activities decay linearly with age. The curve describing the difference is also linear and, depending on the slopes of two parent curves, may rise or fall with age (figure 1.1a,b). The subtraction of concave and convex curves representing the age variation of the inhibitor from a linear curve representing changing enzyme activity can result in curves with peaks or troughs (figure 1.1c,d), whereas other forms of curve can be derived from the combination of more complex parent curves. It is, therefore, possible to explain the presence of rising, falling, peaked, troughed or intermediate curves while still retaining the accepted phenomenon of a continuous reduction in protein synthesis with increasing age.

The isoenzymes of lactate dehydrogenase

Lactate dehydrogenase (LDH; EC 1.1.1.27), catalysing the reversible interconversion of pyruvate and lactate, is a typical example of those enzymes, the synthesis of which is controlled by more than one gene. Others include pyruvate kinase, creatinine kinase, hexokinase, aldolase, esterase, alcohol dehydrogenase, malate dehydrogenase, cytoplasmic alanine amino transferase and adenyl kinase. All of these appear to consist of varying proportions of two or more forms of the enzyme which together form complexes with differing physical properties and, hence, with different kinetic relationships towards their respective substrates.

Wieland and Pfleiderer (1957) demonstrated five isoenzymes of LDH composed of two types of subunit (H and M) which are present as tetramers of differing composition (H_4, H_3M_3, H_2M_2, H_1M_3 and M_4). Shaw and Barto (1963) demonstrated that each subunit has a different amino acid composition and is synthesised under the action of a separate gene. Markert and Möller (1959) suggested that in any given tissue not only was there a specific relationship between the numbers of subunits of each type present in the complex, but also this relationship varied with the degree of differentiation of the tissue. Thus those isoenzymes which are rich in the M-subunit (M_4 and H_1M_3) are present in highest concentrations in foetal tissue, whereas, as development proceeds, H_4 and H_3M_1 become more predominant.

Kirk (1965), Kanungo and Singh (1965), Singh and Kanungo (1968), Schmukler and Barrows (1966; 1967), Wilson (1972) and Mainwaring (1968) have studied the age-related changes in the amounts of total LDH in a variety of tissues, but Kanungo and Singh have extended this work to a study of the changing isoenzyme pattern which accompanies increasing age (figure 1.2). The proportion of the H_4-isomer in the heart of a 96-week-old rat is 4.5 times greater than the amount present in the heart of a 30-week-old animal, and this alteration of the isoenzyme pattern occurs at the expense of those isomers which are rich in the

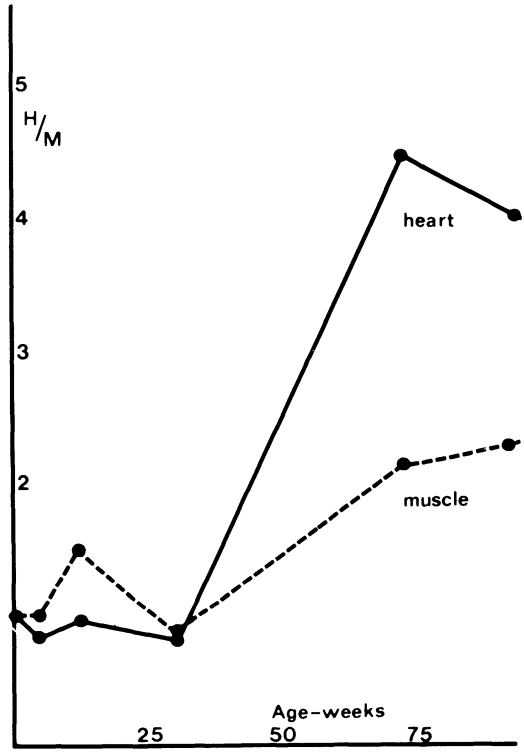

Figure 1.2 The relative concentrations of the two enzymes H-LDH and M-LDH in the heart and skeletal muscle of rats aged from birth to 96 weeks. The ratio at birth is taken as unity. (Adapted from the observations of Singh and Kanungo, 1968.)

M-form of the enzyme. LDH participates in the anaerobic metabolism of carbohydrate, and Dawson, Goodfriend and Kaplan (1964) have shown that the M_4-isomer performs this function at a greater rate than does the H_4-species of the enzyme. Therefore, although Schmukler and Barrows (1967) have shown little change in the overall LDH content of the rat heart between 12 and 24 months of age, the reduction in M_4-LDH reported by Kanungo and Singh (1965) will render this enzyme less capable of contributing to the energy requirements of the organ during periods of anaerobiosis. Therefore the fact that explosive bursts of activity

resulting in excessive contraction of heart muscle will be less easily tolerated by elderly subjects can be explained on the basis of the changing isoenzyme pattern. These alterations in pattern, depending as they do on the changing synthesis of the H and M subunits, may be taken as providing evidence for the genetic control of the ageing process. Since, however, the altered pattern results in the provision of an enzyme which is decreasingly fitted for its function, one is still left with the concept that potentially lethal genetic control of enzyme synthesis occurs even if the extreme possibility of a 'lethal gene' is discounted.

Elastase

The enzyme elastase was first identified in the pancreas in 1949 (Balo and Banga, 1949) in the course of a study aimed at the elucidation of the changes known to take place in ageing and arteriosclerotic vascular tissue. It was assumed that the enzyme must pass from the pancreas through the circulation to its point of action in the elastic lamella of the artery wall, but initially it could not be identified in plasma on account of the inhibitor which is also circulating in the plasma. Hall (1966) reported that it was possible to measure the elastase content of plasma if elastin dyed with Congo Red rather than undyed elastin were used as substrate.

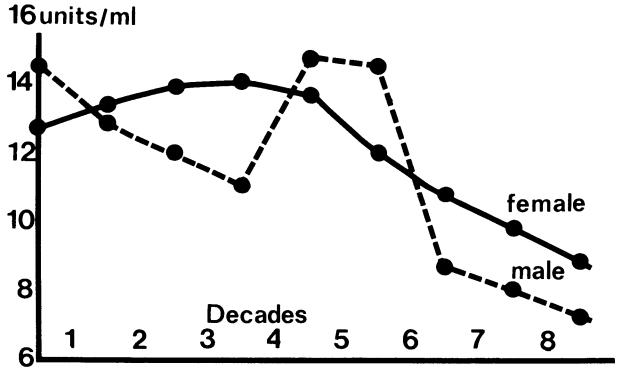

Figure 1.3 Total elastase content of the plasma of normal male and female subjects (mean values for 10 year age groups).

Banga and Ardelt (1967) and others have criticised this method on the grounds that the dye may be released from the elastin solely by physicochemical means by other non-specific proteins present in the plasma. Justification of the method had, however, recently been provided by the isolation of elastase from plasma by electrofocusing techniques (El-Ridi and Hall, 1976). Age-determined changes in elastase have been reported (Hall, 1968; Hall, 1973; Chatterjee, 1975). These are particularly apparent in advanced old age (figure 1.3), but the scatter observed in this specialised population has been shown (Chatterjee, 1975; Hall and El-Ridi, unpublished results) to be due to any one of a number of potentially important conditions which affect the elderly. Although the *effective* activity of the enzyme in the plasma appears to be negligible owing to the simultaneous presence of the inhibitor, this may not necessarily be the situation in the vascular wall itself. The

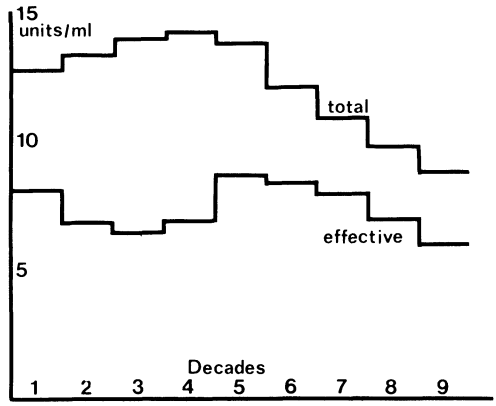

Figure 1.4 The 'total' and 'effective' elastase activities of male human plasma (mean values for 10 year age groups).

interaction of enzyme, inhibitor and the substrate within the tissue may remain high until 40 years of age in the male, when there is a 30 per cent fall in effective activity (figure 1.4). In the female, although the effective activity of the enzyme falls slowly over this age range, an appreciable level of activity is retained until the age of 60, when a 66 per cent reduction occurs. These differences may be directly associated with the differential which exists between the onset of vascular disease in the two sexes.

Metabolism of essential fatty acids

Two enzyme systems take part in the synthesis of polyunsaturated fatty acids of the linoleic acid group—a dehydrogenase and a ligase. The former facilitates the introduction of further double bonds, whereas the latter adds subsequent pairs of carbon atoms to increase the chain length. Studies of the pathways whereby linoleic acid is metabolised to higher homologues in normal adult animals (Bridges and Coniglio, 1970) demonstrated that the most likely of the possible pathways affected alternate chain elongation and desaturation. Peluffo, Ayala and Brenner (1970) and Hall and Burdett (1975) have demonstrated that age has a detrimental effect on the rate of desaturation of linoleic acid to γ-linolenic acid. It appears (Hall and Burdett, 1975) that during growth, especially in tissues such as the testes, in which high levels of polyunsaturated fats are required, the organism may be able to invoke more than one pathway, thus facilitating the rapid accumulation of arachidonic acid and higher homologues. Shortly after sexual maturity, the number of pathways used is reduced to the situation observed by workers such as Bridges and Coniglio (1970) for adult animals, whereas in old age (above 17 months in the case of rats) even this pathway becomes less active.

CURRENT THEORIES OF AGEING

The biochemical evidence presented above is heavily biased in favour of a programmed theory of ageing, but before this is accepted without question, evidence in favour of the error catastrophe theory must be put forward.

Error catastrophe as a cause of ageing

The genetic information present in the nuclear DNA is translated into the form in which it is applied within the cytoplasm for the synthesis of protein, by the production of various forms of RNA. Each of these translational processes is capable of faulty performance with the resultant production of aberrant proteins. Since a proportion of these proteins will be enzyme systems which are themselves involved in the translational or synthetic processes or may be part of the systems which are invoked for the repair of faulty nucleic acid molecules, there may well be a feedback of error. Orgel (1963) suggested that the accumulation of such errors throughout life could result in a progressive decline in cellular function which, if it passed a certain threshold level, could induce a catastrophe which would ultimately occasion the death of the organism. As a corollary to this cumulative error theory (Orgel, 1963, 1970) it was suggested that with increasing age various amino acids might be misincorporated into the proteins synthesised by the cells concerned. There is no simple proof of this in naturally ageing populations of cells, and it has proved easier to study the effect of experimentally induced misincorporation of amino acids on the properties of the cells. Holliday (1975) has, in fact, gone one stage further back, administering abnormal pyrimidines such as 5-fluorouracil which may be expected, over a few generations, to alter the structure and function of one or other of the species of cytoplasmic RNA and, hence, to have a profound effect on the synthetic capacity of the cells. This not only renders these cells prematurely senescent, but also decreases the specific activity of at least one enzyme, glucose 6-phosphate dehydrogenase, in a fashion which is comparable to that occurring in normally ageing cells. The inactive enzyme protein can be demonstrated by immunological techniques which do not distinguish between active and inactive forms of the enzyme. Gershon and Gershon (1976) not only report increased accumulations of antigenically identical material, with little or markedly reduced catalytic activity for nematode isocitrate lyase, nematode aldolase, mouse muscle aldolase, mouse liver aldolase and superoxide dismutase, but also refer to confirmatory studies by Bolla and Brot (1975) on nematode elongation factor I, by Schapira, Waber and Gregori (1975) on rat liver lactic acid dehydrogenase and by Mennecier and Dreyfus (1974) and Kahn *et al.* (1974) on human and rabbit erythrocyte aldolase and glucose 6-phosphate dehydrogenase. However, Rubinson *et al.* (1976), applying similar techniques to the human erythrocyte enzymes referred to earlier, although demonstrating reduced levels of pyruvate kinase, glucose 6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, phosphoglucose isomerase, lactic hydrogenase, mannosidase and β-glucuronidase, were unable to find evidence for decreased specific activity, since they were unable to observe more than 8 per cent difference in the ratios of enzymic to antigenic reactivity of their preparations.

Those gerontologists who subscribe to the programmed theory of ageing have to be able to explain why all members of one species do not die within one or two days of the median lifespan of the species as a whole. The distribution of age-specific deaths is not even Gaussian but skewed towards earlier ages, which indicates that factors are acting that reduce the species-specific lifespan in a certain proportion of individuals.

On the other hand, there is a median lifespan which can be measured and which is characteristic of a species; a fact which those who rely exclusively on the accumu-

lation of random errors for the explanation of ageing, senescence and death must be hard pressed to account for. If the errors are truly random, it would appear unlikely that their accumulation would result, for instance, in 35 per cent of female deaths occurring between 75 and 85. Is there any rational way in which these two apparently opposed theories can be synthesised into a single acceptable whole?

Biochemical studies providing evidence which is in support of the error catastrophe theory have so far been restricted to isolated cells or tissue extracts or to primitive organisms. It is, however, possible in a speculative fashion to extrapolate to intact multicellular organisms and to ascribe complementary roles to both programmed and random processes of ageing (figure 1.5).

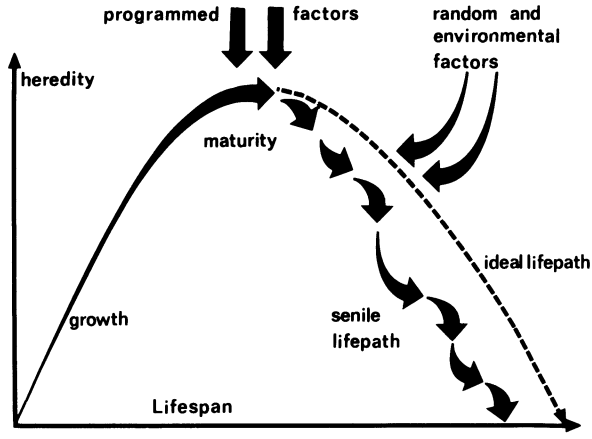

Figure 1.5 Schematic representation of the simultaneous effect of programmed and random ageing factors on the longevity and senility of an individual, by comparison with the factors affecting the passage of a projectile through the atmosphere.

The lifespan of an organism can be compared to the passage of a projectile thrown through the air. In such a model system the distance travelled before the projectile returns to earth depends on a variety of factors–the initial force and angle at which it is thrown; gravitational forces; and environmental conditions, such as contrary winds, changing atmospheric pressure and alterations in wind resistance due, as would occur with a tennis ball, for instance, to the spontaneous fraying and unpeeling of the outer case. In flight, factors such as gravity and certain of the environmental restrictions to an ideal path are effective throughout the whole of the period of forward motion or, conversely, at or immediately after peak height, when the vertical component of motion is at its lowest value. A variety of factors acting at or around this point in the flight can have a considerable effect, not only on the length of the trajectory, but also on the stability of the path of the projectile in the latter half of the flight.

The interplay of initial momentum and the continuously acting forces such as gravitation and atmospheric resistance can be correlated directly with the hypothe-

tical 'vital force' with which an organism commences life. This is a function of the hereditary background of the organism and of those programmed changes which can be assumed to succeed differentiation and development. In general, just as in the model system, this type of factor determines the mean flight path of a series of projectiles with similar characteristics; in the organism it provides the reason why a mouse lives on average 2 or 3 years, whereas a man may live between 70 and 90.

The environmental and disruptive factors which may reduce the distance travelled by the projectile are comparable with random effects in the lifespan of an organism. Not only will such factors reduce the lifespan by amounts which may well vary from individual to individual in any one species, but also they may disturb the smooth passage of the organism from maturity to death leading, in certain individual members of a species, to a higher incidence of senility during the later period of life.

It is, therefore, possible to ascribe different but complementary roles to programmed and random ageing phenomena, the overall determination of the species-specific lifespan being under genetic control, whereas variations about this mean may be due to an accumulation of errors of a truly random nature. These not only will determine whether an individual organism suffers an 'anticipated death' in advance of that typical of its species, but may also provide a basis for deleterious changes which occur in metabolism of the individual during the ante-mortem period.

Looking to the future, therefore, it would appear unlikely that the mean lifespan of the human species can be altered unless gerontologists are willing to engage in genetic engineering. Failing this, the efforts of geriatricians and geropharmacologists would appear to be best directed at an elimination of those random faults in metabolism which modulate the programmed life-pathway: (a) providing precursors or intermediates where pathways are blocked; (b) replacing those enzyme systems which can be shown to fall off with age; or (c) ensuring that the induction of enzyme synthesis by hormone replacement therapy or the administration of pharmacologically active substances is returned to its optimum load.

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2
Pathophysiology of ageing in animal models

C. F. Hollander (Institute for Experimental Gerontology TNO, Lange Kleiweg 151, Rijswijk, The Netherlands)

INTRODUCTION

One of the main goals of experimental ageing research is to understand the mechanisms of ageing in order rationally to approach the health problems of the aged as well as to increase the quality of life in this phase of human existence. In addition to studies in man, animal models are needed to understand the physiology and pathophysiology of ageing in organs and organ systems. With regard to the question of extrapolation of data from animals to man, we have to realise that the fundamental aspects of the ageing process are the same in all mammals. It has to be considered that, as in man, the diseases occurring at old age in animals are superimposed on the normal physiological deterioration. These age-associated physiological deteriorations certainly increase susceptibility to disease, but should be studied apart from diseases occurring in old age.

Animal models allow one to conduct studies in such a manner that most variables which can influence the ageing process are controlled. A basic prerequisite for this type of study is the availability of animals of good quality which also fulfil the criterion of being aged, by definition. Selection of an appropriate model for ageing studies, in either intact animals or in vitro systems, requires knowledge of both the survival characteristics and the age-associated pathological lesions of the species and strain to be studied. The laboratory mouse and rat are animals which are extensively used in biomedical research and which fulfil most of the requirements mentioned above. Both species are becoming more widely used in gerontological research, and a considerable body of knowledge has been collected on them (Burek, in press; Burek and Hollander, in press; Cohen, 1968; Cohen and Anver, 1976; Coleman *et al.*, 1977; Festing and Blackmore, 1971; Hollander, 1976; Hollander and Burek, in press; Kunstyr and Leuenberger, 1975; Rowlatt, Chesterman and Sheriff, 1976; Smith, Walford and Mickey, 1973; Storer, 1966).

ANIMALS FOR AGEING RESEARCH

It must be realised that it is mainly the type of study to be conducted that defines the required health status of the animal. With regard to the variables involved in ageing research (viz. biochemical, functional, morphological), the animals should at least be free of infectious disease. For this reason, specified pathogen-free (SPF) mice and rats are usually used. The costs of producing and maintaining such animals add an extra financial burden to the already expensive longevity studies in these animals (Hollander and Burek, in press).

In order to obtain sufficient information on the survival characteristics of a given species and strain, and baseline data on causes of death and incidence of neoplastic and non-neoplastic diseases, large numbers of animals of that species and specific strain should be permitted to live out their natural lifespans under well-controlled laboratory conditions. To obtain the necessary data on pathological lesions, careful autopsies should be conducted on these animals. From these studies, survival curves can be computed. Such curves generally show a post-weanling plateau corresponding to the adult population, followed by a bend and a period of rapid decline in the number of survivors. Comfort (1964) has defined this period of rapid decline as the onset of senescence for the population studied. Survival curves allow one to define the 90 per cent, 50 per cent, 10 per cent and maximal survival ages for different species, strains and sexes, and to compare them. In rodents an aged population is defined as those animals which have reached the 50 per cent survival age and beyond (Burek, in press; Knook and Hollander, in press; Walford, 1976). It has to be realised that such a definition is arbitrary. However, it serves as a functional definition that does enable one to obtain information on different longevity data among different strains or stocks of rodents. Only complete information on the survival curve, as well as knowledge of the factors which might influence it, provides reliable data to judge whether one is dealing with an ageing population.

All of the ageing studies conducted with inbred rats during recent years at the Institute for Experimental Gerontology TNO were done with cohorts of animals that were born and reared in a closed colony system under strict SPF conditions of inbreeding. Animals used for ageing research were either virgins or retired breeders. Both virgins (at an age of approximately 12 weeks) and retired breeders (at an age of approximately 8 months) were transferred from the SPF quarters to conventional experimental rooms in which the longevity studies were conducted (for detailed information, see Burek, in press; Hollander, 1976). In the past mice which were bred under conventional conditions were studied. In the near future the health regimen to be employed in longevity studies in these animals will be the same as that described above for rats, since it has been shown to be feasible to conduct ageing research under such conditions in that species. This regimen also reduces the costs of these studies, while avoiding a number of problems related to a strict SPF operation in longevity studies.

ANIMAL MODELS FOR AGEING RESEARCH

It is beyond the scope of this paper to discuss exhaustively all existing animal models for studying the physiology and pathophysiology of ageing in animals. Selected examples dealing with aspects related to the use and misuse of rodents for ageing research and with the development of animal models for studying organ

physiology and pathophysiology will be presented. A general rule in choosing a suitable laboratory rodent for the purpose of ageing research is that one should select a long-lived mouse or rat strain free of infectious disease and the age-associated pathology of which is fairly well known.

Recent studies in three different inbred strains of rats (WAG/Rij, BN/Bi, (WAG x BN) F_1) have shown that male rats do not always have shorter lifespans than females and, furthermore, even an F_1 hybrid does not always live longer than its parental strains (Burek, in press). The same observations for survival of males and females have been made in a selected number of inbred strains of mice (Hollander and Burek, in press). In the NZB mouse, a strain most notable for studies on the occurrence of autoimmune disease during ageing, the female actually has a shorter lifespan than the male.

From the study with the three strains of rats mentioned above, it emerged that the 50 per cent survival age for the three strains was around 30 months, the maximal survival age observed being approximately 42 months. Only in the case of the male WAG/Rij rat were both ages lower. This implies that care should be exercised in interpreting data from ageing studies in rats where an old rat is defined as a 24-month-old animal and no further characteristics of the survival of that strain are provided. It is my firm belief that, in a number of ageing studies conducted in rats in the past, data were obtained and interpretations were made which were not relevant to ageing, because the animals used were not old at all. This is due to the fact that the animals were not free of infectious diseases.

In recent years much attention has been devoted to the study of changes in the immune system during ageing (Makinodan, Good and Kay, 1977; Walford, 1969). The immune system itself, the normal aspects of which have been well defined during recent years, can be regarded as a system which is very suitable for studying the pathophysiology of ageing. As in other organs or organ systems, normality is associated with the situation in young adults. In either longitudinal or cross-sectional studies in mice and/or rats the age-related immune dysfunctions can be surveyed.

Table 2.1 Immunology and Ageing (after Hymans and Hollander, 1977)

Normal	Dysfunction	Pathology
1. B- and T-cell system	1. Deficiency	1. Infection
2. Antibody diversity	2. Autoimmunity	2. Autoimmune disease
3. Network system	3. Restriction of heterogeneity	3. Amyloidosis
		4. Malignancy

In addition, age-related pathology, which could be a consequence of age-related dysfunctions, can be studied (table 2.1).

The different aspects of the normal immune system are well described in the literature (for an introduction to this field, see Roitt, 1974). The subsystems recognised are the humoral and cellular ones. The former is known as the B-cell system, because its source of origin is the bursa of Fabricius in birds and it is responsible for the synthesis of immunoglobulins. The thymus is essential for the full develop-

ment of cellular immunity and this system has accordingly been termed the T-cell system. The morphological substrate of both cell systems is the lymphocyte. The second characteristic of the normal immune system is its diversity. Recently Jerne (1973, 1976) has added a new dimension to the model of the normal immune system, having developed the concept that the immune system is a network of antibody molecules and lymphocytes that recognise and are recognised by other antibody molecules and lymphocytes. This network is considered to be a functional network and its properties represent the essential regulatory mechanisms of the immune system.

The immune dysfunctions can be classified into three groups: immune deficiency, autoimmunity and restriction of heterogeneity of immunoglobulins (table 2.1). The age-related immunopathology can be classified into the following groups: infection, autoimmune diseases, amyloidosis and probably also malignancy (table 2.1).

Rather than discussing all of the above-mentioned aspects of age-associated changes in the immune system, one aspect will be dealt with in some detail in order to demonstrate the value of animal models for studying the pathophysiology of ageing. As mentioned, the heterogeneity of immunoglobulins is one of the major characteristics of normal immunity. A restricted heterogeneity can be considered a dysfunction and is observed in certain situations in man. However, with regard to this type of change in the immune system during ageing, both dysfunction and immunopathology are known in man. The classical pathological lesion is multiple myeloma, a malignant proliferation of plasma cells which can result in a greatly increased level of circulating monoclonal immunoglobulins–the M-component or paraprotein–with a concomitant decrease in the other immunoglobulins. The so-called idiopathic or benign paraproteinemia is a far more frequent finding and can be considered a dysfunction. In general, it differs from myeloma in that it is not progressive, the level of the paraprotein is lower and the decrease in the other immunoglobulins is not as pronounced. Its incidence is 1 per cent in the adult population, increasing from 0 per cent in the third decade up to 19 per cent in the tenth decade (Englisová *et al.*, 1968, Radl *et al.*, 1975). An antibody activity of idiopathic paraprotein could be demonstrated only exceptionally. An animal model for studying this age-associated change in the immune system was lacking until recently. The finding of Radl and Hollander (1974) of homogeneous immunoglobulin components in about 50 per cent of aged mice of the C57BL strain, which were free of lymphoreticular malignancies on histological examination, provided the first animal model for studying several aspects of this observed clinical entity in aged man in more detail. This allows one to design experiments to attempt to answer several questions, such as whether the dysfunction is situated at the B-cell level, the T-cell level or both, and whether the expansion of the clone producing the idiopathic paraprotein is due to factors internal or external to the clone. Experiments employing lethally irradiated and non-irradiated young C57BL mice receiving bone marrow or spleen cell suspensions from old mice with idiopathic paraproteinemia are in progress, in an attempt to determine whether factors internal or external to the clone are responsible. Furthermore, this model can also be useful for studies on a potential relationship between benign and malignant paraproteinemias–a question which, in man, is still debatable. This model can also be used to evaluate the hypothesis of a restricted repertoire of immunoglobulins in the ageing individual. The frequent finding of an imbalance in the κ/λ ratio and the occurrence of restricted hetero-

geneity of the immunoglobulins in sera of old humans suggest that the changes are not quantitative but rather qualitative; in other words, that the antibody repertoire is altered during ageing (Radl *et al.*, 1975; Riesen *et al.*, 1976).

Many organs in man show a decrease in functional capacity with age (Shock, 1968). Owing to the complex manner in which organs function and the interaction between different organs, it is very difficult to differentiate between cellular and extracellular causes for impairment in function with age. It seems reasonable to assume that the main cause for the decline in organ function during ageing is localised in the cell. However, it must be realised that an organ is made up of different cell types–for example, parenchymal cells and supporting cells or non-parenchymal cells. Owing to this complexity, the cellular bases for the decline in organ functions are still poorly understood. In order to study the changes in the cells of an organ during ageing, model systems should be developed to provide quantitative information on ageing changes in the various cell classes of the organ to be studied. De Leeuw-Israel (1971) has shown that the rat liver is a suitable model for studying changes in organ function with age in an intact animal. One of the major functions of the liver is the transfer of organic anions such as bilirubin and of several steroids and drugs from the plasma into the parenchymal cells. The ability of the liver to take up organic anions is determined *in vivo* in man by the bromsulphophthalein (BSP) retention, a widely used diagnostic test for liver function. De Leeuw-Israel showed that it was feasible also to use this test in rats. However, these studies in man and the rat *in vivo* do not provide qualitative and quantitative information on what happens in the parenchymal cell of the liver and whether the non-parenchymal cells and extracellular factors influence this function during ageing. The recent development by van Bezooijen, van Noord and Knook (1974) and Knook and Sleyster (1976*a*) of techniques for the separate isolation of intact vital parenchymal and non-parenchymal cells from rat liver opens new avenues for studying fundamental aspects of organ ageing at the cellular level. Knook (1977) has summarised the value of this model for studying the cellular basis of the decline in liver function with age as follows.

(1) The use of an *in vitro* system consisting of isolated cells excludes the influence of extracellular ageing phenomena.

(2) The effect of ageing on functional and metabolic activities can be studied in specific classes of liver cells. These studies can give insight into the contribution of the various cell types to the decrease in the functional competence of the liver.

(3) Cellular ageing phenomena can be compared in long-lived cells (parenchymal cells) and short-lived cells (Kupffer cells and endothelial cells) from the same organ.

With this model system, using separately isolated liver parenchymal cells and non-parenchymal cells from rats of various age groups, studies are under way in the Institute for Experimental Gerontology TNO to determine changes in liver-specific functions during ageing in parenchymal cells. For this purpose, the BSP retention test is employed in both the intact rat liver and isolated parenchymal rat liver cells of groups of rats of different ages, including the very old ones (van Bezooijen, Grell and Knook, 1976*a*). Changes in the capacity of parenchymal cells to synthesise albumin and total protein have also been studied (van Bezooijen, Grell and Knook, 1976*b*, 1977).

The role of lysosomes in liver ageing has been studied in intact total liver and in separately isolated parenchymal and non-parenchymal liver cells (Knook,

Sleyster and van Noord, 1975; Knook and Sleyster, 1976*b*; Knook, 1977). The non-parenchymal liver cells have been further separated into Kupffer and endothelial cells (Knook and Sleyster, 1976*b*). The availability of large numbers of purified Kupffer and endothelial cells which are morphologically intact will make it feasible to study the role of both cell types in the clearance of foreign material. This may be of importance in view of the decline in the competence of the reticuloendothelial system in man and the rat with age (Bilder, 1975). The studies described above using isolated parenchymal and non-parenchymal cells from rat livers of different ages do not exhaust the possibilities for the use of this model system. It can be envisaged that it can also be used to study molecular events in ageing cells as well as the role of the age pigment lipofuscin in cell function.

SUMMARY

Experimental gerontology is a relatively young science with many theories and hypotheses that must be tested. In this respect, laboratory rodents can be used as models to study both the physiology and the pathophysiology of organ ageing.

The need for investigators to know the quality and the background of the rodents used in their experiments has been stressed. Infectious diseases should be absent in any species and strain used for ageing research. Baseline longevity data and information on the incidences of neoplastic and non-neoplastic lesions are also essential in the selection of appropriate species and strains. Knowledge of the survival characteristics of a given species and strain enables one to define the young, adult and aged individuals in the population to be studied.

Examples illustrating the proper use of laboratory rodents for ageing research have been presented. From these selected examples, the usefulness of laboratory rodents as models to study both the physiology and the pathophysiology of ageing clearly emerges. The immune system seems to be an appropriate system to study both the physiology and pathophysiology of ageing in an animal model. The recently developed techniques for separately isolating liver parenchymal and non-parenchymal cells from rats of various groups has provided a new approach for studying the cellular basis of the decline in organ function with age. Furthermore, this system offers an opportunity to study ageing changes in both long-lived and short-lived cells from the same organ.

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3

Criteria for the design of an animal-holding facility for ageing animals as illustrated by the Wolfson Laboratory for Research in Gerontology

J. G. Phillips and G. Walker (Wolfson Laboratory for Research in Gerontology, University of Hull, Hull, UK)

It is generally accepted that advances in experimental gerontology will be made through the use of convenient experimental models and that from these models findings might emerge which are of general applicability in a geriatric context. An interest in gerontology has led to the establishment in the University of Hull of a colony of rats to satisfy the research needs of the Hull group and also the group led by Professor D. Bellamy of Cardiff University.

Our interest in ageing animals extends over a period of 7 years. We embarked on the establishment of our own colony for the simple reason that colonies of animals which can be sampled at regular intervals throughout their lifespan are not available commercially and, where they do exist within research establishments, are usually geared to supply the particular needs of that establishment with understandably very little in terms of excess stocks for use by other research groups. In these days of rapidly proliferating research, it is surprising that within gerontology, despite the recent flowering of interest, progress in our understanding of the ageing process is, in relative terms, slow. The reason for this is twofold. First, the lack of a commercial supply of old animals due almost exclusively to a lack of consistency of demand, and, second, the daunting cost of maintaining animals into old age (which we estimate to be approximately £10 per month of age per animal); the latter consideration is, of course, an explanation of the lack of interest by commercial breeders because of the high risk factor. The words of Danielli (1959) remain essentially true today:

'The investigation of problems of ageing is still in its early stages. One major reason for this is that observations must be made in old animals which are not readily come by. A research worker in this field must have patience above average

or he will not be able to afford to keep his animals sufficiently long. Even where patience is available, the money is usually not.

In view of this, we must remember that, where data seem inadequate, it is usually the cost of getting better information which is the main restricting factor.'

The problem of establishing a colony of animals is beset with difficulties in the standardisation of the procedures to produce a reliably consistent experimental animal.

In 1969 the Nuffield Foundation made a grant to the University of Hull to establish a colony of rats which would be allowed to age naturally. In our initial colony we chose the rat because, to endocrinologists, it provided a conveniently sized animal for the taking of tissue samples and an ability to withstand repeated injections should this be required, with, in addition, a lifespan which is acceptably short. Having chosen our experimental animal, the breeding and holding procedures were rigorously controlled by a well-disciplined staff. This grant enabled a modest building scheme to proceed. The value of this pilot building was that it illustrated the fact that, with good design features in terms of fabric and environment, together with consistency in the practices of the animal house staff, a successful colony of ageing animals can be reliably established at an acceptable level of cost. This experience was important, for it allowed us to proceed with greater confidence in the design of a larger facility provided through a generous building grant from the Wolfson Foundation.

The purpose of this paper is to record the evolution of our ideas in the planning of The Wolfson Laboratory for Research in Gerontology, which provides the facilities for an ageing colony of rats together with research laboratories, holding rooms and operating theatres.

The needs of a research laboratory are fairly simple and straightforward: a pleasant environment within which to work and an internal design layout to produce maximum space, ease of movement and ease of access to utilities. The component of the building devoted to the breeding and holding of animals is surrounded by greater debate. Through our desire to learn by other people's mistakes, we first of all embarked on an examination of the design features of some 20 animal houses in Europe and the United States. What was surprising in this survey was the lack of uniformity of opinion as to what constitutes good design and acceptable standards.

Animal houses seem to be unique in that there is virtually no evolution in their design; they tend to be isolated test-beds of individuals' whims or monuments to dogmatic staff. In general, the buildings are the victim of preconceived schedules of accommodation and of cheap planning; there is an abundance of published information which is so detailed and conflicting that it is seldom of help—for example, one can choose anything between 3 and 33 Btu/h (0.88–9.67 W) as the body heat which a rat produces. There are specific pathogen-free (SPF) units, barrier-maintained units and houses where optimum hygienic conditions prevail. Some barrier buildings have flies gliding in and out of the ventilation system, and others have dirty cracks in walls, floors and ceilings. There are buildings with small rooms, others with large rooms and plenty with empty rooms; there are wall hanging systems, ceiling suspension systems, floor rack systems, and even mixtures of all three. Some SPF units are so sophisticated that the drinking water is pasteurised, and in others the barrier is held in such confidence that the cages

are seldom washed. In some places staff are expected to shower, and in others they do not even wash. There is presterilised food, autoclaved food, heat-treated food and food with no treatment whatsoever.

Ventilation systems produce temperature variations as great as 18–29 °C (64–84 °F), and filtration can be anything from crude to absolute. Mechanical waste and conveyor systems work well for some people, but are impossible for others. 'Dirty corridors' are used as part of operational units, and in other places purely for maintenance works. There are buildings with expensive and space-consuming plant which is only used a few hours a week, and rooms which are used for the equivalent of a few working days a year. Animal houses vary from farms to 'space ships'.

Among all this variation we have been able to find little guidance on the relative importance of the various options open to us, or which are necessities and which merely insurances. It takes a courageous man to reach rational conclusions from all of this. On the other hand, it is staggering to realise that the end result in all cases is acceptable experimental animals!

The success of an animal house is equally as dependent upon the quality and discipline of its staff as it is upon the building and its environment. On this everybody seems to agree. The building solution to our particular problem is based largely on the following conclusions.

(1) Pathogenic organisms and stress, as far as is practical, must be kept from the experimental animals, and to approach this ideal a barrier and a stable environment are essential.

(2) Modern and sophisticated barriers are no guarantee against invasion by pathogenic germs as long as staff are in direct contact with the animals.

(3) Continuous war must be waged against pathogenic organisms within the barrier, by the use of disinfectants and by a high standard of housekeeping.

(4) Tiling to walls and floors makes a dramatic contribution to the internal environment and to the attitutde of the staff to cleanliness.

(5) A temperature range of 20–23 °C (68–74 °F) over the year, a humidity range of 50–65 per cent, filtration to 99.6 per cent (0.3 μm) and 20 air changes per hour would seem, from previous experience, to be satisfactory for our ageing colony of rats. Positive pressures must be maintained (animal rooms 15 mmHg, work rooms 10 mmHg and corridors 5 mmHg above that of the outside air), and the building must be airtight. The building must be insulated thermally to a U-value of 0.4 metric units.

(6) A building in which all these conditions can be achieved is very expensive to build and very expensive to run. The space should therefore be filled to a maximum capacity.

(7) Dead spaces, such as stores, should be in a cheaper building.

(8) On a campus site an animal house must be a self-contained operational unit.

(9) A set of small rooms offers very little advantage, other than the tidy packaging of groups of animals or research projects. Large rooms are more economical to stock and staff.

(10) Air flow in small animal rooms is difficult to control, and stratification among tiers of cages against walls is likely to result.

(11) The most economic building form is a cube, and vertical circulation reduces travel distances.

(12) A duplicate circulation system in the form of a corridor for dirty traffic is considered wasteful of money.

(13) Once there is a breakdown behind a barrier, all animals are suspect.

(14) Cage movement and washing is the most disruptive activity in a building. Its economics are similar to those for washing-up in catering establishments, where decentralisation occurs if the operation is on any scale. Dirty cages are no more difficult to wash, if done regularly, than dirty plates.

(15) Piped conveying of waste to a central container, and conveying food to and from a central hopper through pipes, are practical and economic propositions. The similar conveying of new bedding introduces technical difficulties, and its economics are doubtful—the use of mobile containers would seem to offer a better solution.

(16) Bedding is the most suspect source of infection, and must be autoclaved.

(17) If food is bought from a reputable and known source, it may not be necessary to autoclave it, but machine capacity should be provided initially to handle the food, should this ever be proved necessary.

(18) Animal husbandry can be operated on a flexi-hour basis, which avoids peak demand on the showers and changing locks. Staff should have exclusive work areas, and should keep out of each other's territory. Staff appear to be happier with a variety of work.

(19) A stand-by generator is essential for emergency power cuts.

The plan which eventually emerged comprised a roughly cubic building in which the plant in terms of heat and cooling and filtering was situated on the ground floor, with complete insulation of the plant room from the rest of the building, and the main research facilities, in terms of laboratories, computer terminal and offices, were situated on the top floor. Access to the animal rooms is, in the main, secured through a ground floor barrier, and a barrier joins the research laboratory suite to the animal house on the top floor (figures 3.1 and 3.2); this reflects the burden of usage in that the technicians normally use the ground floor access point, whereas scientists, who almost exclusively work within the laboratories of the top floor, can gain access through the lock at that level. Staff routinely go through a procedure which involves washing of hands up to the level of the elbows and optional whole-body showering. Outside clothes are removed and each individual is supplied with footwear and overalls on the 'clean' side of the lock. An additional feature, in order to cut down unnecessary visits to the inside of the animal house, is a system of closed circuit television in which contact with staff on the 'clean' side of the building can be established and individual rats and cages viewed by this remote method. Within the animal house itself, which is sandwiched on three floors (figure 3.3) between the top research floor and the service ground floor, are three essentially similar animal-holding units. Each is self-sufficient and all are independent of one another. Staff allocated to one floor need, in theory, never trespass onto another floor. The animal-holding rooms were designed to provide corridors of racks of cages which are automatically supplied with water and environmental controls achieved through ducting which allows air to fall from the ceiling to ground floor level and circulate upwards through the racks of cages to be ventilated to the outside of the building via suitably located slots lateral to the point

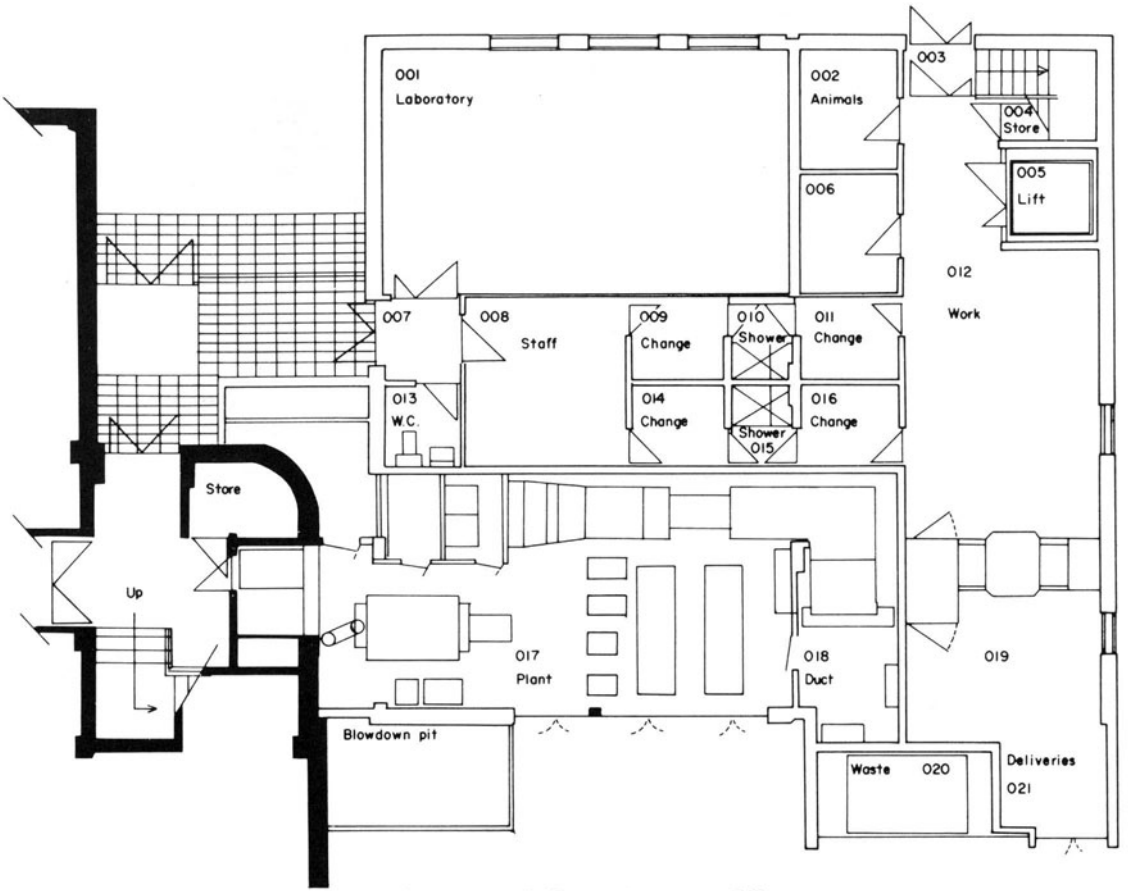

Figure 3.1 Plan of Wolfson Laboratory for Research in Gerontology, ground floor.

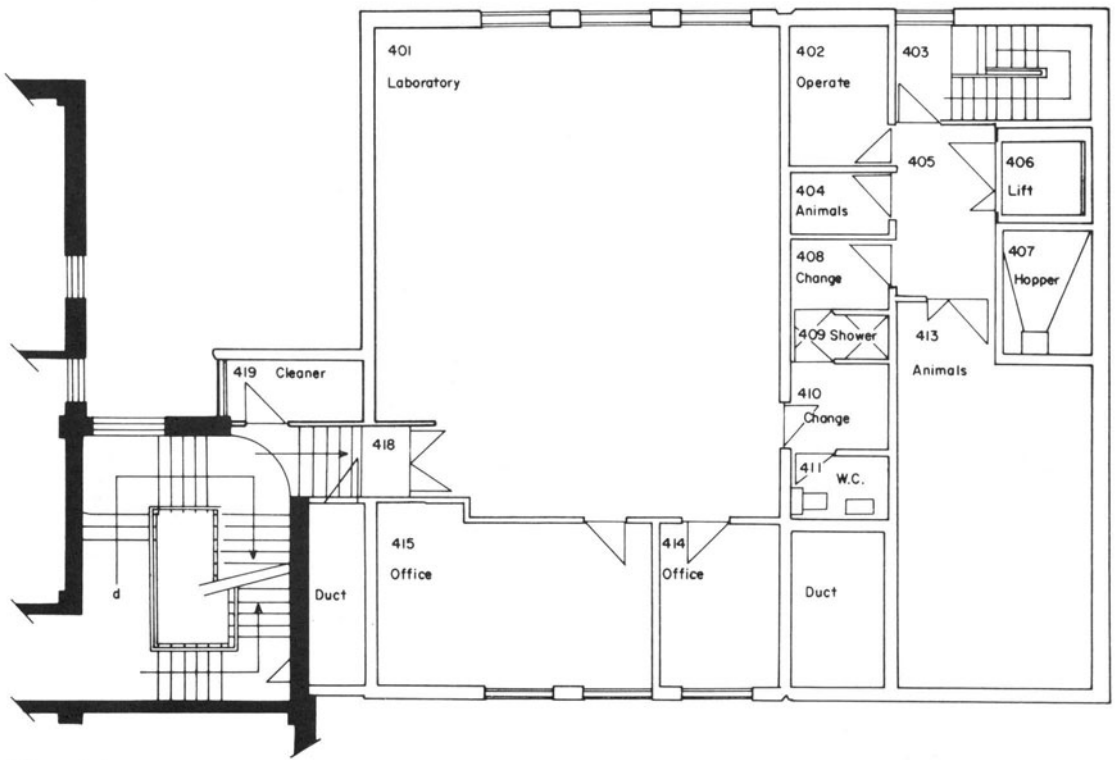

Figure 3.2 Plan of Wolfson Laboratory for Research in Gerontology, fourth floor.

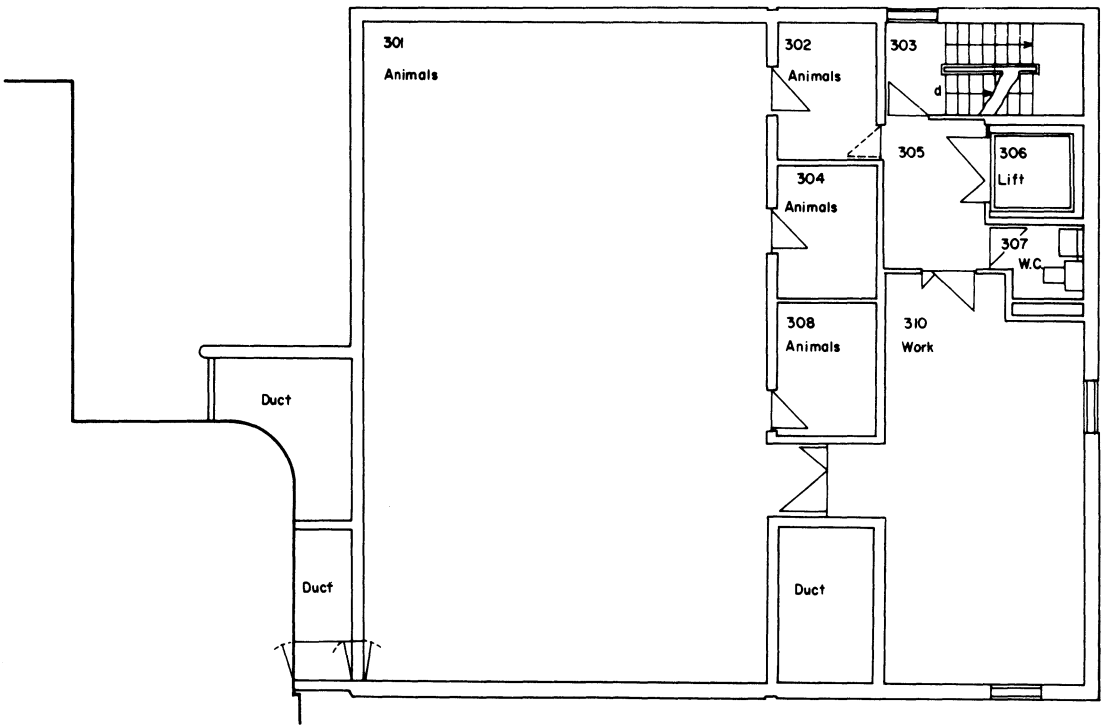

Figure 3.3 Plan of Wolfson Laboratory for Research in Gerontology, third floor.

Figure 3.4 Animal-holding room, Wolfson Laboratory for Research in Gerontology.

at which the air falls from the ceiling (figure 3.4). Such an arrangement was designed by the consultant engineers, Messrs Rosser and Russell, of Leeds, who rigorously tested the dynamics of the system through a pilot mock-up in which racks of cages were situated in various positions and smoke bomb tests carried out to ensure satisfactory circulation of air.

The wall and floor finishes are of high-quality tiles which are easily maintained in a clean state. The noise level is reduced to a minimum by the use of all-plastics cages and rubberised castors on the racks and trolleys; staff use rubberised shoes at all times. The established routine with cage washing involves removal of the cages from the main holding room, an automated system of disposal of waste, rough washing and high-temperature washing and transfer to a clean part of the work room where bedding and food are returned to the cages for re-use back in the animal room. The established routine is strictly adhered to by the animal staff, and through the adoption of flexi-time arrangements, they find the strictness of the routine acceptable.

The design features of the new facility which impart a pleasant working environment have contributed to the success of the work routines established for the technical staff and, in turn, these arrangements have provided a satisfactory environment for the breeding and holding of a colony of rats which cover the whole lifespan and which provide the research material for our ongoing interests in the physiological changes which occur in the mammal throughout the ageing process.

Buildings of this type are expensive to build, largely owing to the plant involved in environment control. Such expense, in turn, suggests maximum occupancy,

since this provides the most economic return on investment. In part, therefore, we are prepared to consider making available our colony of rats to other workers in the field on a no-profit basis, and enquiries to this end would be welcomed by the author.

ACKNOWLEDGEMENTS

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4

The pathophysiology of ageing in man: the place of the cell

C. Rowlatt (Imperial Cancer Research Fund, Lincoln's Inn Fields, London, UK)

Ageing is associated with a progressive deterioration of physiological function and an increase in the variety of pathological conditions in the individual. In this paper I shall summarise the position of cell ageing studies in relation to ageing in man, indicating the particular ways in which different cell systems within the individual may become vulnerable. This is only one level at which one may consider the deterioration of function, but it is appropriate to consider it now because of recent work on cell turnover in the whole animal, on maximum cell lifespan both *in vivo* and *in vitro* and on intercellular and subcellular processes. At the subcellular level the sophistication of the genetic control of specific chemical processes is becoming apparent, and as a conclusion it will be intriguing to speculate that this plays some part at least in dictating differences in lifespan between long-lived and short-lived families and individuals.

Cowdry (1952) classified cells in terms of their mitotic activities into undifferentiated cells (continuously dividing populations–e.g. basal cells of skin), functionally differentiated cells (expansion stocks, still dividing), highly differentiated cells (parenchyma, capable of division) and fixed post-mitotic cells (neurones). Hypotheses as to which particular class of cell in fact governed lifespan led to work to demonstrate, say, the accumulation of abnormal components such as lipofuscin in a particular cell type. The essential difference between the two extremes is that the fixed post-mitotic cell is susceptible to deterioration in its cellular mechanisms, while the rapidly dividing stem cell may express its deterioration in terms of the production of defective differentiated cells (although these may be relatively rapidly lost from the individual).

Nowadays we would add to Cowdry's four classes an extra group of stem cells (Cairnie, Lala and Osmond, 1976). These do not normally divide, and only if the dividing cell population is eliminated by some anti-mitotic treatment (irradiation, drug, etc.) are the stem cells stimulated to repopulate that part of the organ which would be otherwise denuded of cells. These quiescent stem cells are difficult to identify without killing the whole population and observing this repopulation. An

anticancer chemotherapy regime depends on this principle (Price and Hill, 1976), as many tumour cell types appear not to have these quiescent stem cells. Such stem cell situations have been demonstrated both in epithelial tissue in the intestine and epidermis and in mesenchymal tissue in the haemopoietic and lymphoid tissue systems (Cairnie *et al.*, 1976).

These concepts are important when testing the survival of cells both by organ transplant and by cell culture. Organ transplants have shown that cells with aged characteristics retain at least some of them when transplanted into young animals and also that abnormal responses to the humoral environment may occur in the young adult animal (Franks and Chesterman, 1964). Organ transplants in which the histological structure of the tissues is maintained can be carried for several whole animal lifespans but these experiments present technical problems (Krohn, 1966).

More recently attempts to assess proliferative cell survival have been made with two systems: serial transplantation of breast into cleared immature fat pads (Daniel *et al.*, 1975) and of bone marrow cells into irradiated recipients (Micklem and Ogden, 1976). A limited regenerative capacity was demonstrated in both systems. When spontaneous or carcinogen transformed cells were used in the breast system, there was apparently an unlimited division potential. These manoeuvres are rather similar to those which are performed when cells are grown in tissue culture, and cells grow out to fill the dish, being transferred at some specific dilution to new dishes. Hayflick (1965) described different finite lifespans (population doublings) for human lung cultures derived from embryos and adults. The cultures, in well-defined conditions, went through three phases—rapid multiplication, decrease in proliferation and a phase of decline and death. The average cell population doublings (passages) were 48 from the embryo with a range from 35 to 63, and 20 from adult with a range from 14 to 28, although there was no exact correlation. These observations have been confirmed and extended (for example, Martin, Sprague and Epstein, 1970) for normal diploid fibroblasts. The proportion of cells undergoing division in these cultures decreases. In similar cultures from patients with genetically determined abnormalities there was also a reduction in total *in vitro* lifespan (Martin *et al.*, 1970; Goldstein, 1971).

However, Swim and Parker (1957) had also obtained limited lifespan from human embryo and adult cell cultures, but they found no direct relationship between donor age and lifespan in culture. Also, in Hayflick's report the oldest donor (at 87) happened to have the greatest doubling capacity. Parallel cultures subcultured at 1:10 and 1:2 dilutions had different cell doublings but cell growth ceased after the same time. The constant feature of limited lifespan *in vitro* seems to be the diploid state. Permanent cell lines almost always show chromosomal abnormalities, although these may be difficult to detect. They are described as transformed and are considered to represent neoplastic transformation.

The nature of the process in the so-called ageing cell cultures is not clear. There is alteration in the proportion of cells which divide in the later passages (Macieira-Coelho, Loria and Berumen, 1975), reflected, for example, in the increase in lysosomes and lysosomal enzymes in the inert cells. There is considerable variability in the doubling capacity in clones of cells from cultures of intermediate ages (Smith and Hayflick, 1974), although the population doubling level never exceeded that of the original culture. Biochemical studies of cells *in vitro* do not resemble

those found *in vivo* (Cristofalo, 1970; Wilson, 1973). In the old cultures there is an exponential increase in the number of cells which are not incorporating thymidine (Cristofalo, 1976), and the efficiency of the DNA repair is reduced (Little, 1976), although this may not be causally related. Hydrocortisone extension of lifespan by stimulation of RNA synthesis only lasts a short time after the withdrawal of the drugs (Macieira-Coelho and Loria, 1976), and if the age of the cells is greater than the cell lifespan, they only survive two further passages after withdrawal, which indicates that the preceding ageing effects were masked but not prevented by the hydrocortisone therapy. Although some work has been done on testing cell systems for incorrect protein synthesis (Holliday and Tarrant, 1972), as a demonstration of Orgel's original (since modified) error theory (Orgel, 1970), the interpretation is debated (Gershon and Gershon, 1976), and it is contended that, for the theory to hold, many more conditions than can be demonstrated *in vitro* need to be fulfilled.

One of the problems in interpretation is that most studies are done using standardised cell lines (such as WI 38, MRC 5, etc.) from relatively few individuals. Cell lines from other individuals may differ, and Hill (1976), using HE 108 cells from early and middle passages, found that the decline in division potential (assessed by growth rate, DNA/dish and thymidine incorporation) was not associated with reduced chromatin template activity and therefore was not due to alterations in nuclear RNA synthesis.

Criticism of cell culture experiments as models for the whole organism can be made on at least two other counts. First there is selection of cells, and only those which survive in culture are able to grow. In rodents, at least, the cells appear to be derived from vasoformative tissue (Franks and Wilson, 1970), and if transformed cells from these cultures are implanted in syngeneic animals, the tumours are haemangiopericytomas (Franks, Chesterman and Rowlatt, 1970). This selection may be nutritional, and the optimal conditions have not yet been achieved. Another possibility is that in terminally differentiated cell types the number of subsequent divisions is fixed and expanded stocks of differentiated cells on the scale that is necessary for *in vitro* growth are numerically impossible. The second major criticism concerns the fact that these cultures are relatively homogeneous and that two or more cell types are normally needed for organogenesis in the embryo, and probably for the maintenance of normal physiological and differentiating activity in the adult. In a very elegant monograph on organogenesis of skin structures by Sengel (1976) the whole question of dermoepidermal interaction and the relative components of each tissue in determining the structure of skin appendages is discussed. Another neat recombination experiment indicating genetic/metabolic interdependence in this field (Drews and Drews, 1977) has demonstrated that the testosterone-induced regression of the male mammary gland anlagen is mediated through the mesenchymal tissue. A mouse mutant which is androgen insensitivite was used.

The use of a feeder layer of irradiated fibroblasts extends the life of various fragile cell types. It has also been used (see, for example, Rheinwald and Green, 1977) to grow differentiating keratinocytes in culture. Rheinwald and Green found that lifespan was extended from 50 to 150 generations by adding epidermal growth factor, a well-characterised polypeptide. In untreated cultures the lifespan ended with a terminal differentiation to a keratinised state, and the effect of the agent

was to delay this phenomenon. Presumably *in vivo* this is the sort of phenomenon which would cause hyperplasia by increasing the population of intermediately differentiated cells.

I propose to consider two topics at the subcellular level: the question of mitochondria because of its practical interest, and the question of DNA repair because of its theoretical interest.

There is considerable evidence that mitochondria are different in some cells in aged animals, and histochemical results (see, for example, Wilson and Franks, 1971) provide good evidence for this, because they deal with the cells in their actual location. Mitochondria have a considerable amount of autonomy (Baxter, 1971), with their own DNA and RNA which specifies for some of the enclosed proteins and the inner mitochondrial membrane. This DNA and RNA conforms to the prokaryotic model rather than the eukaryotic model, which suggests that these organelles were originally obligatory symbiotic bacteria, although now they are an integral part of all eukaryotic cells. In addition to their function in oxidative phosphorylation, some degree of nuclear gene regulation and a contribution to the structure of the plasma membrane have been attributed to them (Evans, Egilsson and Wilkie, 1976). Therefore, in addition to altering the respiratory metabolic pathways, an interruption to their function may restrict the ability of the cell to divide or may be an important aspect of carcinogenesis (Egilsson, Evans and Wilkie, 1976). Mitochondrial deficiency may be brought about by selective inhibitors of mitochondrial protein synthesis (chloramphenicol) or nucleic acid synthesis (acriflavine, ethidium bromide or daunomycin), and some consequent lesions in the DNA give rise to hereditary respiratory deficiency (Wilkie, Egilsson and Evans, 1975). At a practical level a treatment with antibacterial agents may cause a cohort of cells deficient in mitochondria. The implications of this line of thought are really too wide to be considered in detail here.

My second example of a subcellular component is DNA. The function of this material is clear. The sequence of nucleotides codes for synthetic activities in the cell, providing the basis for the major part of the genetic material of the whole organism, only part of this being actually of use to the cell. Before a cell divides, a set of DNA is synthesised, a process known as scheduled synthesis. Unscheduled synthesis also occurs at other stages in the cell cycle in response to agents known to damage the DNA. There are several types of unscheduled DNA synthesis (Lieberman, 1976; Little, 1976), depending on the degree of damage, and the repair is made with various degrees of efficiency. When the cell divides, if it is going to, the repaired message is copied, however incorrect it may be. If division occurs before the repair is complete, larger abnormalities may be transferred permanently to one or both of the daughter cells. These concepts form a central part in current thinking about carcinogenesis. Their relevance in the human is demonstrated by the now classical example of xeroderma pigmentosum (for review see Giannelli, 1977), in which the primary lesion is a genetically determined inability to repair the normal damage to DNA (bonding of adjacent pyrimidines) which we all sustain from the sun's ultraviolet irradiation. Even in this condition there appear to be five genetic types, and Giannelli (1977) thinks that carriers of mutation at gene loci which control replication and repair in general may represent a not inconsiderable fraction of the population. Perhaps it is this sort of difference which dictates the differences in lifespan between long-lived and short-lived families and individuals.

Where does this get us? The increasing variety of pathological conditions with increasing age is also found in animals. This increased variety of disease processes is seen in long-lived, inbred, genetically homogeneous strains (Rowlatt, Chesterman and Sheriff, 1976), although short-lived strains tend to die of a predominant disease process, often in part genetically predetermined. Degenerative disease processes in humans, who are rarely genetically uniform, are also in part hereditary. Genetically transmitted disease processes are expressed in the first instance in cellular metabolic processes. The nature of the metabolic defect will determine with which cell type the deterioration in function will be associated–for example, endothelium, vascular disease; colonic epithelium, neoplasia; neurone, Alzheimer's disease; and so on. An individual expressing a predisposition to, say, endothelial degeneration, given a suitable environment, must be considered to be ageing although the disease may be clearly defined, it may occur well before maximum lifespan, and the other aetiological factors may be known.

To extrapolate, it is reasonable to predict that there are as yet undetermined degenerative syndromes which are only expressed in extreme old age. These must in part be genetically predetermined with some basis in metabolic function. Clinical pharmacologists, as users of drugs, may have one of the keys. Discrepancies between individuals in responses to drugs may indicate that differences exist in selected long-lived populations and may provide clues from which metabolic differences can be identified.

CONCLUSION

The individual is therefore a complex balance of physiological systems composed of self-replicating units (cells) which have their own lifespan characteristics. Although a pacemaker organ for the ageing process is sometimes postulated (Franks, 1974), there is no reason why this should not be different for slightly different genotypes. The study of each individual will indicate which systems are liable to fail, while the study of cellular and subcellular processes show how this occurs. Continued reassessment at all levels should indicate the way ahead in the future.

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5
Ageing and nutrition

P. Payne (London School of Hygiene and Tropical Medicine, London, UK)

INTRODUCTION

Manipulation of diet composition or the imposition of controlled feeding are the only means known for increasing the lifespan of homeotherms and for changing the pattern of incidence of degenerative diseases. For this reason, a review of the subject of ageing and nutrition will necessarily deal largely with the results of a variety of nutritional studies on small laboratory animals.

As far as nutrition and ageing in humans is concerned, our state of knowledge is still rudimentary. We know something about how people's eating habits change with age, and about age-dependent trends in some of the aspects of metabolism and physiological function which are related to nutrition. However, we know little of the cause and effect relationships involved, or of the quantitative nutrient requirements of the elderly. The laboratory animal experiments are therefore likely to give us most insight into the nutrition-ageing relationship. However, even these present a very complex picture, involving as they do the metabolic interactions between dietary components, the interactions between changes in early growth and later senescence, and the effects of changes in early mortality patterns on the overall survival patterns of animal colonies. It would be useful to have the answer to at least the following questions.

(1) Are there specific effects of some nutrients upon ageing and morbidity patterns? In particular, does manipulation of protein intake have a distinctive effect, as opposed to regulation of dietary energy?

(2) Are there critical periods in the life of an animal during which diet regulation exerts an effect, and if so, how would these periods relate to human development?

(3) When we see that a dietary manipulation extends life expectancy in a group of animals, can we say to what extent this is due to a change in the rate of the ageing process, rather than simply to a postponement of the onset of degenerative disease?

Really, of course, what we want to know is 'would it work in man?' and, if so, could it be applied in ways which would be acceptable both individually and socially? In fact, however, I believe we cannot yet give sufficiently satisfactory

answers to these questions, and perhaps we shall only be able to when we have a more fundamental understanding of the mechanisms of ageing. However, at the very least, the nutritional studies may offer some clues as to the nature and operation of these mechanisms.

EARLY EXPERIMENTS

Undoubtedly the first experimental work on diet and lifespan to excite general interest was that of McKay, Crowell and Maynard (1935), who showed that animals whose growth was almost completely arrested soon after weaning, by severe restriction of the amount of diet supplied, lived much longer than those fed *ad libitum*. The young animals were held in a retarded state for a period of time, and then re-fed, which resulted in an almost normal pattern of growth and maturation, with total lifespans apparently extended by the period of initial 'cold storage'.

Part of the effect was clearly due to a high mortality during the restriction phase, and, to a degree, this is a problem of interpretation common to most such experiments; we are looking at the survivors of a period of treatment which in its immediate effects is detrimental with respect to, for example, resistance to infectious diseases, but which may be more detrimental to the genetically 'weaker' individuals, who are thus screened out of the experiment by earlier mortality, leaving the inherently tougher ones to live on to a great age. There was none the less a genuine effect in McKay's experiments, in that the proportion of very long-lived individuals was increased. This is more clearly seen in some of the later experiments by Berg and Simms (1961) and by Ross (1961). Table 5.1 shows the results of a number of experiments on adult body weight and lifespan of rats. These studies are not complicated by differences in early mortality, since the dietary treatments were much less severe than those used by McKay *et al.* (1935). Table 5.2 shows results (Payne and Wheeler, unpublished) on the effects of two different diets on breeding colonies of two inbred strains of rats maintained for

Table 5.1 Effect of different programmes of restriction on initial growth rate and lifespan of rats

Regimen	Initial weight gain (g/day)	Maximum weight (g)	Lifespan (days)	
ad libitum stock diet	5.0	610	730	Ross (1961)
54% of *ad libitum*, low-protein diet intakes	0.9	280	935	
ad libitum stock diet	5.0	448	800	Berg and Simms (1961)
54% of *ad libitum* stock diet intakes	2.9	275	1000	
ad libitum stock diet	2.5	550	760	Miller and Payne (1968)
changed at 100 days age to 4% protein	2.5	380	980	

Table 5.2 Adult body weight and lifespan of two genetic strains of rats from colonies maintained on control and low-protein diets

Strain and sex	Regimen	Maximum weight (g)	Lifespan (days)
Wistar ♂	control diet	749	321
	low-protein	719	356
Wistar ♀	control diet	487	381
	low-protein	496	424
Hooded ♂	control diet	398	565
	low-protein	343	651
Hooded ♀	control diet	243	463
	low-protein	213	524

several generations. This shows another problem of interpretation and comparison, namely the large differences in lifespan between different strains of rat maintained on control diets. In this instance there was a higher perinatal mortality associated with the diet which produced the longer average life. Thus some component of the effect on longevity is due to selection rather than to a general reduction in mortality.

From this first general overview, we can say that diet manipulation does prolong life in the laboratory rat, to a maximum extent of about 20–30 per cent of average lifespan, and that this can be brought about without using treatment so severe that some of the effect is simply to screen out the weaker animals at an early stage. Nevertheless, it is true that significant extensions in life expectancy are only seen when the treatment has also brought about a reduction in adult body weight.

EFFECTS OF DIFFERENT DIET COMPONENTS–PROTEIN VERSUS ENERGY

The main point to be made here is that there is no way in which the effects of protein *per se* can be totally separated from that of energy, or vice versa. Indeed, as in the area of child malnutrition, it would be more sensible to talk about the effects of 'protein-energy' changes. The reasons for this are too complex to describe here in detail, but the main points to be remembered are these:

(1) Dietary protein serves a dual purpose–firstly as a source of essential amino acids for tissue synthesis, and secondly as a source of energy. Even in a young animal with a high demand for amino acids for growth, some protein is used for energy, and the amount oxidised increases with the proportion of protein to energy in the diet.

(2) Priority is always given to energy needs. When diets are fed in amounts so restricted that energy is a limiting factor, dietary protein will be oxidised rather than used to synthesise new tissue.

(3) Appetite and, hence, *ad libitum* food intake of rats is affected by the proportion of protein in the diet. In general, *ad libitum* intake increases to a maximum as the protein content is raised from a low level. In some cases also, protein levels

above some 30 per cent in the diet may reverse this effect and reduce *ad libitum* intakes. As the rats age, these effects on appetite become less marked, but probably always continue to exert some influence.

Figure 5.1 shows the effect of energy intake on the amount of protein which is utilised for protein synthesis. The diagram is scaled in units of metabolic body size (body weight in $kg^{0.75}$); in these units the daily intakes of energy and of protein needed for maintenance are approximately 450 kJ and 1.6 g of protein, respectively. The two linear sections of the graph show the amounts of protein which

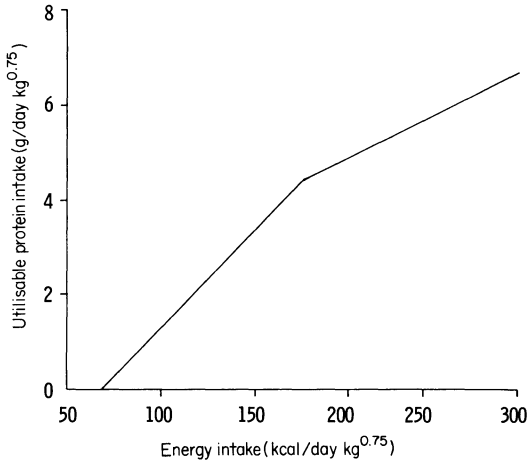

Figure 5.1 Effect of restriction of energy intake on protein utilisation.

would actually be retained by a young animal when fed different amounts of a high-protein stock diet. The upper line reflects mainly the trivial fact that altering the intake of calories inevitably alters the intake of protein for a diet of a given composition. The lower section, however, illustrates that, as the severity of energy restriction is increased, more and more protein is utilised for energy purposes, so that at energy intakes as low as that corresponding to the basal metabolic rate (about 295 kJ/day) no nitrogen retention is possible. Thus an experimental regimen which involves restriction of food supply inevitably introduces an element of both energy and protein deficiency. However, using the diagram, it is possible to estimate the effective level of protein intake corresponding to any given level of energy intake, and this is of value in interpreting the results of diet restriction experiments.

Figure 5.2 shows the result of feeding semi-synthetic diets containing different proportions of casein to rats at two different ages. Clearly, diets of the kind usually described as 'low-protein', that is having between 5 and 10 per cent casein, induce a very severe degree of restriction of energy intake in the young (30-day-old) animals, but a very much smaller depression of intake in older (70-day-old) rats. This influence of age means that an apparently constant low-protein, *ad libitum* regimen may in fact result in a complex pattern of both protein and energy restriction throughout the growing period. It is therefore very difficult again to interpret such

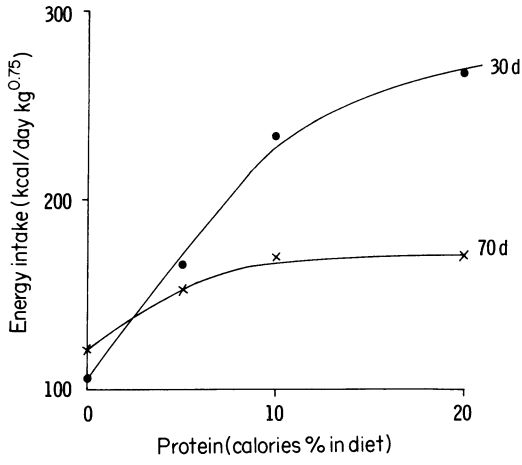

Figure 5.2 Effect of dietary protein level on voluntary energy intake of 30- and 70-day-old-rats.

experiments as indicating an effect of either protein or energy restriction alone upon ageing.

This is further emphasised by the observation already made that all treatments extending lifespan seem to result also in some restriction of growth. Irrespective of whether this is done by restricting the amount of a high-protein diet, or by *ad libitum* feeding of a low-protein diet, it probably makes little sense to ascribe the effects as due purely to lack of energy.

In practice, a number of different experimental designs have been used: (1) Programmed restricted feeding, in which animals are allotted a fixed fraction of the amount of diet consumed by a control or 'pilot' group of animals fed either a stock (for example, Berg and Simms, 1961) or a low-protein diet (for example Ross, 1961). (2) Low-protein diet *ad libitum* feeding (for example Miller and Payne, 1968). (3) Meal feed training (for example Leveille, 1972), where rats are offered food only for 2 h per day. (4) Self-selection of diets (e.g. Ross and Bras, 1974). In this design, rats are offered food *ad libitum* but of three different compositions with respect to protein level. The result is that rats choose varying proportions of dietary protein throughout their lives.

Viewing all of these experiments as a whole, and bearing in mind the problems of protein–energy interactions, leaves one with the strong impression simply that any treatment which effectively increases lifespan will also reduce maximum body weight and in most cases inevitably also will reduce the velocity of early growth. Thus table 5.3 shows an analysis of the results of one of the larger sets of data published by Ross (1969). The intent of the design was to distinguish between the effects of protein and energy intakes. However, neither protein nor sucrose intakes *per se* are well correlated with lifespan, but energy/kg, maximum adult weight and initial growth velocity are all highly correlated. The figures in parentheses under protein are calculated from the energy intakes using the relationship shown in figure 5.1. Not surprisingly, they also are highly correlated with lifespan.

Table 5.3 Nutrient intake and average lifespan of rats*

Daily intake (adult period)				Maximum weight (g)	Initial weight gain (g/day)	Average lifespan (days)
kcal	kcal/kg$^{0.75}$	Protein	Sucrose			
79	115	5.0 (1.2)	0	610	5.0	730
58	117	1.1 (2.8)	11.0	390	0.8	818
58	111	4.3 (0.9)	8.6	440	1.8	904
35	89	4.3 (0.3)	2.9	280	0.9	935
22	87	1.1 (0.3)	2.8	170	0.2	929
0.87	0.77	0.23 (0.85)	0.15	0.86	0.80	Correlation coefficient versus lifespan

*Data from Ross (1969).

Two further aspects of the more recent experiments of Ross and Bras (1974) and Ross, Lusbader and Bras (1976) on the effects of self-selected diets are interesting. Firstly, self-selection of diets (according to the scheme outlined above) seems to be generally detrimental to life expectancy. The self-selecting rats are faster-growing and shorter-lived than those fed *ad libitum* on fixed composition diets. Secondly, self-selection reveals the existence of a group of relatively slower-growing animals with lower and more stable adult body weights and longer lifespans, distinct from the remainder of fast-growing, early-dying animals.

However, broadly the same conclusions hold—that those animals which choose diets consonant in either amount or composition with reduced growth performance turn out to be those who live longer.

EFFECTS OF NUTRITION ON SPECIFIC CAUSES OF DEATH

Most of the emphasis has been on the effect of nutrition on neoplastic disease, apart from one or two studies on renal dysfunctions, to which the rat seems particularly prone and which, not surprisingly, tend to increase in frequency with protein intake. Ross and Bras (1965, 1973) have published by far the most comprehensive study of diet-induced changes in the incidence and pattern of tumours.

It seems that those dietary treatments which prolong lifespan also postpone the age at which the attack rate of tumours in general begins to rise and, when intakes of protein, carbohydrate and total calories are low, there is the lowest overall incidence of tumours and the lowest proportion of these are malignant.

In this area alone, there seems to be unequivocal evidence of a specific effect of protein intake. However, the effect is complex, in that some types of tumour are commonest with high intakes and others with low.

EXISTENCE OF SENSITIVE PERIODS

McKay, Maynard and Osgood (1941) fed to adult (200-day-old) rats diets having either 8 or 20 per cent protein derived from casein or from liver. These diets were fed in controlled and slightly restricted amounts, producing 'thin' rats or, with an

ad libitum calorie supplement, 'fat' rats. The effect of forced exercise on all these groups was also tested.

There were only slight differences in lifespan between any of the groups. But, such as they were, these favoured combinations of diet and exercise treatment which would probably have resulted in the greatest degree of energy restriction and the leanest body compositions. There was some evidence of differences due to the source of dietary protein. Since food intakes were not reported, however, it is not possible to say whether this was an effect of protein quality as such or whether it was due to an appetite effect. The relationship in figure 5.2 shows, however, that the effect on an adult rat of a reduction of protein level to 8 per cent is probably negligible in so far as reduction of *ad libitum* intake is concerned. In retrospect this negative finding is therefore not surprising.

Unfortunately, however, this result was, at the time, generally taken to indicate that dietary effects on lifespan were restricted to the very early stages of life.

Miller and Payne (1968) tried the effect of changing the diet to one containing only 4 per cent protein on animals which had previously been given a stock diet *ad libitum* until skeletal growth had ceased. This treatment resulted in an increase in average lifespan of the same order as that induced by lifelong restriction (see table 5.1). X-ray studies of these animals showed that, compared with the controls, there was a conspicuous absence of large accumulated body fat. It seems likely therefore that in the rat, as in man, one important effect of protein-energy restriction is the avoidance of adult obesity.

Table 5.4 Influence of diet restriction on body weight and mortality: restriction imposed at different ages

Food allotment during restriction and age of imposition	Body weight (g)		Mortality ratio*
	at time of restriction	at final maintenance	
ad libitum controls	–	915	100
10 g/day imposed at 365 days	800	350	44
8 g/day imposed at 365 days	784	280	79
6 g/day imposed at 365 days	748	220	320
6 g/day imposed at 70 days	364	200	35
6 g/day imposed at 21 days	40	197	18

*Mortality rates for the period after imposition of restriction expressed as a percentage of control mortality over the same period. Low values of the ratio mean an increase in life expectancy for the restricted group; high values mean a decrease.

Ross and Bras (1974) also studied the effect of dietary changes at different ages. Table 5.4 summarises their findings and shows again that, almost regardless of when during growth the change is made, or by what dietary means, nutritional treatment that restricts adult body weight extends lifespan. Thus, although it may be said that treatments which are continued for a longer fraction of the lifespan generally have a greater effect, it is certainly not true to say that only very early treatment is effective, and there is little evidence of increased *sensitivity* at younger ages.

AGEING AND NUTRITION IN MAN

In view of the comment above on the effect of diets which restrict maximum adult weight and fat deposition, it is appropriate to begin by noting that in human adults, too, excess weight is the best predictor of mortality risk. Also, body fat *per se* does not constitute a risk, but is associated with increased mortality from a range of degenerative conditions. Moreover, these risks are known to be reduced when weight is lost by dieting. It seems, therefore, that there is a direct analogy between at least one feature of the animal experiments and experience with humans. In fact, in a limited sense we already know it does work in man. However, this being said, we know very little more. The science of nutrition in relation to the elderly is still in a descriptive phase.

It has for long been maintained on more or less anecdotal evidence that a frugal diet ensures longevity, and Cornaro (1558) is a much-quoted authority on the benefits of restraint. Whether his low intake (1200 calories) was the cause of his longevity or the result we shall never know. What we do know now is that, in general, the older people are, the less they eat. More precisely, on average energy intake declines for men over the age of 40 years by about 3 kJ/day for each extra year they live. Approximately half of this is accounted for by reduced physical activity and half is due to a reduced metabolic rate (Barrows and Beauchone, 1970). Similarly, we know that body-protein turnover declines with age, and that smaller losses of endogenous nitrogen in the elderly imply smaller protein needs (Scrimshaw, Perera and Young, 1975). We can add to this that a decline in body potassium, calcium and total weight also seems to be an inevitable aspect of ageing (Exton-Smith, 1972).

Faced with this in a young person, most nutritionists would say, firstly, that these changes are bad and, secondly, that if they are not due to disease, they can be reversed by dietary changes. In our present state of knowledge, we can say neither with regard to the elderly. This points to one of the main deficiencies of the animal experiments: they describe the effects of nutrition on life expectancy and on some aspects of morbidity; however, they throw little if any light on the ageing process *per se*, in terms either of nutrition or of a fundamental understanding of the mechanisms involved.

CONCLUSION

Returning briefly to the three questions with which we started:

(1) There is little evidence for a specific effect of protein or any other single nutrient upon life expectancy, except in relation to changes in protein level or intake which are inseparably related to changes in energy intake–that is, there is a protein-energy effect on lifespan. There is some evidence that dietary protein *per se* has an influence on tumour incidence in that by changes in protein intake risk may be either increased or decreased, according to type of tumour. In general, however, higher protein intake seems to lead to higher risk and to increased risk of malignancy in particular.

(2) With regard to sensitive periods, the picture is by no means clear. The earlier experiments seemed to suggest that major effects could only be induced by dietary restriction imposed on young animals, or by lifelong restriction. Newer evidence shows that a major component of the life-extending effect results simply from pre-

venting animals from reaching maximum adult weight and from becoming obese. Most types of diet treatment which are effective in doing this will prolong life, regardless of the period of growth at which they are applied. As a general rule, however, it is clear that the kinds of dietary regimen that are optimal for growth rate are not optimal for longevity, and vice versa.

(3) As far as the mechanisms operating are concerned, we can say even less. So far none of the experiments has measured parameters of ageing as distinct from mortality rates and incidence of specific degenerative diseases.

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Section 2
Pharmacokinetics in the elderly

CHAIRMAN: Professor F. Sjoqvist (Sweden)

6
Studies on drug absorption and metabolism in the elderly

I. H. Stevenson, S. A. M. Salem* and A. M. M. Shepherd† (Department of Pharmacology and Therapeutics, University of Dundee, Ninewells Hospital Medical School, Dundee, UK)

INTRODUCTION

A number of studies have compared pharmacokinetic parameters in young and elderly subjects, and two extensive reviews have been published (Triggs and Nation, 1975; Crooks, O'Malley and Stevenson, 1976). Unfortunately, however, many of the data available on drug handling in the elderly are rather unsatisfactory, since the study designs have not allowed adequate kinetic analysis of the results obtained. A further criticism of much of the work is that individual pharmacokinetic parameters have been measured in isolation, and complete data on the effect of ageing on all the main pharmacokinetic processes are available for only a few drugs.

This present paper deals with some aspects of drug absorption and metabolism in the elderly.

ABSORPTION

There are a number of changes which occur in the gastrointestinal tract with ageing which might be expected to alter drug absorption (for review, see Bender, 1968). They include:

(1) a decrease in basal and maximal (histamine-stimulated) acid output, with consequent increase in gastric pH, thus affecting the ionisation and solubility of some drugs;

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*Present address: Department of Therapeutics and Pharmacology, Whitla Medical Building, Belfast, Northern Ireland.

† Present address: Division of Clinical Pharmacology, University of Texas, Health Sciences Center San Antonio, San Antonio 78084, Texas, USA.

(2) a pronounced decrease in splanchnic blood flow, possibly reducing or delaying drug absorption;

(3) a probable reduction in the number of absorbing cells;

(4) a decreased rate of gastric emptying;

(5) an increased incidence of duodenal diverticula which, as a result of bacterial colonisation of the small intestine, appears to be the principal cause of malabsorption in this age group.

The absorption of several dietary constituents absorbed by active or specialised transport mechanisms appears to be reduced in the elderly–for example galactose, 3-methyl glucose, calcium and iron (Bender, 1968). Most drugs, however, are absorbed not by active transport mechanisms but by passive diffusion across the gut wall. Few studies of the passive absorption of dietary constituents have been undertaken in the elderly. Fat absorption in the small intestine has been shown to be reduced, and several workers have demonstrated, by measuring urinary excretion rates, an apparent reduction of xylose absorption in the elderly (Bender, 1968). More recent work, involving concurrent intravenous xylose administration, has indicated that this is probably related to deterioration in renal function rather than to a reduction in intestinal absorption (Kendal, 1970).

To date, little work has been specifically undertaken to determine the rate and extent of drug absorption in the elderly and, for the most part, the information available (table 6.1) has been obtained from the early phases of drug elimination.

Table 6.1 Drug absorption in the elderly

Drug	Effect in old age	Reference
Propicillin	K_{abs} unchanged	Simon *et al.* (1972)
Indomethacin	Absorption probably unchanged	Traeger *et al.* (1973)
Paracetamol, sulphamethizole	Rate and extent of absorption unchanged	Triggs *et al.* (1975)
Aspirin, practolol	K_{abs} unchanged	Castleden *et al.* (1977)
Aspirin, quinine	K_{abs} unchanged	Salem and Stevenson (1977)

The effects shown relate to possible differences in drug absorption between young and elderly subjects.

Definitive studies on the extent of drug absorption involve comparison of the plasma drug concentration versus time profiles following both oral and intravenous administration of the same drug dose, and, so far, no age-related studies of this type have been carried out. The data listed in table 6.1, while less satisfactory, indicate, however, that no significant alteration in drug absorption occurs with ageing.

Perhaps one of the most comprehensive investigations to date on drug absorption is that of Simon *et al.* (1972) on propicillin. In a detailed study of the absorption and elimination of oral propicillin administered to young and elderly subjects, they

found no differences in the absorption rate (K_{abs}) of the drug. Peak plasma concentrations were much higher and were achieved earlier in the elderly group, but this appeared to be associated with decreased tissue distribution in the elderly. This study demonstrates two important points. Firstly, it shows that detailed pharmacokinetic analysis of plasma level data must be undertaken in order to allow correct interpretation of the data. Thus, failure to analyse fully the data of Simon *et al.* (1972) could lead to the impression that alteration in rate and extent of absorption or drug elimination rate was responsible for the differing plasma propicillin concentration versus time profiles obtained in young and elderly subjects. Secondly, it shows how alteration in drug distribution can affect plasma drug concentrations.

In the case of oral indomethacin given to young and elderly patients, absorption rates appeared to be similar, the peak plasma levels being identical and occurring at the same time in the two groups (Traeger *et al.*, 1973).

Triggs *et al.* (1975) showed that the rate and extent of absorption of sulphamethizole and paracetamol (measured by the time to reach peak plasma concentration and by the proportion of the dose excreted in urine in 24 h) were similar in young and elderly subjects. The same authors studied phenylbutazone absorption but, because of insufficient early data points, were unable to comment on the relative absorption rates. The observed 4-h plasma concentrations were similar in the two age groups, however.

Table 6.2 Absorption pharmacokinetics of aspirin and quinine in young and elderly subjects

	Peak plasma concentration ($\mu g\ ml^{-1}$)	Time to peak plasma concentration (min)	Area under curve ($\mu g\ ml^{-1}\ h^{-1}$)	Absorption rate constant (h^{-1})
(a) Acetylsalicylic acid				
Young subjects ($n = 6$)	35.0 ±3.0	48.0 ±32.0	136.0 ±36.0	13.8 ±2.5
Elderly subjects ($n = 5$)	40.5 ±11.7	69.0 ±29.9	287.0* ±142.0	12.5 ±6.2
(b) Quinine				
Young subjects ($n = 6$)	1.1 ±0.4	77.2 ±28.8	10.0 ±3.2	2.1 ±1.6
Elderly subjects ($n = 5$)	2.3† ±0.7	110 ±75	25.7* ±13.5	6.0 ±4.6

Results are expressed as means ± s.d. and significance values refer to the difference between the corresponding results in elderly and young subjects.
* $P < 0.05$
† $P < 0.01$

In their study of aspirin and practolol absorption, Castleden, Volans and Raymond (1977) found the absorption rate constants of both drugs to be unchanged with age and, in the case of aspirin, similar lag times, peak plasma concentration, time to reach peak and total amount in plasma. With practolol, the higher plasma levels occurring in the elderly were probably related to a lower volume of distribution.

Our studies on the absorption kinetics of aspirin and quinine were carried out in two separate groups of 5 geriatric inpatients (> 65 years) and a group of healthy volunteers (20–40 years). The drugs were given on an empty stomach in aqueous solution in a dose of 4 mg/kg and the subjects remained seated for the following 3 h. Six blood samples were taken through an intravenous cannula over the first 2 h (absorption phase) and a further four over the following 7 h (elimination phase). The data obtained are shown in tables 6.2 (absorption data) and 6.3 (elimination data).

With both drugs, the peak plasma concentration tended to be higher and the time to reach peak plasma level longer in the elderly, although with only one of the four values was this significantly so. There were no significant age differences between the absorption rate constants, but the comparison in the case of quinine is unsatis-

Table 6.3 Elimination pharmacokinetics of aspirin and quinine in young and elderly subjects

	Half-life (h)	Elimination rate constant (h^{-1})	Clearance ($l\ kg^{-1}\ h^{-1}$)	Apparent volume of distribution ($l\ kg^{-1}$)
(a) Acetylsalicylic acid				
Young subjects ($n = 6$)	2.3 ±0.7	0.32 ±0.07	0.024 ±0.004	0.078 ±0.014
Elderly subjects ($n = 5$)	5.2* ±1.2	0.15† ±0.07	0.017 ±0.011	0.106 ±0.033
(b) Quinine				
Young subjects ($n = 6$)	5.7 ±0.6	0.12 ±0.01	0.397 ±0.115	3.17 ±0.75
Elderly subjects ($n = 5$)	6.6 ±1.6	0.11 ±0.03	0.193* ±0.079	1.74* ±0.68

Results are expressed as means ± s.d. and significance values refer to the difference between the corresponding results in elderly and young subjects.
* $P < 0.05$.
† $P < 0.01$.

factory owing to a large scatter of values in the elderly group. The only significant difference occurring with both drugs was a very large increase in the area under the drug concentration versus time curve in the older group. From the other absorption data obtained, it is most unlikely that this results from an increased absorption of these drugs in the elderly. As is apparent from table 6.3, both drugs are eliminated more slowly in the elderly group, thus contributing to a greater area under the curve, and, in the case of quinine, a decreased apparent volume of distribution would contribute further to this.

Another feature of the data in tables 6.2 and 6.3 is the greater scatter of values in the elderly group (in almost all cases the s.d. values are very much greater), thus indicating that a very variable drug handling ability exists in an elderly population.

With none of the drugs studied so far is there any evidence of impaired absorption of drugs in the elderly. Indeed, according to some of the parameters studied (table 6.2), if anything, the extent but not the rate of absorption may actually have increased in this age group. All of the drugs investigated are well absorbed, however, and there is a dearth of data and a great need for future studies on poorly absorbed drugs such as digoxin.

METABOLISM

As with absorption, there are a number of physiological changes in the elderly which might be expected to influence drug metabolism. Liver weight and the number of functioning hepatic cells decrease with increasing age (Sato, Miwa and Tauchi, 1970). Hepatic blood flow, like splanchnic blood flow, may also decrease with age, but as yet, because of methodological limitations, no systematic investigations have been carried out. There is, however, no convincing evidence of impaired hepatic function in the healthy elderly population. Bromsulphophthalein retention by the liver has long been used as an index of hepatic cell function, and although several workers have shown reduced bromsulphophthalein clearance in the elderly, others have been unable to confirm this finding (for review, see Kampman, Sinding and Moller-Jorgensen, 1975).

The early studies of Kato and co-workers (Kato, Chiesara and Frontino, 1962; Kato *et al.*, 1964; Kato and Takanaka, 1968) demonstrated that the increased sensitivity of aged rats to pentobarbitone, strychnine and other agents was associated with a reduction in liver microsomal drug-metabolising enzyme activity. They reported a lower liver weight/body weight ratio in aged rats as well as a reduced liver cytochrome P_{450} content and also showed that liver microsomal preparations had a lower activity in metabolising a number of substrates. There have as yet been no studies on age-related microsomal drug-metabolising enzyme activity in human liver biopsy samples, but the results from several studies using indirect methods (plasma half-lives or clearance of drugs extensively metabolised in the liver) indicate that elderly patients may have a reduced ability to metabolise a number of drugs. The studies of O'Malley *et al.* (1971) on antipyrine (figure 6.1) provided the first indication that this might be the case. Antipyrine is a drug which is extensively oxidised in the liver, the plasma clearance of which has been used by many workers as an index of hepatic drug-metabolising ability (Stevenson, 1977). The results of O'Malley and co-workers demonstrated that the

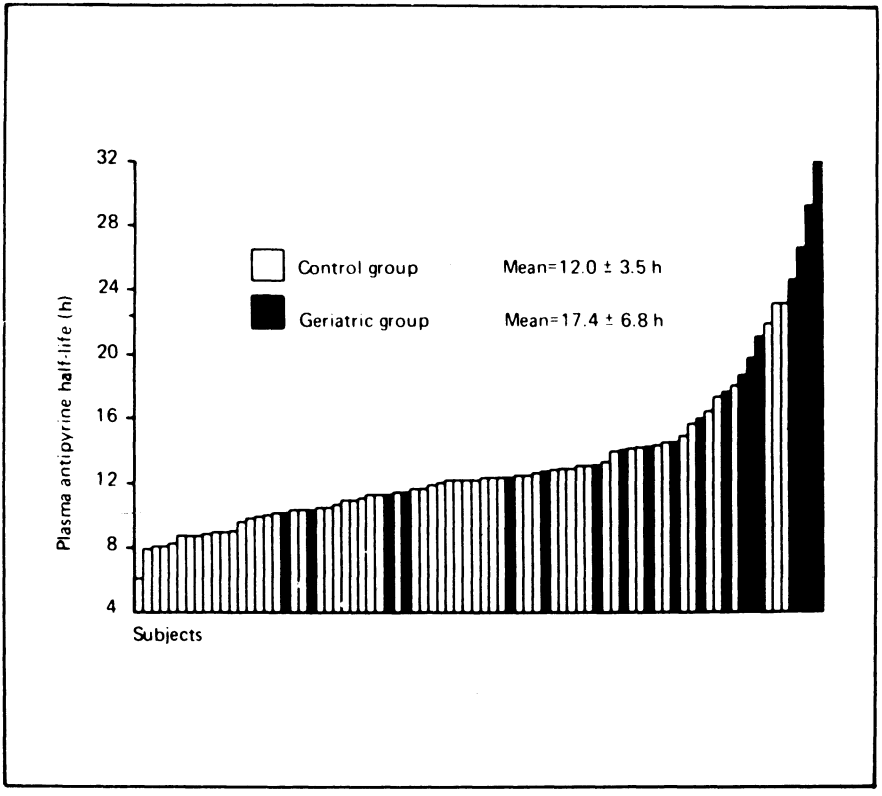

Figure 6.1 Plasma antipyrine half-life values in young and elderly subjects. After O'Malley *et al.* (1971). Reproduced by permission of the Editor of the *British Medical Journal.*

plasma half-life of antipyrine was 50 per cent longer and the clearance 40 per cent lower in elderly compared with young subjects (see Crooks *et al.*, 1976) and, furthermore, that in some elderly individuals the plasma half-life was approximately three times the mean young group value.

Table 6.4 lists the metabolised drugs whose plasma elimination has to date been compared in young and elderly groups. Most drugs are oxidised (primarily by hydroxylation or demethylation) by the hepatic drug-metabolising system and it is therefore not surprising that most of the studies undertaken so far have been of drugs metabolised by this route. As is evident from table 6.4, a significant reduction in plasma clearance (indicating a lower rate of metabolism) occurs in the elderly with antipyrine, chlormethiazole, phenylbutazone and quinine. That reduction in drug oxidation in the elderly is not universal, however, is illustrated by similar clearances of diazepam, lignocaine and warfarin in the two age groups. The plasma half-lives of acetanilide and desmethylimipramine have been reported to be significantly longer in the elderly group but, in the absence of clearance data, no clear-cut interpretation of the results can be made, since the differences found may be related to altered drug distribution rather than to impaired metabolism. Similarly,

Table 6.4 The influence of age on the plasma elimination of extensively metabolised drugs

Drug	Major route of metabolism	Effect in old age		Reference
		Plasma half-life	Plasma clearance	
Acetanilide	hydroxylation	↑	–	1
Antipyrine	hydroxylation	↑	↓	2
Aspirin	glycine conjugation	↑	N.S.	table 6.3
Chlormethiazole	hydroxylation	N.S.	↓	3
Diazepam	demethylation	↑	N.S.	2
Desmethylimipramine	hydroxylation	↑	–	4
Imipramine	demethylation	N.S.	–	4
Indomethacin	demethylation	N.S.	–	2
Isoniazid	acetylation	N.S.	–	1
Lignocaine	demethylation	↑	N.S.	3
Nitrazepam	reduction	N.S.	N.S.	5
Nortriptyline	hydroxylation	↑	N.S.	6
Paracetamol	glucuronide and sulphate conjugation	↑	N.S.	2
Phenylbutazone	hydroxylation	N.S.	↓	2
Phenytoin	hydroxylation	–	↑	2
Quinine	hydroxylation	N.S.	↓	table 6.3
Warfarin	hydroxylation	N.S.	N.S.	2

↑ and ↓ denote significantly increased and decreased, respectively.
N.S., no significant difference; – indicates no data available.
References: 1, Farah *et al.* (1977); 2 see Crooks *et al.* (1976); 3, Triggs (1978); 4, Nies *et al.* 1977; 5, Castleden and George (1978); 6, Braithwaite, Montgomery and Dawling (1978).

no definitive statements may be made as yet regarding the metabolism of desmethylimipramine, imipramine and indomethacin in the elderly. With only one drug so far, phenytoin, is there any evidence of clearance increasing with age. The kinetics in this case, however, are complicated, being both dose dependent and influenced by plasma albumin concentrations and the maximum binding capacity of albumin for phenytoin (Hayes, Langman and Short, 1975).

As far as drugs metabolised by routes other than oxidation are concerned, the plasma clearance of aspirin and paracetamol were not significantly influenced by age. The plasma half-lives of isoniazid were also similar in the two age groups, which suggests that the rate of acetylation of this drug is not altered with ageing. The ability to acetylate isoniazid follows a bimodal distribution and there was, in addition, no age-related displacement of the antimodes (Farah *et al.*, 1977). In an important study on the pharmacokinetics and effects of nitrazepam in young and elderly subjects, no age-related differences occurred in either plasma half-life or clearance (Castleden and George, 1978), and other mechanisms must operate in the increased sensitivity of the older age group to this drug.

There appears, therefore, to be no uniform change in plasma clearance of drugs in the elderly. Prolonged plasma half-lives in the elderly may be offset by increased distribution volumes resulting in similar plasma clearance values–for example, as is the case with diazepam. The clearance of several drugs undergoing oxidation in the

liver is reduced, while that of a few others is unaltered with age. As yet, insufficient information is available on drugs undergoing conjugation, hydrolytic or reduction steps to allow any conclusions to be drawn.

While pharmacokinetic comparisons following single doses of drugs given to young and elderly subjects are interesting, of much greater clinical relevance are studies on steady state concentrations of drugs given in the same dose to the two age groups. The limited data so far available on this aspect are summarised in table 6.5.

Table 6.5 The influence of age on plasma steady-state drug concentrations

Drug	Correlation coefficient for age versus plasma steady-state drug concentration	Reference
Phenytoin	0.31*	Houghton *et al.* (1975)
Imipramine	0.54†	Nies *et al.* (1977)
Desmethylimipramine	0.30†	
Amitriptyline	0.42†	
Nortriptyline	N.S.	
Propranolol	0.77*	Feely and Stevenson (1978)
Chlorpropamide	N.S.	McLaren *et al.* (1978)

* $P < 0.001$.
† $P < 0.05$.
N.S. denotes no significant correlation.

Houghton, Richens and Leighton (1975) demonstrated that age and plasma phenytoin concentrations were positively correlated in 170 epileptic patients receiving 300 mg phenytoin daily. In an extensive study on the tricyclic antidepressants, Nies *et al.* (1977) showed significant age-related increases in plasma steady state level with three out of four drugs studied (that is, imipramine, desmethylimipramine and amitriptyline but not nortriptyline). In a study on 21 hyperthyroid patients receiving 160 mg propranolol daily, Feely and Stevenson (1978) found a marked effect of age on plasma steady-state concentrations, the values increasing approximately fourfold between ages 40 and 70 years. With the remaining drug examined, chlorpropamide, steady state concentrations related to dose were similar throughout the whole age range (McLaren *et al.*, personal communication).

A further aspect of drug metabolism in the elderly which has been examined is that of induction of drug-metabolising enzymes. This has been studied in this department in young and elderly subjects, the hypnotic dichloralphenazone being used as an inducing agent (Salem *et al.*, 1978). The extent of induction of liver microsomal drug metabolism was assessed from alteration in the plasma clearance of quinine and antipyrine following a 2 week course of dichloralphenazone (Welldorm) given in a dose of 20 mg/kg nightly. Antipyrine (Stevenson, 1977) and, to a lesser extent, quinine (Padgham and Richens, 1974) have been used in a number of studies to assess drug-metabolising ability in man, and it is likely that increased plasma

Table 6.6 Effect of dichloralphenazone treatment on plasma antipyrine and quinine elimination

	Antipyrine				Quinine			
	No. of subjects		Plasma $t_{\frac{1}{2}}$ (h)	Plasma clearance ($l\ kg^{-1}\ h^{-1}$)	No. of subjects		Plasma $t_{\frac{1}{2}}$ (h)	Plasma clearance ($l\ kg^{-1}\ h^{-1}$)
Young	8	pre	16.1 ± 4.8	0.022 ± 0.008	6	pre	6.2 ± 0.6	0.36 ± 0.13
		post	10.9 ± 1.4*	0.029 ± 0.006*		post	4.5 ± 1.6*	0.47 ± 0.11*
Elderly	6	pre	13.1 ± 3.3	0.029 ± 0.016	6	pre	7.2 ± 0.1	0.12 ± 0.15
		post	11.4 ± 3.6	0.030 ± 0.017		post	6.0 ± 1.2	0.15 ± 0.04

Results are expressed as means ± s.d.
*$P < 0.05$ relative to corresponding value before treatment.

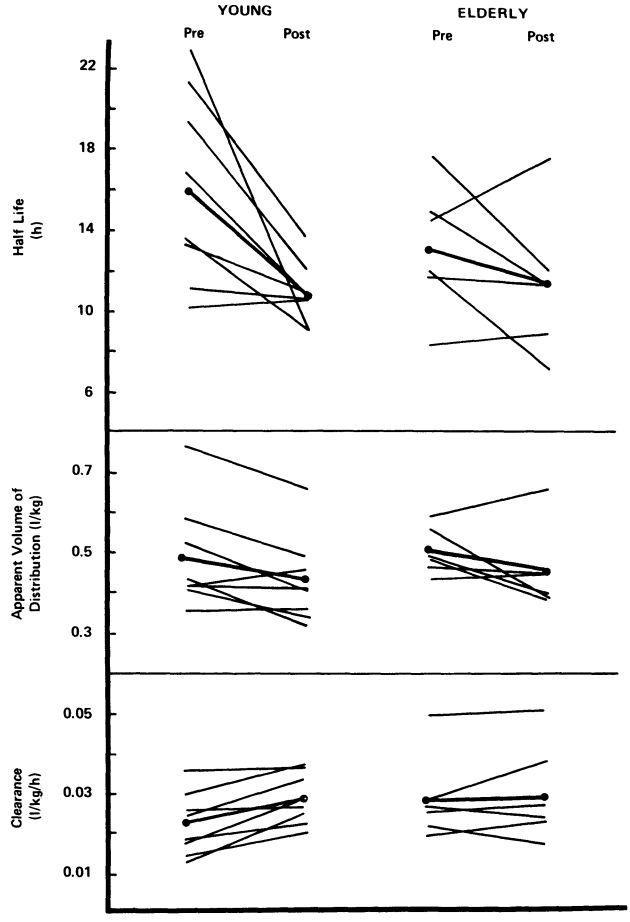

Figure 6.2 Effect of dichloralphenazone treatment on antipyrine elimination in young and elderly subjects. After Salem *et al.* (1978). Reproduced by permission of the Editor of *Age and Ageing.*

elimination of these drugs provides a valid index of induction, especially where plasma clearance of the drugs is calculated.

Figures 6.2 and 6.3 show data for individual young and elderly subjects on the plasma half-life, clearance and apparent volume of distribution of antipyrine and quinine, respectively, before and after the 2 week period of treatment with dichloralphenazone. Table 6.6 shows the mean results for the groups studied. With both drugs in the young group, there was a significant decrease in plasma half-life and a significant increase in clearance. Dichloralphenazone treatment in the elderly had a less marked effect, and with neither clearance nor half-life was the change significant.

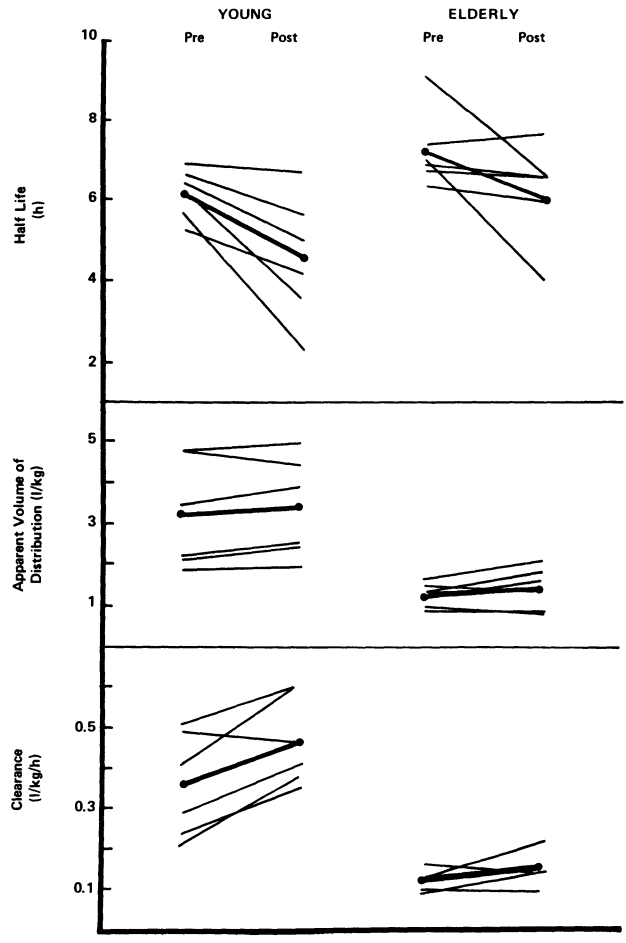

Figure 6.3 Effect of dichloralphenazone treatment on quinine elimination in young and elderly subjects. After Salem *et al.* (1978). Reproduced by permission of the Editor of *Age and Ageing.*

The possibility has long been recognised of a reduced induction response in the elderly following treatment with inducers of drug metabolism such as dichloralphenazone. Previously no formal comparisons have been made, however, of the relative effects of such treatment in young and elderly subjects. In view of the early animal studies (Kato and Takanaka, 1968) which demonstrated in aged rats a less marked increase in liver microsomal cytochrome P-450 and protein following phenobarbitone treatment, a diminished response might be expected. The present data are certainly suggestive of a reduced induction response in the elderly but this requires further study, involving assessment at several time points after initiation of treatment with inducing agents and also of the effect of inducing drugs on drug

steady state concentrations in elderly patients. Owing to an impaired induction response, elderly patients may be less likely to become tolerant to those drugs which are inactivated by metabolism. This lower base-line drug-metabolising ability, together with the reduced induction effect, may contribute to the higher frequency of adverse drug reactions which occurs in this age group (Hurwitz, 1969).

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7
Drug distribution in the elderly

M. Mitchard (Clinical Pharmacokinetic Group, Department of Medical Research, Synthélabo - L.E.R.S., 75013 Paris, France)

FACTORS DETERMINING THE DEGREE OF DRUG DISTRIBUTION

The physicochemical properties of a drug predetermine its basic pattern of distribution within the body after administration. In general, lipophilic drugs will pass across membranes easily, will accumulate in lipid tissues and will be extensively distributed, whereas polar compounds will be restricted to the extracellular fluids and will not transfer into tissues readily. These basic principles were first discussed by Brodie and his co-workers in the early 1950s (for review, see Brodie, 1964) and later by Bender (1969). More recently, Klotz (1976) has emphasised that 'distribution is a physicochemical interaction between a drug and the body' and that 'the pattern of this distribution is determined by the properties of the two partners'.

Within the body, membranes dominate distribution patterns with their essential phospholipid structure. Except where active transport processes allow otherwise, membranes form an effective barrier against polar molecules. Other factors, such as pH differences between tissues, modify the proportion of the lipid soluble form of a drug, so that its rate of entry into different tissues can vary. The composition of a tissue is also important, for the amount of drug entering and remaining in a tissue will depend on the proportion of fat deposited or on the concentration of proteins having a high affinity for the drug. In addition, changes in blood supply to and degree of vascularisation of a tissue will facilitate or reduce the access of a drug. This latter factor has recently been recognised as often being the most important determinant in the disposition of a drug, although its effect is to influence the clearance more than distribution (Rowland, Benet and Graham, 1973; Wilkinson, 1975).

TISSUE AND PHYSIOLOGICAL CHANGES IN THE ELDERLY

Patients differ in many respects, among the most important of which is their age. It is now clearly understood that tissue characteristics and physiological processes vary considerably during a lifetime, with the most significant differences being

Table 7.1 Age-related changes in body composition and function

Weight	Decreases, particularly in the very old.
Tissues	Adipose tissue doubles at expense of functional tissue (Gregerman, Gaffney and Shock, 1962; Forbes and Reina, 1970; Novak, 1972).
Body water	Decreases (Edelman and Leibman, 1959).
Plasma	Albumin decreases (10%) and globulin increases (Woodford-Williams *et al.*, 1964; Goldman, 1971; Leask, Andrew and Caird, 1973).
Membrane permeability	Possibly is increased.
Blood flow	Cardiac output decreases by 30–40% (Brandfonbrener, Landowne and Schock, 1955). Splanchnic and renal flows decreased > 40% (Bender, 1965; Sherlock *et al.*, 1950).
Renal function	Age-related deterioration.

found in the very young and in the old (over 65 years). The most important changes which influence the distribution of drugs are listed in table 7.1.

The principal effect of all of these changes is to alter the apparent volume of distribution of a drug.

KINETIC ANALYSIS OF PLASMA DRUG LEVEL DATA

Pharmacokinetic analysis of different plasma or blood drug level data obtained in two groups of subjects provides the only certain means of identifying the reason for the difference. There is at present a considerable amount of confusion in the literature—in spite of many excellent books and papers on the subject—as to the precise scope and limitations of such analysis, particularly with respect to the interrelationship and significance of apparent volume of distribution (V_d), half-life ($t_{1/2}$) and clearance, and it is precisely in terms of these characteristics that a change in the distribution of a drug can be defined. It appears difficult for some workers to conceive that a change which produces an increased plasma half-life need not be associated with a change in the clearance of the drug but can be the result of a change in the volume of distribution. Much of the confusion arises from the inappropriate extrapolation of principles which apply, if the distribution of a drug can be described according to compartment theory, to one-compartment systems.

A plot of the plasma concentrations of such a drug against time together with the model describing the kinetic behaviour of the drug is shown in figure 7.1.

In such a case, and only in such a case, is the rate of elimination of the drug a direct function of the slope of the logarithmic plot of its plasma concentration against time, and only in this case is the volume through which the drug is distributed a parameter with a straightforward meaning. This volume can best be determined at the time when the drug is injected, for at this time the amount put into

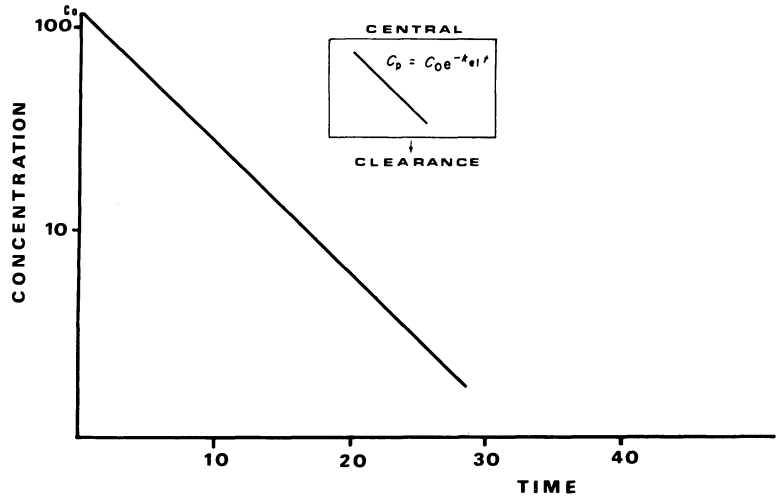

Figure 7.1 Change in plasma concentration of a drug whose distribution can be described by a one-compartment mathematical model.

the body is known and the initial concentration can be obtained by extrapolating the straight-line log plasma concentration plot to zero.

However, immediately after the administration of most drugs, there is a period during which the drug is being distributed, and, if a sufficient number of plasma samples are collected during this time, it is possible to characterise a distribution phase. Sometimes the distribution phase is simple; at other times it is more complex–consisting of two or more components. The shortcomings of analysing such data by applying 'one-compartment principles' have been already discussed by Riegelman, Loo and Rowland (1968), but in view of the fact that these concepts still appear to be but poorly understood and in view of the present discussion (that is the determination of V_d), it is considered important to re-state the fundamental differences between the two models.

TWO-COMPARTMENT VERSUS ONE-COMPARTMENT ANALYSIS

Pharmacokinetic analysis depends upon defining the blood-plasma drug concentration-time curve by a mathematical equation. Since the absorption, transfer and metabolism of drugs are normally first-order processes, the equations are poly-exponential functions. Integration of these exponential functions yields the logarithmic function which forms the basis of classical pharmacokinetic compartmental analysis.

An example of a drug which after intravenous administration shows an initial single distribution phase is shown in figure 7.2. The plasma concentration-time curve is described by the well-known two-exponential equation. In order to distinguish the distribution phase, α must be greater than β, but this also means that the initial term approaches zero more rapidly than the second. The initial term approxi-

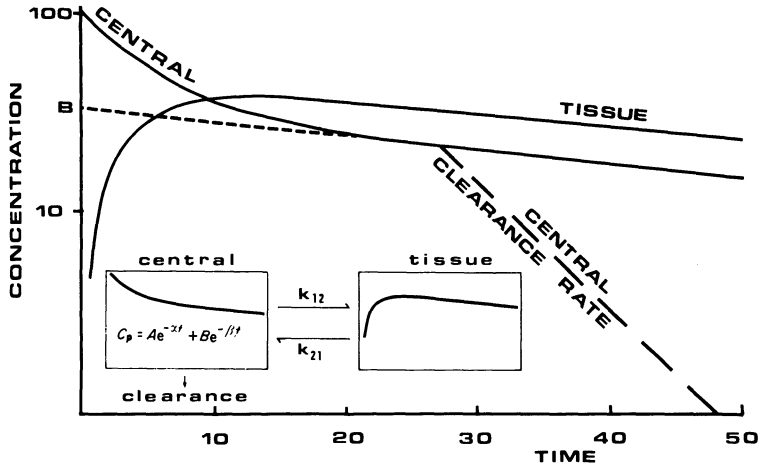

Figure 7.2 Change in plasma and 'tissue' concentrations of a drug whose distribution can be described by a two-compartment open model. The difference between apparent plasma half-life and plasma clearance is emphasised by the computer-calculated dashed line, corresponding to clearance from the central compartment in the hypothetical situation of abruptly removing the second compartment.

mates to zero when distribution is complete, and after this time, during the so-called 'elimination phase', the curve is described by the $B_e{}^{-\beta t}$ term—that is the semilogarithmic plot is a straight line (better known as the β or terminal regression), with a slope of β and a zero-time intercept of B. *β is not the elimination constant* K_{el}; it is a hybrid constant which *includes* K_{el}. Nor is B the initial concentration (C_0) for when $t = 0, C_p = A_e{}^{-\alpha t} + B_e{}^{-\beta t}$ reduces to $C_0 = A + B$.

As can be seen from figure 7.2, during the *distribution phase* there is a net transfer of drug into the tissues, while during the *elimination phase* there is a net transfer of drug from the tissues into the plasma.

This means that instead of the plasma drug concentrations falling in proportion to the amount of drug cleared they are supplemented by a return of drug from the tissues. Only if it were theoretically possible to block the return of drug from the tissues would the rate of decrease of the plasma drug concentration (as indicated by the dotted line in figure 7.2) directly reflect the rate of drug clearance. The relationship between plasma clearance and plasma half-life is discussed elsewhere by Rowland *et al.* (1973).

Therefore, when drugs are distributed in tissues, firstly, the apparent plasma half-life is always longer than the plasma elimination half-life, and, secondly, values of V_d calculated by extrapolating the terminal regression to zero time (figure 7.2) will always be greater than the true value.

CALCULATION OF THE VOLUME OF DISTRIBUTION

Apparent volume of distribution is a mathematical concept which indicates the degree to which a drug is concentrated outside the plasma in those fluids which are in equilibrium with the plasma; in principle this is the extravascular water.

The apparent volume of distribution is that volume which the amount of drug in the body at any given time would occupy if it were evenly distributed at the same concentration as occurs in plasma. V_d is therefore a proportionality constant relating the total amount of drug in the body at any given time to the plasma concentration and, therefore, it can only be meaningfully calculated from data obtained when the tissue and plasma concentrations are in equilibrium.

The methods used to calculate V_d have been discussed by Klotz (1976) in his paper on the pathophysiological and disease-induced changes in this parameter. It is important to emphasise that the value can only be calculated from data obtained after intravenous administration, because losses due to incomplete absorption and first-pass metabolism make it impossible to determine exactly what proportion of the administered dose reaches the systemic circulation.

Probably the best method of calculating V_d is to calculate the value at steady state–that is, at that time when there is no net transfer between the tissues and plasma. This value can be determined from the following relationship:

$$V_{d\ (ss)} = \frac{\text{dose}}{C_0}\left(\frac{K_{12}+K_{21}}{K_{21}}\right) = V_i\left(\frac{K_{12}+K_{21}}{K_{21}}\right)$$

where C_0 is the plasma concentration at zero time and K_{12} and K_{21} are the classical rate constants for transfer between the central and tissue compartments. For other methods of calculating V_d using measures of clearance or the area under the curve, see Klotz (1976).

FACTORS ASSOCIATED WITH A CHANGE IN DRUG DISTRIBUTION IN THE ELDERLY

Volume of distribution per se

There have as yet been few studies which show a clear age-related change in the volume of distribution of specific drugs. What information there is suggests that there are potentially four types of change which influence the volume of distribution, as indicated in table 7.2.

Since most drugs are administered as unit doses, small patients will have higher plasma and tissue drug levels for a given dose than large patients. However, not only are the elderly smaller, but also they have a higher proportion of fat in their tissues and a smaller proportion of body water. This means that a higher proportion of a lipid-soluble drug will pass into the tissues and that, although the drug clearance may be unaffected (most lipid-soluble drugs are cleared principally by metabolism), the apparent plasma half-life of the drug will be increased. On the other hand, a highly polar drug will produce higher plasma concentrations in the elderly.

In a study with digoxin, Ewy *et al.* (1969) clearly established that the initial blood digoxin plus metabolites levels obtained after intravenous injection of digoxin were nearly twice as high in an elderly group of subjects as in a control group. Digoxin is a highly polar drug and, in principle, is confined to the extracellular fluids and, although the mean 24 h creatinine clearances of the older group (70–80 years) was only half that of the younger subjects (20–30 years), the authors were able to show that, during the first 24 h, the plasma levels were elevated owing to a smaller V_d. This they did by correcting the plasma concentrations for the differ-

Table 7.2 Drugs with changed distribution pattern in the elderly

Parameter which changes with age	Drugs whose distribution characteristics are changed
V_d	digoxin propicillin K diazepam chlormethiazole
Protein binding	pethidine (meperidine) phenylbutazone phenytoin
Erythrocyte binding	pethidine
Urine concentration	amoxycillin pivmecillinam

ence in body weight by converting all values to drug concentration per unit volume of blood per unit body weight. There was then no significant age-related difference between the concentrations obtained during the first 24 h.

Similar results were obtained by Simon *et al.* (1972) with the antibiotic, propicillin K. This also is a highly polar drug the distribution of which is restricted to the extracellular fluid. Serum concentrations remained higher in the elderly (60–80 years) than in the young (20–30 years) throughout the course of the 6 h study. The area under the plasma drug concentration-time curve for the old group was larger by a factor of 2, whereas the V_d only averaged 18.4 litres against a mean of 29.1 litres in the young group. In the absence of renal pathology, neither the apparent plasma half-life nor the elimination rate constant was significantly different as between the two groups, although the main K_{el} for the young was in fact higher (1.24 against 1.06). In addition, the authors noted that the 9 h urine recovery of the drug was the same in the two groups, all of which is consistent with a simple decrease in the volume of distribution in the old group with perhaps a smaller decrease in clearance.

The most important study to examine the volume of distribution of a drug in the young and old is that of Klotz *et al.* (1975) with diazepam. This study is discussed elsewhere in this publication by Dr G. Wilkinson. However, it is emphasised here, as it appears to be one of the few well-defined examples of an increased volume of distribution of a lipid-soluble drug in the elderly, presumably owing to the increased fat deposition in their tissues. In this study it was also shown, according to prediction, that, although the β-phase plasma half-life of diazepam increased by about 1 h per year between the age of 20 and 80 years, the total plasma clearance remained constant.

Recently Nation *et al.* (1976) have reported a well-designed study in which they have investigated the disposition of chlormethiazole in the elderly after constant intravenous infusion. From the post-infusion data they determined that the apparent half-life was doubled in the elderly (69–91 years) and that plasma clearance was decreased to about two-thirds of the value in a young group (20–27 years), the values for the young group being taken from an earlier study. It also appeared that

the volume of distribution was increased from 8 to 11 l/kg in the elderly, when calculated from the area under the curve data by the method of Perrier and Gibaldi (1973). However, because the value of V_d calculated in this way is influenced by changes in clearance, the authors were reluctant to comment upon the practical significance of the difference observed, nor were they able to calculate a meaningful initial volume V_i or steady-state volume (V_{ss}), since it was necessary to use both two- and three-compartment models to analyse the data obtained from the elderly subjects. However, an increase in the volume of distribution of chlormethiazole in the elderly would appear to be likely when all the facts are taken into consideration.

There do not appear to be other well-documented examples in the literature of drugs whose volume of distribution is changed with age, independently of the other parameters discussed below. Often when a difference in V_d has been reported for a drug, the value has been incorrectly calculated and frequently after an oral administration.

Thus there is some confusion in the literature as to whether the V_d of phenylbutazone is increased (O'Malley *et al.*, 1971) or not (Triggs *et al.*, 1975). Both studies were carried out after oral administration and in neither case is the parameter calculated accurately.

In summary, the actual volume of distribution for a drug changes with age but the way in which it changes depends on the nature of the drug. For lipid-soluble drugs, V_d will *increase* and blood levels will *decrease*, whereas for polar drugs, V_d will *decrease* and blood levels will *increase*.

Plasma protein binding

The phenomenon of protein binding and its significance to pharmacokinetics has recently been reviewed in an excellent and comprehensive paper by Jusko and Gretch (1977).

A number of workers have investigated the influence of age on the proportion of drug bound to plasma proteins, and there appears to be a significant reduction in the proportion of phenytoin, pethidine and phenylbutazone bound to protein in the plasma of elderly persons.

The effect of a change in the proportion of a drug which is bound to plasma protein depends on the extent to which the drug is normally bound. If only a small proportion of the drug is bound, a significant change of 20–50 per cent in the proportion will not materially affect the disposition of drug in the body. However, if the drug is highly bound, a reduction of 10 per cent in the proportion bound will mobilise considerably more drug for redistribution. Whether a drug has a large volume of distribution or a relatively small volume of distribution further modifies the effects resulting from these changes.

If the protein-bound proportion of a drug with a small volume of distribution is reduced, the rate of drug clearance will be increased (that is the plasma clearance will remain constant but the amount of drug per ml of plasma available for clearance will have increased), whereas if a drug has a large volume of distribution, more drug will partition into the tissues if the protein-bound proportion is decreased (that is tissue concentration will rise and the volume of distribution will *increase*, but, as before, plasma clearance will remain unaltered).

Studies by Hooper *et al.* (1974) and Hayes, Langman and Short (1975*b*) suggest that the protein binding of phenytoin is decreased in the elderly, the former report-

ing a significant age-related increase in the proportion of phenytoin unbound in plasma from 9.9 per cent at 17 years to 12.7 per cent at 53 years. The latter group, on the other hand, investigated the maximum protein binding capacity for phenytoin of plasma obtained from old and young persons, and obtained significantly different values correlating well with the smaller albumin concentration in the plasma samples obtained from the elderly subjects. Bender *et al.* (1975), however, reported no difference in the extent of plasma protein binding in young or elderly subjects.

Studies with warfarin (Shepherd *et al.*, 1977) show that a similar, high proportion of the drug is bound to plasma protein in young (20–40 years) and old (65–90 years). However, Hayes *et al.* (1975*a*) have again established a significant correlation between the total binding albumin concentrations, indicating that the total binding capacity for warfarin is reduced in the elderly. This observation appears to have clinical significance, for, although the concentrations of warfarin required to saturate the binding capacity exceed the therapeutic concentrations, the presence of other drugs may compete for the binding site available. For example, recent studies in elderly patients (Wallace, Whiting and Runcie, 1976) have shown that as the number of other drugs present in the plasma increases, so the proportion of free salicylate, phenylbutazone and sulphadiazine increases.

There appears to be a clear age-related decrease in the proportion of pethidine (meperidine) bound to plasma proteins, as reported by Hather *et al.* (1975). They collected plasma after an intravenous injection of pethidine from subjects aged 18–73 years, and established that a highly significant correlation existed between age and fraction of unbound drug in plasma. They were able to relate age to proportion of unbound pethidine by the following expression: FFP = 0.175 + 0.0052 × age (yr), where FFP = proportion of pethidine unbound.

My own group (Chan, Kendall and Mitchard, 1974; Chan *et al.*, 1975) failed to show a conclusive age-related difference in the protein binding of pethidine. Our studies differed from those of Mather *et al.* (1975) in that we studied the binding over a range of concentrations from 0.2 to 3.0 μg/ml and showed that the percentage of pethidine bound to protein decreased with increasing concentration.

In view of the low correlation coefficient ($r = 0.58$) for the relationship established by Mather and his group, it is probable that in our initial studies we failed to use sufficient subjects. Subsequently, I have measured the protein binding in other, larger groups of young (mean age, 24 years) and elderly (mean age, 78 years) subjects and obtained mean values for unbound pethidine of 45 (± 15.2) and 60 (± 12.1) per cent ($n = 10$), respectively (unpublished data). These values are in reasonable agreement with the values of 32 and 65 per cent calculated from the equation of Mather *et al.*—that is, proportion unbound = 0.175 + 0.0062 × age (yr).

Only one other group of workers (Wallace *et al.*, 1976) appear to have established significant age-related differences in their protein-binding studies with phenylbutazone. Again there was a significant decrease (from 96 to 94 per cent) in the proportion bound by plasma obtained from elderly subjects (69–85 years) as compared with a younger group (19–40 years). Of particular interest in this study was the observation that the proportion unbound not only of phenylbutazone but also of salicylate and sulphadiazine was increased in elderly patients on multiple drug therapy when compared with a younger group also receiving treatment with other drugs.

Erythrocyte binding

A study by my group in Birmingham (Chan *et al.*, 1975) established that a significantly greater proportion of pethidine was associated with erythrocytes in blood obtained from young patients (under 30 years) undergoing eye surgery than from blood obtained from a similar group of elderly patients (over 70 years) as shown in figure 7.3. The haematocrit values were similar in the two groups. We postulated that this difference was reponsible for the twofold higher plasma pethidine concentrations in elderly subjects.

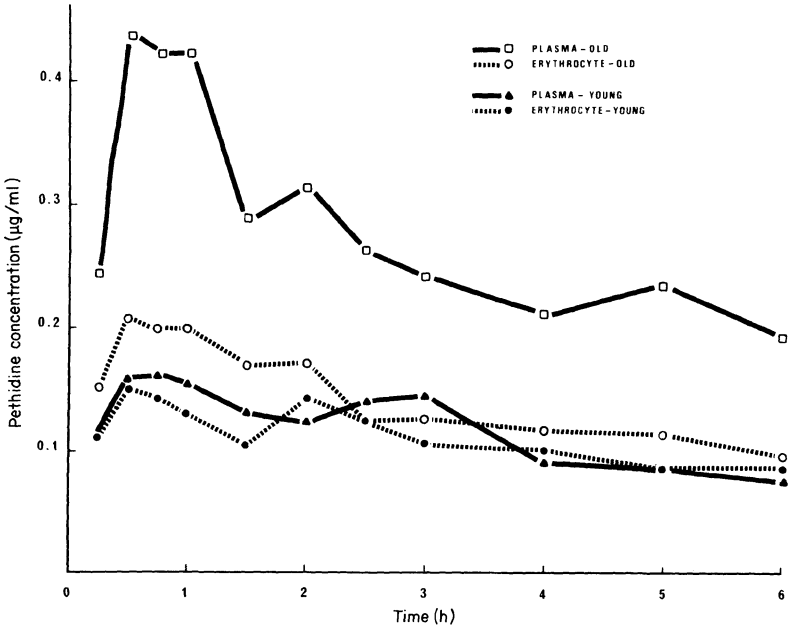

Figure 7.3 Mean plasma and erythrocyte pethidine concentrations in young (< 30 years) and elderly (> 70 years) subjects.

Subsequently, I attempted to characterise by electrophoresis the protein composition of erythrocyte ghosts obtained from young and elderly patients. 'Ghosts' were prepared by the method of Dodge, Mitchell and Hanahan (1963) and the proteins were subsequently dissolved either in butanol, as described by Maddy (1966), or in sodium dodecyl sulphate solution, as described by Rosenberg and Guidotti (1968). Electrophoresis was carried out on (1) acrylamide gels containing urea, as described by Gomperts, Cantrell and Zail (1971), and (2) acrylamide gels containing dodecyl sulphate, as described by Vinuela, Algratini and Ochoa (1967). Ten and fifteen protein bands were present from both samples in the two systems, respectively. There was in this study no significant difference between the protein components of the erythrocytes obtained from old and young people.

It seems relevant to comment on the work of Evans and Shand (1973), Evans, Nies and Shand (1973) and Wilkinson and Kurata (1974). These workers have

shown for drugs such as diazepam, propranolol and diphenylhydantoin that the blood : plasma ratio of drug increases with increase in percentage of unbound drug in plasma and concluded that 'binding was responsible for the decreased erythrocyte distribution'. These studies used drugs which normally have a blood : plasma ratio of < 1.0 and which are highly bound (> 80-90 per cent) to plasma protein. Our studies with pethidine, which has a blood : plasma ratio of >1.0 and is 40-80 per cent bound, shows that the percentage of unbound drug decreases as the blood : plasma ratio increases and that these changes may be related to ageing factors (figure 7.4).

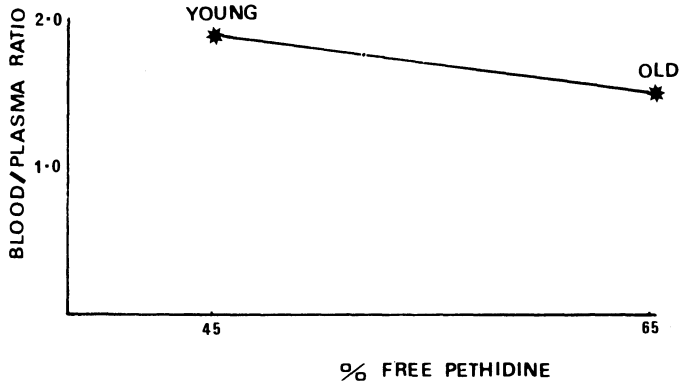

Figure 7.4 Relationship between the blood:plasma ratio and percentage free pethidine when the changes are due to an age-related factor.

DISTRIBUTION IN URINE

Urine is usually considered as a means of excretion and is not normally considered as a site into which a drug must be distributed in order to produce an effect. However, when antibiotics are used to treat urinary tract infections, it is essential that levels in urine be above the minimum inhibitory concentration. Our recent studies with mecillinam (Ball *et al.*, 1977) and amoxycillin (unpublished results) have established that in elderly people with normal serum creatinine for their age and, therefore, normal renal function, the apparent serum antibiotic half-life is 3–4 times that of a young control group. Urinary concentrations were correspondingly low (less than 20 μg/ml in some cases) and this was associated with a failure to clear the infection. We have shown that this is due to a reduced rate of elimination and is presumably directly attributable to the age-related deterioration in renal function. In this particular situation the associated change in distribution of the drug is important in terms of clinical effect.

CONCLUSION

Absorption and disposition processes are interrelated functions and a change in the rate of one process alters the distribution and clearance pattern in a complex but

predictable manner. It appears that for some drugs the pattern of distribution changes with age but that such changes rarely occur independently.

The major difficulty in establishing that significant changes occur in the disposition of drugs in the elderly is the large variation in values obtained from subjects classed as elderly. Perhaps in future another index of age such as plasma albumin concentration which can be rapidly determined and does not introduce ethical problems should be used instead of biological age.

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8
Renal excretion of drugs

J. P. Kampmann and J. E. Mølholm Hansen (Medical Department T, Bispebjerg Hospital, 2400 Copenhagen NV, and Department of Medicine and Endocrinology F, Herlev Hospital, 2730 Herlev, Denmark)

PHYSIOLOGICAL BACKGROUND

An age-dependent decrease in renal function seems to be one of the most important physiological factors responsible for altered pharmacokinetics in the elderly–a subject recently reviewed elsewhere (Triggs and Nation, 1975; Crooks, O'Malley and Stevenson, 1976).

The decrease in renal function with increasing age was originally demonstrated by Lewis and Alving (1938). Later, Davies and Shock (1950) and Miller, McDonald and Shock (1952) measured the inulin clearance, diodrast clearance and diodrast and glucose transport maximum in 70 males between the ages of 20 and 90 years with no evidence of renal disease and found that all the mentioned parameters decreased almost linearly from the age of 30. Both the glomerular filtration rate and tubular secretion or absorption capacity were reduced by approximately 50 per cent. In addition, renal blood flow decreased, resulting in an unchanged extraction ratio for inulin and diodrast. These results were confirmed by van Pilsum and Seljeskog (1958) using endogenous creatinine clearance as an indicator of glomerular function. Contrary to the age-dependent decline in endogenous creatinine clearance, the serum concentration of creatinine in larger groups of healthy persons has shown no significant change with age after termination of puberty (Kuhlbäck, Eriksson and Forsius, 1964; Dubach, Metz and Schmid, 1967). The findings of decreased glomerular filtration rate and unaltered serum creatinine indicate a decrease in the endogenous production of creatinine with age. A fall in urinary excretion of creatinine per kg body weight has also been demonstrated by Howell (1956), Ahlert *et al.* (1967) and Bulusu *et al.* (1970). The decrease in urinary excretion of creatinine in relation to age is probably due to a greater reduction in lean body mass than in total body weight (Miller and Blythe, 1952; Forbes and Reina, 1970).

In a recent study Kampmann *et al.* (1974*b*) reported, with special reference to age-dependent changes, on the excretion of urinary creatinine per kg body weight, along with values for serum creatinine and endogenous creatinine clearance (figure 8.1). Two hundred and nineteen women with serum creatinine concentration be-

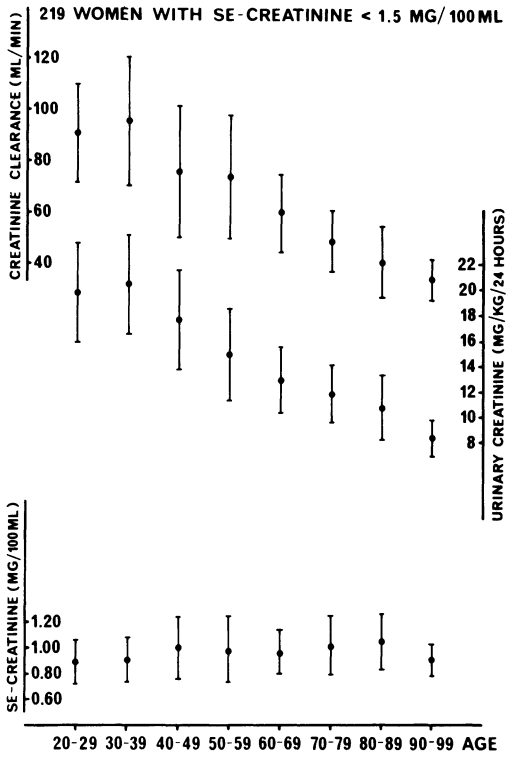

Figure 8.1 Mean values of endogenous creatinine clearance, urinary excretion of creatinine per kg body weight per 24 h and serum creatinine concentration in 219 females divided into eight age groups.

low 1.5 mg per 100 ml were divided in eight age groups from 20 to 99 years. The mean serum concentrations of creatinine showed only small and insignificant variations with age. Endogenous creatinine clearance in ml/min showed constantly decreasing mean values with a gradual fall of about 10 ml/min per decade. The mean urinary creatinine value in mg/kg body weight per 24 h showed a constant decrease from age group 30-39 to the oldest age group, and the average value decreased from 20.4 to 8.4 mg per kg per 24 h. The results from 149 males showed changes comparable to those of the women. No significant difference in the mean value of creatinine excretion per kg body weight per 24 h was found between patients with serum creatinine values of 1.5-5.0 mg per 100 ml and those in corresponding age groups with serum creatinine values below 1.5 mg per 100 ml. The consequence is that serum creatinine can be used as a substitute for endogenous creatinine clearance only if the age-dependent decrease in renal function is taken into account.

Besides age, creatinine clearance is known to depend upon sex (about 10 per cent higher in males) and body weight. From the study it was possible to construct a nomogram and a slide-rule for the evaluation of the endogenous creatinine clear-

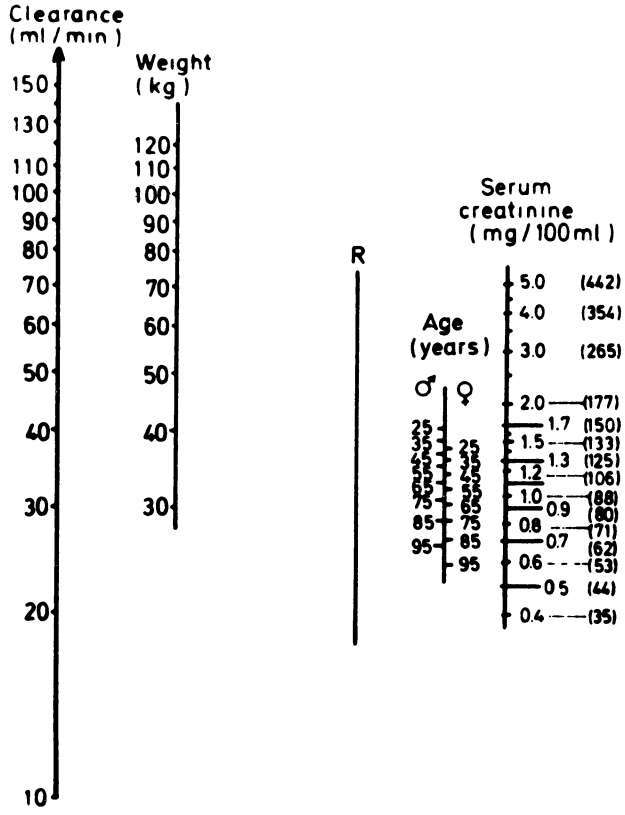

Figure 8.2 Nomogram for evaluation of the endogenous creatinine clearance. Use of the nomogram: Connect with a ruler the patient's weight on the second line from the left with the patient's age on the fourth line. Note the point of intersection on R and keep the ruler there. Turn the right part of the ruler to the appropriate serum creatinine value, and the left side will indicate the clearance in ml/min. Serum creatinine values in μmol/l are given in parentheses.

ance (figure 8.2). The nomogram is well suited for use in elderly people but is not applicable to uraemic patients with serum creatinine above 5.0 mg per 100 ml or to other severely disabled patients where the muscle mass and creatinine production is diminished to a larger extent than the total body weight (Enger and Blegen, 1964). The precision of the nomogram has recently been studied by Cockcroft and Gault (1976). In 236 males a correlation of 0.84 was found between the measured and nomogram-predicted values of endogenous creatinine clearance.

PHARMACOLOGICAL STUDIES

Physiological observations on renal function and age have, in general, been confirmed by pharmacological studies. Table 8.1 shows some renally excreted drugs which have been studied in the elderly.

Table 8.1 Renally eliminated drugs, the kinetics of which have been studied in elderly compared with younger subjects

Drug	Result	Reference
Benzylpenicillin and procaine penicillin	Higher serum levels of both drugs in the elderly.	Leikola and Vartia (1957)
Dihydrostreptomycin and tetracycline	Higher serum levels of both drugs in the elderly.	Vartia and Leikola (1960)
Digoxin	Increased half-life in the elderly.	Ewy *et al.* (1969)
Propicillin	Unchanged half-life, but smaller volume of distribution and, possibly, clearance in the elderly.	Simon *et al.* (1972)
Benzylpenicillin	Increased half-life in the elderly.	Kampmann *et al.* (1972)
Cephalothin	Increased half-life in the elderly.	Kampmann *et al.* (1974*a*)
Kanamycin and gentamicin	Increased half-life in the elderly.	Lumholtz *et al.* (1974)
Phenobarbitone	Increased half-life in the elderly.	Traeger *et al.* (1974)
Lithium	Unchanged half-life and decreased volume of distribution in the elderly.	Lehmann and Merten (1974)
Sulphamethizole	Increased half-life and reduced clearance in the elderly.	Triggs *et al.* (1975)
Practolol	Unchanged half-life in the elderly.	Castleden *et al.* (1975)

The work of Leikola and Vartia (1957) on benzylpenicillin and procaine penicillin was the first to demonstrate a correlation between age and drug excretion. Serum levels of both drugs were substantially higher in elderly than in younger patients. Similar results were reported with dihydrostreptomycin and tetracycline (Vartia and Leikola, 1960). Digoxin kinetics in the elderly were studied by Ewy *et al.* (1969), who demonstrated a significant correlation between age and the half-life of digoxin. Patients between the age of 20 and 30, with endogenous creatinine clearance of 122 ml/min per 1.73 m^2, had a half-life of digoxin of 51 h, while elderly patients aged from 73 to 81 years had an average digoxin half-life of 73 h and a creatinine clearance value of 56 ml/min per 1.73 m^2 on average. These results were later confirmed by Falch (1973).

Kampmann *et al.* (1972) studied the elimination of penicillin in relation to age and the influence of probenecid. Table 8.2 shows penicillin half-life influenced by probenecid and by age-dependent variations in endogenous creatinine clearance. In

Table 8.2 Penicillin half-life influenced by probenecid and by age-dependent variations in endogenous creatinine clearance

Variable	Young subjects	Older subjects
Number of subjects	9	13
Age (mean years)	30.6	80.0
Serum creatinine (mg/100 ml)	0.98 ± 0.26	1.11 ± 0.18
Creatinine clearance (ml/min)	98 ± 15	41 ± 9
Urine creatinine (mg/kg per 24 h)	21.2 ± 3.8	10.7 ± 3.0
$t_{1/2}$ before probenecid (min)	23 ± 3	52 ± 14
$t_{1/2}$ after probenecid (min)	70 ± 23	128 ± 43

the elderly penicillin half-life was significantly increased and endogenous creatinine clearance decreased. After probenecid (2 g daily for 7 days), penicillin half-life increased in both groups, but to a different degree, the increase being greater in the younger subjects. The results indicate that the effect of tubular-blocking drugs is dependent upon renal function, and that the half-life values obtained in younger patients with maximally effective doses of probenecid are not much larger than the half-life values measured spontaneously in elderly patients.

The half-life of phenobarbitone was found by Traeger, Kiesewetter and Kunze (1974) to be approximately 50 per cent greater in elderly patients over the age of 70 than in younger subjects. A larger age-dependent increase in plasma half-life of some 75 per cent has been reported for sulphamethizole (Triggs *et al.* 1975), a finding in agreement with a larger renal elimination of this drug compared with phenobarbitone. The author found that the proportion of an oral dose that was absorbed was similar in young and old subjects and that this was not a contributing factor to the increased half-life in elderly patients. A significant correlation of −0.84 was demonstrated between age and elimination rate constant.

The age-dependent kinetics of two aminoglycosides, kanamycin and gentamicin, were studied by Lumholtz *et al.* (1974). The half-life of both drugs increased with

advancing age: kanamycin from 107 ± 27 min to 330 ± 154 min; gentamicin from 93 ± 26 to 216 ± 60 min. The values of serum creatinine in the patients investigated were between 0.7 and 1.3 mg per 100 ml. The findings of considerable age-dependent variations in measured drug half-lives in subjects of different age but with almost identical serum creatinine values implies that dose regimens based solely upon serum creatinine cannot be satisfactorily applied in all age-groups (Cutler and Orme, 1969; McHenry *et al.*, 1971). The influence of age on the elimination of cephalothin was in accordance with the above-mentioned studies, the half-life altering from about 15 min in younger persons to about 40 min in elderly subjects (Kampmann *et al.*, 1974*a*).

Recently Castleden, Kaye and Parson (1975) found higher plasma levels of practolol in old subjects compared with younger ones following single oral doses. The difference, however, was mostly explained by an age-correlated reduction in the volume of distribution, there being no significant alteration in half-life. Another study in which there was no evidence of a decreased rate of drug elimination in old age was that of Simon *et al.* (1972) on propicillin. The half-life, the volume of distribution and the area under the serum drug concentration versus time curve were calculated after intramuscular administration of propicillin to two groups of subjects aged 20–30 and 60–80 years. No significant differences were found between the half-lives but the areas under the drug concentration versus time curve were much greater, and the volume of distribution smaller in the older age group. Although not calculated in the study, it can be inferred from the data that the total body clearance, mainly consisting of renal excretion, must have been reduced by some 50 per cent in the elderly subjects. This is in accordance with previous studies on other penicillins. The data illustrate the misleading use of half-lives in situations where alteration in the volume of distribution occurs.

RATIONALE FOR ADJUSTING THE DOSAGE IN ELDERLY PATIENTS

Many drugs are eliminated unchanged by the kidneys and the age-dependent decrease in renal function may often be of importance when giving drugs to the elderly. In general, changes in endogenous creatinine clearance relate well to changes in the renal clearance of the drug (Fabre and Balant, 1976). It appears to be less important to know whether the drug is excreted by glomerular filtration or tubular secretion, since the total renal clearance of most drugs parallels the glomerular filtration rate even when tubular secretion is the main route of excretion.

The clinical importance of modifying drug dosing in elderly people to compensate for a reduced renal clearance depends on two factors: (1) the fraction of drug excreted unchanged by the kidney and (2) the therapeutic safety of the drug.

The first prerequisite is obvious. Drugs such as tolbutamide or warfarin which are extensively metabolised by hepatic processes to predominantly inactive and non-toxic compounds need not be considered further with regard to renal failure. However, drugs such as gentamicin and lithium, mainly eliminated unchanged by renal excretion, are drugs which should be reduced in dose when given to elderly people. The second point is of great practical importance. Although the penicillins and the cephalosporins are eliminated largely unchanged by the renal route, the therapeutic index is so large that no adverse reactions are to be expected when prescribing those drugs in standard doses for elderly people, even when clearance values are reduced to about 20 ml/min.

That alteration in drug metabolism occurs in uraemia is well known (Reidenberg, 1975). However, it is not known whether the age-dependent reduction in renal function affects the metabolism of drugs. Active metabolites are another potentially important factor (Drayer, 1976). Some drug metabolites such as *N*-acetyl procainamide from procainamide, norpethidine from pethidine, acetylated sulphonamides, oxypurinol from allopurinol and glycinexylidide from lignocaine are almost exclusively eliminated by renal excretion, but so far no information is available on the accumulation of these metabolites in old age. Recently the 24 h recovery of the major lignocaine metabolite 4-hydroxyxylidine showed a significant reduction in elderly compared with young subjects (Nation, Triggs and Selig, 1977). Interactions with non-toxic compounds influencing the formation of active drug metabolites is another yet unexplored area.

Table 8.3 Renally excreted drugs, which should be reduced in dose when given to elderly patients

Aminoglycosides, i.e. streptomycin, gentamicin, kanamycin, tobramycin, amikacin and sisomicin
Tetracyclines (except doxycycline)
Colistin
Lithium
Digoxin
Procainamide
Methotrexate
Ethambutol
Phenobarbitone

Taking these points into consideration, table 8.3 shows some commonly used drugs which are potentially toxic in elderly patients and where reduction of dosage should be considered.

CALCULATION OF THE DOSAGE ADJUSTMENT FACTOR

When necessary, the dosage regimen can be modified by using one of the methods outlined for uraemic patients (for reviews, see Tozer, 1974; Fabre and Balant, 1976; Dettli, 1976; Mawer, 1976). The overall objective is to reduce the rate of drug administration to equal the decrease in drug elimination, thereby achieving the same average amount of drug in the body. It is important to realise that only the average amount of drug in the body can be maintained constant. With the exception of intravenous infusions, no dosage regimen produces a serum concentration curve in a patient with decreased renal function comparable to that in a normal patient. In our opinion, the most practical approach is the method indicated by Tozer (1974).

The dosage adjustment factor is derived as follows. The elimination rate constant K, is the sum of the individual rate constants from all organs involved in the elimination of the drug. As the liver and the kidney are the major elimination organs, K is composed of k_r and k_h, where the subscripts denote renal and hepatic, respectively:

$$K = k_r + k_h \tag{1}$$

The relationship between K values at two different conditions can be expressed as:

$$\frac{K_1}{K_2} = \frac{k_{r,1} + k_{h,1}}{k_{r,2} + k_{h,2}} = \left[\frac{k_{r,2}}{k_{r,1} + k_{h,1}} + \frac{k_{h,2}}{k_{r,1} + k_{h,1}}\right]^{-1} \tag{2}$$

If the fraction of drug excreted unchanged by the kidneys is F ($=k_r/K$) and hepatic elimination is assumed to be unchanged (i.e. $k_{h,1} = k_{h,2}$) and the relation between the renal function at the two conditions is denoted $K_f = k_{r,2}/k_{r,1}$, it is found that:

$$\frac{K_1}{K_2} = \frac{1}{F(K_f - 1) + 1} = \frac{t_{1/2(2)}}{t_{1/2(1)}} \tag{3}$$

The dosage adjustment factor is thus the ratio between the half-life in an abnormal condition compared with the half-life in a normal state—for example, an endogenout creatinine clearance of 120 ml/min. For the present purpose $t_{1/2(2)}$ is the half-life of a drug in elderly subjects and $t_{1/2(1)}$ the half-life in young persons. Different values of the factor are given in table 8.4.

Table 8.4 The dosage-adjustment factor

% Excreted unchanged in urine	Creatinine clearance (ml/min)						
	0	10	20	40	60	80	120
10	1.1	1.1	1.1	1.1	1.1	1.0	1.0
20	1.3	1.2	1.2	1.1	1.1	1.1	1.0
30	1.4	1.3	1.3	1.2	1.2	1.1	1.0
40	1.7	1.6	1.5	1.4	1.3	1.1	1.0
50	2.0	1.8	1.7	1.5	1.3	1.2	1.0
60	2.5	2.2	2.0	1.7	1.4	1.3	1.0
70	3.3	2.8	2.3	1.9	1.5	1.3	1.0
80	5.0	3.7	3.0	2.1	1.7	1.4	1.0
90	10.0	5.7	4.0	2.5	1.8	1.4	1.0
100	–	12.0	6.0	3.0	2.0	1.5	1.0

At steady state the average amount of drug in the body is calculated as:

$$\text{Amount in body} = \frac{F \,.\, D}{K \,.\, T}$$

where F is the bioavailability, D the dose and T the dosing interval. If the value of K changes because of decreased renal function, appropriate alterations in D or T are required. In elderly subjects K is decreased to a value related to renal function and to the fraction of drug excreted unchanged. The decrease in K can be compensated for by a reduction in dose or a prolongation of the dosage interval.

PRACTICAL GUIDELINES FOR ADJUSTING THE DOSAGE OF DRUGS IN ELDERLY PATIENTS

(1) Decide the appropriate dosage regimen for the patient as if the renal function were that in a normal young patient–that is, creatinine clearance of 120 ml/min (most dosage regimens are derived from studies in younger subjects).

(2) Determine the fraction of drug (and any active metabolite) which is excreted unchanged by the kidneys.

(3) Determine the renal function by measurement of endogenous creatinine clearance. If this is not available, the nomogram from figure 8.2 can be used.

(4) Calculate the dosage-adjustment factor from equation (3) or obtain from table 8.4.

(5) Use the dosage-adjustment factor in one of the following ways (after considering which is most appropriate for the specific drug):

(a) Divide the dose for normal renal function by this factor and continue with the same dosage interval.

(b) Continue with the same dose and multiply the dosage interval determined for normal renal function by this factor.

(c) Reduce the dose and prolong the dosage interval appropriately.

The decision to reduce dose, increase the dosage interval, or modify both depends primarily on knowledge of the correlation between serum drug concentration and therapeutic/toxic effect. If, like digoxin, the drug is excreted relatively slowly, reduction of dose seems most convenient. For drugs with shorter half-lives–for example, many antibiotics–prolongation of dosage interval is the most usual method. This regimen

Table 8.5 Data from 12 sepsis patients treated with gentamicin

Variable	Mean	Range
Age (yr)	71.3	53–82
Weight (kg)	63.0	47–73
Serum creatinine (mg/100 ml)	1.5	0.8–3.0
Creatinine clearance (ml/min)	45.8	22–65
Gentamicin dosage (mg/kg)	1.1	1.1–1.3
Dosage interval (h)	11.8	7–20
Duration of treatment (days)	9.9	5–14
Maximum concentration (μg/ml)	6.5	4.0–10.5
Minimum concentration (μg/ml)	1.9	0.8–2.8

may result, however, in high, potentially toxic, serum drug concentrations followed by long periods with low sub-therapeutic levels. A combination of dose reduction and dosage interval prolongation often offers the best dosage regimen modification.

The reliability of the dosage modification procedure suggested has recently been verified in 12 patients treated with gentamicin because of sepsis (table 8.5). Keeping the dose almost constant, the dosage interval was varied, based upon calculations from the nomogram and the dosage-adjustment factor. The average maximum and minimum serum concentrations of gentamicin after 10 days of treatment were well below the usual accepted toxic level (10 and 2 μg/ml, respectively). However, many more trials are urgently needed to validate the method with different drugs.

CONCLUSION

Drug dosage in the elderly can be difficult, but it has to be remembered that old age itself is no contraindication for a well-planned therapy. Proper treatment of elderly patients can be most rewarding and may often considerably improve their quality of life. Knowledge of the physiology of old age, pharmacokinetic experience and, most important, careful clinical observation should make the clinician better-equipped to treat this constantly increasing proportion of the population.

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9

Digoxin pharmacokinetics in the elderly

B. Whiting and J. R. Lawrence (Department of Materia Medica, University of Glasgow, Stobhill General Hospital, Glasgow, UK) and D. J. Sumner (Department of Clinical Physics and Bio-engineering, West of Scotland Health Boards, Glasgow, UK)

INTRODUCTION : CLINICAL OBSERVATIONS

Treatment of the elderly patient presents the physician with a special challenge. To a greater or lesser extent, ageing exerts a significant influence on the principal determinants of drug disposition and effect, and treatment is most successful when patient requirements are equated with both altered physiological and altered pathological circumstances. This is of particular relevance to drugs with a narrow therapeutic ratio, exemplified by digoxin. Unfortunately the potential toxicity of this

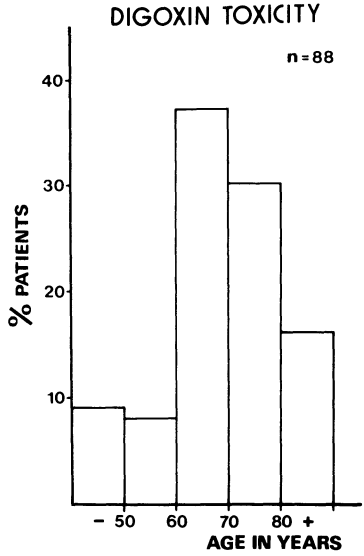

Figure 9.1 Histogram of patients experiencing digoxin toxicity in relation to age group. Data obtained from the Glasgow Drug Surveillance Programme, 1973–1976.

drug is realised to its full extent in the later decades (figure 9.1), and this implies that closer attention should be paid to the factors which determine overall response to the cardiac glycosides in the elderly. Figure 9.1 was constructed from data obtained by the Glasgow Drug Surveillance Programme over a period of three years (1973–1976) and represents the situation in general medical wards (Lawson, personal communication, 1977). As part of the more comprehensive Boston Collaborative Drug Surveillance Program, 2580 patients, with a mean age of 57 years, were monitored in Glasgow during this period. The 438 who received digoxin had a mean age of 67 years and 88 (20 per cent) of these patients experienced digoxin toxicity,

Table 9.1 Glasgow Drug Surveillance Programme, 1973–1976 : age and digoxin toxicity

Age range (yr)	Numbers monitored	Digoxin recipients	Cardiac toxicity	Other toxicity
<49	800	33 (4.1%)	3 (9.1%)	5 (15.2%)
50–59	486	71 (14.6%)	3 (4.2%)	4 (5.6%)
60–69	646	156 (24.1%)	14 (9.0%)	19 (12.2%)
70–79	473	122 (25.8%)	10 (8.2%)	16 (13.1%)
>80	175	56 (32.0%)	4 (7.1%)	10 (17.9%)

again with a mean age of 67 years. Further details are shown in table 9.1. It is obvious that the majority of patients receiving digoxin in hospital are over the age of 60 and that a considerable proportion (20 per cent) are liable to toxicity. Another recent study, designed specifically to assess the use of digoxin in a group of 42 elderly patients, revealed that approximately 1 in 3 was receiving an ideal dose (Whiting *et al.*, 1977). Plasma levels attained on previously established maintenance doses were compared with those generated by a computer program designed to tailor doses to suit individual requirements. Discrepancies between measured and computed plasma levels and between established and computed doses dictated withdrawal of the drug, or revision of dosage, in 26 patients (62 per cent) with obvious clinical benefit. Reduction in dosage abolished toxicity in 7 patients, while an increase in dosage resulted in alleviation of congestive cardiac failure in 2 patients and improved control of atrial fibrillation in another 7 patients. Withdrawal of the drug without detriment was possible in 6 patients who showed no evidence of cardiac failure and who were receiving inappropriately low doses of digoxin. These results, together with the drug surveillance data, suggest that there is room for improvement in the overall quality and safety of digoxin therapy in the elderly. This improvement will depend, to a large extent, on the application of basic clinical pharmacokinetic principles.

PHARMACOKINETICS

The interplay of absorption, distribution, metabolism and excretion determines the pharmacokinetics of digoxin. The crucial questions are (1) what effect does ageing have on these processes? and (2) to what extent are digoxin pharmacokinetics

altered? With the exception of the effect of impaired renal function on digoxin excretion (Bloom and Nelp, 1966; Halkin *et al.*, 1975), little is known of its pharmacokinetics in the elderly. Indirect evidence for alterations in various kinetic parameters has been presented (Aronson and Grahame-Smith, 1977; Caird and Kennedy, 1977), but little in the way of *direct* estimates has appeared. This is in contrast to the effort directed at younger subjects (particularly volunteers) where a precise definition of digoxin disposition has been arrived at (Sumner, Russell and Whiting, 1976). This provides a suitable basis for comparison as well as a set of guidelines upon which rational therapy can be based.

Multicompartmental analysis

Sumner *et al.* (1976), using 12α-[^{3}H]-digoxin and isotopic tracer techniques, analysed digoxin kinetics in terms of a three-compartment open model (figure 9.2).

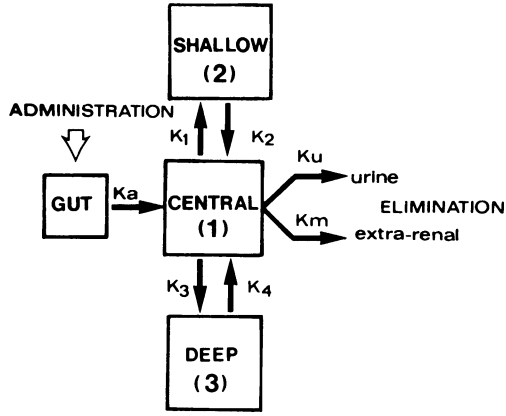

Figure 9.2 Open three compartment model for digoxin kinetics. All rate constants are first order. $K_1 - K_4$ are the rate constants describing uptake and release from the shallow and deep compartments. K_a is the absorption rate constant and K_u and K_m are the rate constants describing renal and extrarenal (biliary) elimination, respectively.

Thus, in parallel with the central compartment, which represents plasma water and those fluid spaces with which the free drug achieves rapid equilibrium, are two 'side' compartments, referred to as the shallow and deep compartments. These represent various body tissues, and while no real anatomical significance can be attributed to them, they denote tissues in which the myocardial receptors, sensitive to the action of digoxin, are located. K_a is the absorption rate constant, K_u the renal elimination rate constant and K_m the extrarenal elimination rate constant, largely accounted for by *biliary* excretion. K_1, K_2, K_3 and K_4 are the first-order rate constants which identify the rates at which digoxin diffuses into and out of the tissues and the rates of binding to, and dissociation from, drug receptors. The time-course of drug in the body is determined by the movement of digoxin between the various compartments and does not depend solely on absorption and elimination. An important rate-limiting step is the release of drug from the deep compartment, characterised by the rate constant K_4. Overall clearance from the body appears to depend largely

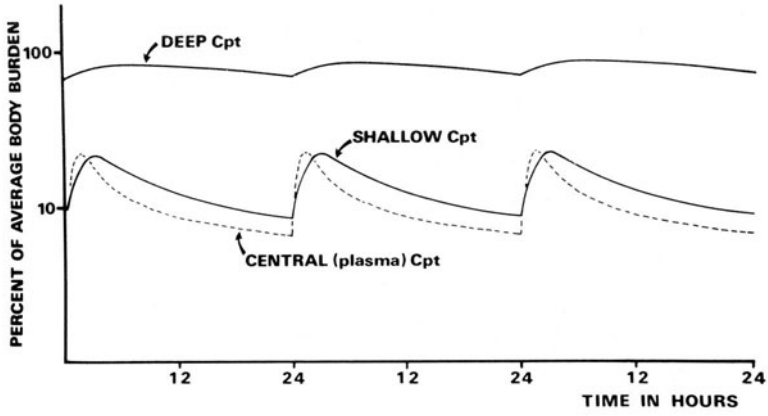

Figure 9.3 Simulated curves showing how the fraction of digoxin in the central (plasma), shallow and deep compartments varies with time during maintenance therapy : the dose is administered every 24 h.

on glomerular filtration, but a significant contribution is made by extrarenal routes, notably the bile. As glomerular filtration decreases with advancing age (Davies and Shock, 1950; Watkin and Shock, 1955), this biliary contribution assumes increasing importance.

One of the virtues of multicompartmental analysis is that it allows prediction of the time-course of digoxin levels in the shallow and deep compartments in relation to the central compartment. Figure 9.3 illustrates the changes in these compartments during steady state—that is during established maintenance therapy. These relationships are derived from analysis of plasma concentration/time data according to the tri-exponential equation

$$C_p^t = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$$

where C_p^t is the plasma concentration at any time t, and A, α, B, β and C, γ are obtained by suitable non-linear least squares fitting programs such as BMD X85 (BMD Biomedical Computer Programs, 1968) or NAG (Numerical Algorithms Group). The dimensions of the three-compartment model (volumes of distribution and K values) indicate that shallow compartment changes lag somewhat behind those of the central (plasma) compartment, with peak amounts occurring at approximately 3 h and 1.5 h, respectively, after oral administration (figure 9.3). Changes in the deep compartment are obviously quite remote from those in the other two compartments, with minimal fluctuation and a 'peak' at approximately 8 h. These changes are reflected by typical rate constants obtained in normal volunteers after intravenous administration of 12α-[^{3}H]-digoxin (100 μCi, 0.013 mg): $K_1 = 0.35\ h^{-1}$ $K_2 = 0.30\ h^{-1}$, $K_3 = 0.44\ h^{-1}$ and $K_4 = 0.06\ h^{-1}$. Distribution within the compartments is clearly dependent on the rate-constant ratios K_1/K_2 and K_3/K_4—that is 1.17 and 7.33, respectively. It is not known whether ageing *per se* alters digoxin distribution, but there is some evidence that renal impairment is associated with a decrease in the apparent volume of distribution (Reuning, Sams and Notari, 1973; Szefler and Jusko, 1973; Jusko, Szefler and Goldfarb, 1974). This may be related

to the generalised inhibition of membrane Na^+/K^+-transport ATPase which has been described in experimental uraemia in animals (Jelliffe, Buell and Kalaba, 1972) because it has been established that Na^+/K^+-transport ATPase represents a major tissue binding site of digoxin (Jusko and Weintraub, 1974). Whether or not the inevitable age-related decrease in renal function has a similar effect is not known, but the reduced volumes of distribution which have been indirectly determined in elderly patients (Aronson and Grahame-Smith, 1977; Caird and Kennedy, 1977) suggest that changes in renal function may play a part. It is also possible that reduction in the lean body mass is an important factor. A definitive statement on the determinants of digoxin distribution in elderly patients will depend on the derivation of rate-constant ratios (K_1/K_2, K_3/K_4) by the kind of pharmacokinetic analysis outlined above. The value of this approach was shown recently by Lawrence *et al.* (1977) in a study which defined important differences between the distribution of digoxin in patients with thyroid disease. The ratio of K_3/K_4 was significantly higher in hyperthyroid compared with hypothyroid patients, in keeping with previous observations that there is a significantly increased myocardial digoxin concentration in hyperthyroid animals (Doherty and Perkins, 1966; Bakoulas *et al.*, 1976). Again, this may well be related to changes in Na^+/K^+-ATPase digoxin binding sites (Lindsay and Parker, 1976).

Absorption

There is little or no evidence that the absorption of orally administered digoxin in the elderly differs from that in younger subjects. Minor age-related anatomical and functional changes in the gastrointestinal tract are probably not sufficiently important to alter absorption, which therefore remains dependent on the usual physicochemical and biopharmaceutical factors.

Protein binding

Although drug protein-binding relationships have been shown to alter with age (Hayes, Langman and Short, 1975*a*,*b*; Wallace, Whiting and Runcie, 1976), this is unlikely to have any bearing on the kinetics of digoxin because of its low degree of binding (Wallace and Whiting, 1974) and relatively high volume of distribution (of the order of 4–6 l/kg of lean body weight in the elderly).

Metabolism

Digoxin metabolism is of minor importance in determining overall kinetics, and any age-related changes will be of little consequence.

CLEARANCE

A great deal of interesting information can be obtained from the pharmacokinetic parameters discussed above, but the concept of clearance is much more clinically meaningful, as it can be readily used in dosage calculations. In general, the daily dose of digoxin is designed to replace the amount of drug eliminated by renal excretion and by all other routes, collectively described as 'extra-renal'. The renal clearance of digoxin, which is generally assumed to be very similar to that of creatinine (Bloom and Nelp, 1966), is determined largely by glomerular filtration. There is also evidence that the renal handling of digoxin involves other mecha-

nisms, including tubular reabsorption (Doherty, Ferrell and Towbin, 1969) and secretion (Marcus, 1972; Steiness, 1974), but the important determinant of renal clearance with respect to age is glomerular filtration. Extrarenal clearance is almost wholly accounted for by secretion into the bile and subsequent loss from the gut.

The amount of drug eliminated in 24 h ($\bar{D}$) can be derived from the equation

$$\bar{D} = \begin{matrix}\text{average plasma}\\ \text{level required}\\ \text{(ng/ml)}\end{matrix} \times \begin{matrix}\text{total}\\ \text{clearance}\\ \text{(ml/min)}\end{matrix} \times \frac{60 \times 24}{10^6} \text{ mg} \qquad (1)$$

If the average plasma concentration required is 1.5 ng/ml, then drug eliminated in 24 h

$$= 1.5 \times \text{total clearance} \times \frac{60 \times 24}{10^6} \text{ mg}$$

$$= 0.0021 \times \text{total clearance mg} \qquad (2)$$

Total clearance is the sum of renal and extrarenal clearances, and if it is assumed that digoxin renal clearance approximates to the creatinine clearance,

$$\bar{D} = 0.0021 \left(\begin{matrix}\text{creatinine}\\ \text{clearance}\end{matrix} + \begin{matrix}\text{extrarenal}\\ \text{clearance}\end{matrix}\right) \text{mg} \qquad (3)$$

The bioavailability (F) of the individual product is important in determining the amount absorbed, and the daily dose, D, is given by the formula

$$D = \frac{0.0021 \text{ (creatinine clearance + extrarenal clearance)}}{F} \qquad (4)$$

Notwithstanding the effects of renal disease *per se*, this formula assumes considerable importance in advancing age, where the inevitable deterioration in renal function leads to considerably reduced creatinine clearance levels– of the order of 30–40 ml/min (Whiting *et al.*, 1977)–despite maintenance of normal serum creatinine levels. Inspection of equation (4) also reveals that extrarenal clearance is of considerable importance in determining dosage requirements. Unlike renal clearance, which can be readily estimated on the basis of creatinine clearance, extrarenal clearance has no similar parallel and cannot, as yet, be estimated by any simple means. Its *direct* determination, as in a pharmacokinetic study, such as that described by Sumner *et al.* (1976), depends on measurement of total digoxin clearance (Cl_{tot}), defined as

$$\frac{100}{\begin{matrix}\text{area under plasma concn. curve (\% dose } l^{-1} \text{ min)}\\ \text{from } t = 0 \rightarrow \infty\end{matrix}} \qquad (5)$$

and renal clearance (Cl_r), defined as

$$\frac{\text{\% dose excreted in urine from } t = 0 \rightarrow t}{\begin{matrix}\text{Area under plasma concn. curve (\% dose } l^{-1} \text{ min)}\\ \text{from } t = 0 \rightarrow t\end{matrix}} \qquad (6)$$

Extra-renal clearance (Cl_{er}) is then determined by the equation

$$Cl_{er} = Cl_{tot} - Cl_r \qquad (7)$$

These authors found a value of 47 ± 7 ml/min (mean ± s.d.) in a group of four healthy volunteers, which implies that extrarenal clearance *normally* accounts for approximately 30 per cent of the total clearance. In advancing age, however, as creatinine clearance falls, total digoxin clearance may depend increasingly on extrarenal, biliary mechanisms. If, for example, creatinine clearance falls to 30 ml/min and extrarenal clearance is maintained at normal levels, it will then account for 60 per cent of the total clearance. Indeed, in uraemia the ultimate is reached when extrarenal clearance accounts for almost 100 per cent of the total clearance, and Jusko (1974) has reported values of approximately 50 ml/min in this situation, similar to the Cl_{er} values of 47 ml/min reported by Sumner *et al.* (1976).

Extrarenal clearance in the elderly

It is very important, however, to ask the question: Is the extrarenal clearance of digoxin influenced by age? Very little evidence has been presented to answer this, but it is obvious from the foregoing discussion and equation (4) that any associated

Table 9.2 Indirect estimation of extrarenal clearance : patient details

Patient number	Sex	Age (yr)	Weight (kg)	Digoxin dose (mg/day)	Mean steady-state plasma digoxin concentration (ng/ml)	Measured creatinine clearance (ml/min)	Estimated extrarenal clearances (ml/min)
1	F	64	62	0.25	1.6	69	9
2	F	68	59	0.25	2.1	50	9
3	F	68	58	0.25	1.9	30	36
4	F	68	48	0.25	1.2	37	67
5	F	70	43	0.125	1.4	20	25
6	F	73	50	0.25	2.1	40	20
7	F	74	69	0.25	1.4	48	41
8	F	74	57	0.25	1.3	40	56
9	F	75	39	0.125	1.8	30	5
10	F	85	54	0.125	1.5	26	16
11	M	70	65	0.25	1.2	61	43
12	M	70	51	0.25	1.6	63	15
13	M	82	63	0.25	1.9	45	21
14	F	70	53	0.1875	1.2	52	26
15	F	78	42	0.125*	1.2	22	23
16	M	74	51	0.25†	1.9	40	8
17	F	73	41	0.1875*	1.8	28	17
18	F	84	40	0.125	1.6	35	5
Mean ± s.d.	–	73.3 ± 5.8	52.5 ± 9.2	–	–	40.9 ± 14.2	24.5 ± 17.7

* Six days out of seven.
† Five days out of seven.

reduction in extrarenal clearance will again compromise dosage. No study in man has yet demonstrated an absolute reduction in metabolic capacity, but in elderly cardiac patients there may well be significant reductions in hepatic function and hepatic blood flow which would lead to reduced biliary clearance. Table 9.2 presents details of 18 of the elderly patients studied by Whiting *et al.* (1977) in whom

indirect calculation of extrarenal clearance was possible. Rearranging equation (4), if C represents the mean steady state plasma concentration,

$$Cl_{er} = \frac{F.D}{C} - Cl_r \tag{8}$$

i.e.
$$Cl_{er} = \frac{F.D}{C} - \text{creatinine clearance} \tag{9}$$

Assuming a bioavailability factor of 0.7, the mean extrarenal clearance in this group of elderly patients (age 73.5 ± 5.8 years) was 24.5 ± 17.7 ml/min (mean ± s.d.), which differs considerably from that of 'normal' values of 50 ml/min. The range of values, however, was quite large, from 5 to 67 ml/min. These results, together with extrarenal clearance values determined *directly* by pharmacokinetic analysis both in normal volunteers (Sumner *et al.*, 1976) and in patients with thyroid disease (Lawrence *et al.*, 1977) are plotted against age in figure 9.4. The correlation coefficient of 0.68 ($P < 0.001$) indicates a significant relationship between extrarenal clearance and age, but the relatively wide variation in results precludes any accurate prediction on the basis of age. Similar results have been presented by

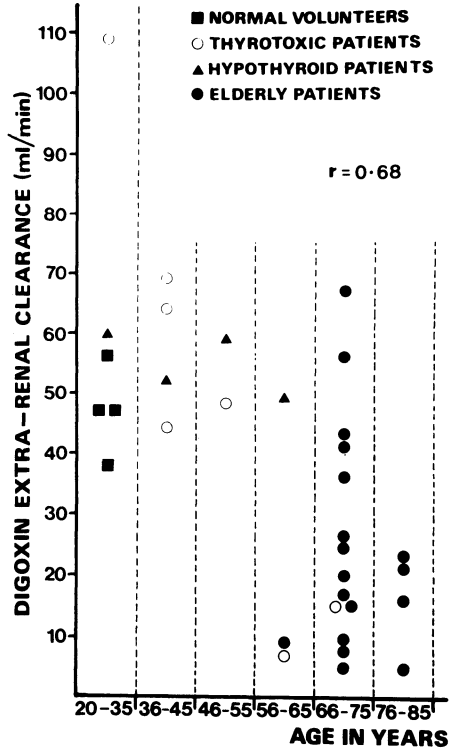

Figure 9.4 Variation of digoxin extrarenal clearance with age ($r = 0.68, P < 0.001$). Data sources : normal volunteers, Sumner *et al.* (1976); thyroid patients, Lawrence *et al.* (1977); elderly patients, Whiting *et al.* (1977).

Roberts and Caird (1976), who found even lower values of 18 ± 17 (s.d.) ml/min in a group of 20 elderly cardiac patients (age 73.5 ± 6.5, s.d., years). Again, a wide variation in the results was noted.

At the present time, it is impossible to correlate extrarenal clearance with any established measure of hepatic function. It must be accepted, therefore, that this component of the dosage equation (equation 4) can only be arrived at by approximation.

The variation inherent in extrarenal clearance will, however, have an important bearing on dosage at low creatinine clearance levels and this is illustrated in the nomogram presented in figure 9.5. An oblique line drawn at the appropriate creatinine clearance level intersects the extrarenal clearance curves at appropriate digoxin doses. These can be read off by drawing a vertical line from the point of intersection to the upper or lower dosage scales. The nomogram was based on the important assumptions that approximately 70 per cent of a dose would be absorbed and that an average steady-state digoxin level of 1.5 ng/ml would be therapeutically adequate. Variations in absorption could be compensated for by small lateral shifts in the dosage scale (reduced absorption, left shift; increased absorption, right shift).

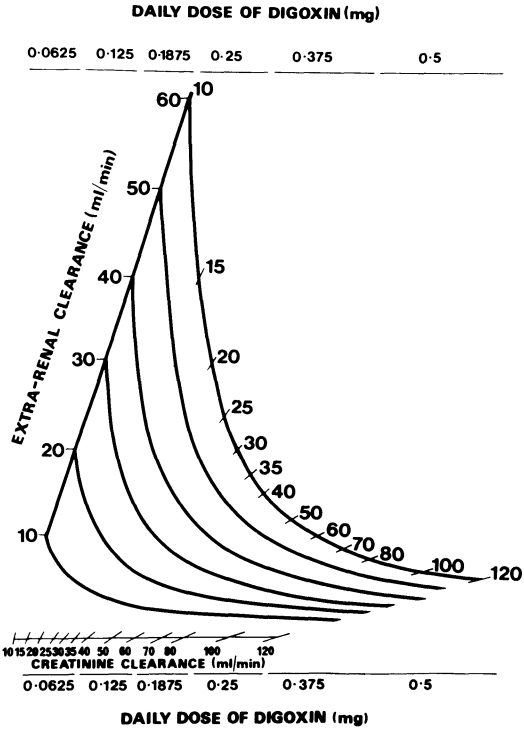

Figure 9.5 Extrarenal clearance nomogram. An oblique straight line is drawn at the appropriate creatinine clearance level to join a point on the 10–120 scale. From the points of intersection with the curved lines describing extrarenal clearance (10–60 scale), corresponding digoxin doses can be determined by drawing vertical lines which will intersect with the upper or lower dosage scales.

Using this nomogram, examples of dosage implications in elderly patients are shown in table 9.3.

It goes without saying that these considerations are only meant to illustrate some of the important principles which determine digoxin kinetics and dosage in the elderly. There is no substitute for careful clinical observation in the individual case,

Table 9.3 Extrarenal clearance nomogram : dosage implications in the elderly

Creatinine clearance (ml/min)	Dose range covered by creatinine clearance line (mg/day)	*Assumed* extrarenal clearance (ml/min)	'Safest bet' dose (mg/day)
25	0.1–0.25		0.125
		10–30	
40	0.15–0.3		0.1875

but adherence to basic clinical pharmacokinetic principles should improve the overall quality of treatment with this drug. Indeed, it has been shown that use of calculations similar to those presented above reduced the frequency of adverse reactions to the cardiac glycosides from 35 to 12 per cent (Jelliffe *et al.*, 1972). It is therefore reasonable to encourage this kind of approach when digoxin therapy is contemplated.

LOADING DOSES

A great deal has been written about 'digitalisation regimes', but this aspect of digoxin therapy can be simplified. A consideration of its pharmacokinetics shows quite clearly that high initial plasma concentrations associated with a single dose are relatively remote from sensitive cardiac tissues. The time-honoured practice of giving repeated small doses to achieve 'digitalisation'—or anorexia, nausea and vomiting—is not necessary. An initial total loading dose can be followed thereafter by the appropriate maintenance dose. Alternatively, the loading dose may be fractionated over the first 24 hours. Three 0.25 mg doses administered at 8 h intervals may be more suitable than 0.75 mg given as a single dose. This is of particular relevance to patients who may develop gastric intolerance to relatively large single doses—an event which is rather difficult to predict.

A good approximation of the loading dose can be made on the basis of the body weight or, more correctly, the lean body weight, since digoxin does not distribute well into fat tissue. The appropriate loading dose (L.D.) can be estimated on the basis of the desired average steady state plasma concentration C, and the apparent volume of distribution, V_d, thus

$$\text{L.D.} = C.V_d \qquad (10)$$

The loading dose must, however, be adjusted for incomplete gastrointestinal absorption:

$$\text{L.D.} = \frac{C.V_d}{F} \tag{11}$$

where F is the bioavailability of digoxin.

Assuming that (1) a concentration of 1.5 ng/ml will produce a satisfactory response, (2) the volume of distribution in the elderly is 4–6 l/kg of lean body weight and (3) 60–70 per cent of a dose of digoxin is absorbed, the loading dose for a 60 kg patient, determined by substitution in equation (11), is 0.75 mg.

PRESCRIBING AIDS

In conclusion, there is no doubt that rational treatment with digoxin depends to a large extent on the application of the kinetic principles outlined in this paper. Apart from extrarenal clearance–which at present can only be guessed at–creatinine clearance is the one important determinant of dosage which can be estimated fairly accurately. If not measured directly, it can be derived from the patient's serum

Table 9.4 Patient variables entered into programmable calculator (Texas Instruments SR-56 or SR-52) and display or printout

Entries:
Sex: male = 1; female = 0.8
Weight
Age
First serum creatinine (S_1)
Second serum creatinine (S_2)
Interval between S_1 and S_2 in days
Estimate of extrarenal clearance
Display or printout:
(1) Creatinine clearance (ml/min)
(2) Digoxin dose (mg/day)

creatinine concentration, lean body weight, age and sex, using the nomogram devised by Kampmann *et al.* (1974). Substitution into equation (4), with an appropriate estimate of extrarenal clearance, then gives a useful guide to maintenance dosage. Similar patient determinants have been incorporated into computer programs designed to calculate individual dosage schedules (Jelliffe *et al.*, 1972; Peck *et al.*, 1973; Sheiner *et al.*, 1975; Mawer, 1976) and into digoxin nomograms (Jelliffe and Brooker, 1974). It is also relatively easy to program small electronic pocket calculators to estimate creatinine clearance and digoxin dosage on the basis of equations presented by Kampmann *et al.* (1974) and Sumner *et al.* (1976). With specific reference to the problems of prescribing for elderly patients, such pro-

Table 9.5 Typical input/output data for digoxin program on Texas Instruments SR-56 or SR-52

	Patient 1	Patient 2
Input:		
Sex	1 (male)	0.8 (female)
Weight (kg)	65	50
Age (yr)	60	78
S_1 (μmol/l)	80	141
S_2 (μmol/l)	75	124
Interval (days)	7	7
Extrarenal clearance (ml/min)	40	15
Output:		
Creatinine clearance (ml/min)	85.8	23.6
Digoxin dose (mg/day)	0.375	0.125

grams may include a facility for varying extrarenal clearance values. Table 9.4 shows patient variables which can be entered into a program designed for the Texas Instruments SR-56 or SR-52 calculators and table 9.5 shows two typical sets of input/output data.

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10
The effects of ageing on the disposition of benzodiazepines in man

G. R. Wilkinson (Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, USA)

INTRODUCTION

The benzodiazepines are among the most widely prescribed drugs in the Western world (Greenblatt and Shader, 1974) and are used across the whole adult age range. However, epidemiological data indicate that this usage is not without its problems in the treatment of elderly patients. Central nervous system side effects, of sufficient magnitude to warrant discontinuation of the prescribed dosage regimen, were found to increase significantly with age after the chronic administration of either diazepam or chlordiazepoxide (Boston Collaborative Drug Surveillance Program, 1973). Similar results were found with flurazepam (Greenblatt, Allen and Shader, 1977). Additionally, the benzodiazepines constitute about 50 per cent of the prescription drugs associated with clinical problems of psychotropic origin in elderly patients (Freeman, see pp. 223–229). Such an apparent increase in drug sensitivity may be multifactorial in nature, but the changes involved may be generally classified into those which arise because of (1) alterations in the disposition of the drug within the body and/or (2) alterations in the pharmacodynamics of the pertinent drug-receptor interactions. While there is suggestive evidence that the latter may well occur during the ageing process, the precise definition of its role and importance in any observed change in drug response requires knowledge of any concurrent alterations in the drug's disposition. Accordingly, over the past several years we have investigated the effect of ageing in adult man on the pharmacokinetics of a number of commonly prescribed benzodiazepines.

DIAZEPAM

The most widely prescribed benzodiazepine is undoubtedly diazepam. In all species of animals studied, this drug is almost completely biotransformed to a variety of metabolites, several of which have a similar pharmacological profile to the parent drug (Randall *et al.*, 1961; Randall, Scheckel and Banzinger, 1965; Coutinho,

Cheripko and Carbone, 1970). In man the major route of metabolism is by dealkylation to desmethyldiazepam which is subsequently hydroxylated to form oxazepam. The latter, after glucuronide conjugation, is then excreted into the urine (Schwartz *et al.*, 1965; Schwartz and Postma, 1968; Marcucci *et al.*, 1968; de Silva, Koechlin and Bader, 1966).

During a study of the effects of liver disease on the disposition of diazepam the mean elimination half-life was found to be significantly different between two of the groups used as normal controls. Since a significant age difference existed between the two groups, the possibility existed that this factor might be involved. To investigate this hypothesis, a total of 33 healthy adults (27 men, 6 women) with normal laboratory values and ranging in age from 15 to 82 years were studied. In 20 individuals, diazepam (0.1 mg/kg) was administered by rapid intravenous injection into an antecubital vein. The remaining subjects received 10 mg diazepam orally in tablet form after an overnight fast. Heparinised venous blood samples were collected frequently over the first few hours and then every 12 h for 3–4 days. The plasma concentrations of diazepam and its metabolite, desmethyldiazepam, were determined by gas-liquid chromatography (Klotz *et al.*, 1975).

After both intravenous and oral administration, and subsequent to the distributive and absorptive phases, respectively, the plasma concentration of diazepam declined monoexponentially. The half-life of this process ($t_{1/2(\beta)}$) exhibited a striking linear age-dependency ranging from about 20 h at 20 years to about 90 h at 80 years (figure 10.1). The time-course of accumulation of desmethyldiazepam was also dependent upon the age of the subject. In the younger individuals, the metabolite was first detected after 1–2 h, increasing slowly to reach a shallow max-

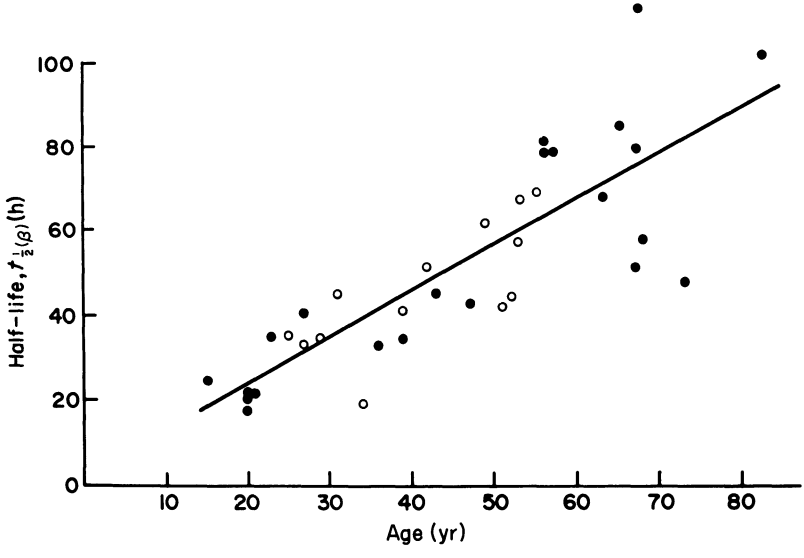

Figure 10.1 Correlation between the $t_{1/2(\beta)}$ of diazepam and age in 33 normal individuals. The solid symbols and open symbols indicate non-smokers and smokers (more than 20 cigarettes/day), respectively. After Klotz *et al.* (1975). Reproduced by permission of the Editor of the *Journal of Clinical Investigation.*

imum between 24 and 48 h, before gently declining. With increasing age, the metabolite was detected later and peak concentrations, which were lower, occurred later.

At first sight these observations might suggest an impairment in the metabolism of diazepam with age, similar to that reported for several other drugs. However, pharmacokinetic analysis of the data obtained after intravenous administration indicated that neither the total plasma nor blood clearance of diazepam was significantly related to age (figure 10.2). The majority of subjects aged between 20 and

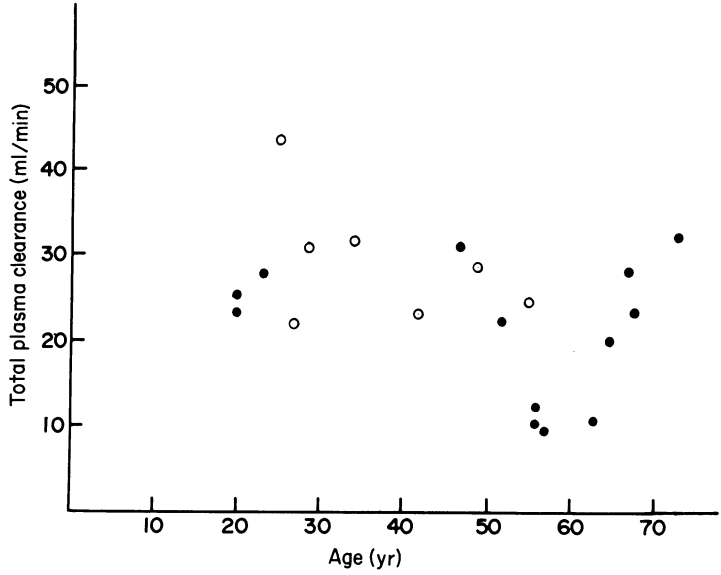

Figure 10.2 Correlation between total plasma clearance of diazepam and age in normal individuals. Symbols as in figure 10.1. After Klotz *et al.* (1975). Reproduced by permission of the Editor of the *Journal of Clinical Investigation.*

72 years exhibited plasma clearances in the range of 20–32 ml/min. Four individuals aged 56–63 years, however, had clearance values less than half that in the other subjects. Accordingly, the prolongation of $t_{1/2(\beta)}$ in the absence of any changes in clearance must result from an alteration in drug distribution. Examination of both the initial distribution space (V_1), into which diazepam distributes almost instantaneously after rapid intravenous injection, and the distribution volume at steady-state ($V_{d(ss)}$) indicated that this was indeed the case. Both parameters showed a significant linear age dependency, whether calculated as absolute volumes or corrected for body weight (figure 10.3). Interestingly, this altered distribution was not associated with any significant effect of age on the plasma protein-binding of diazepam or on its distribution between erythrocytes and plasma.

The Boston Collaborative Drug Surveillance Program survey (1973) reported that, in addition to age, the incidence of drowsiness after diazepam and chlordiazepoxide administration was also influenced by tobacco smoking–central nervous system depression being less common the greater the number of cigarettes smoked. Such an observation might be explained by the stimulation of the metabolism of

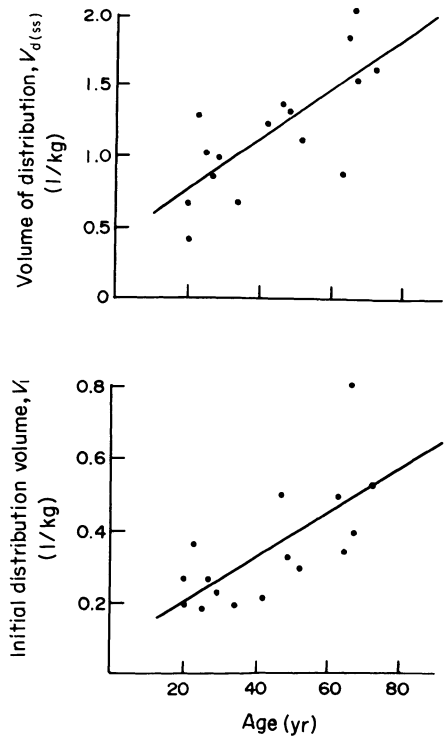

Figure 10.3 Correlation between the volumes of distribution of diazepam and age in normal individuals. After Klotz *et al.* (1975). Reproduced by permission of the Editor of the *Journal of Clinical Investigation.*

diazepam by one or more of the constituents of cigarette smoke. However, no obvious differences were detectable in either the plasma clearance or $t_{1/2(\beta)}$ of diazepam in individuals smoking more than 20 cigarettes/day compared with non-smokers (figures 10.1 and 10.2). Accordingly, it may be inferred that factors other than altered disposition are involved in the greater incidence of side effects of diazepam in non-smokers (Bhattacharya, Goldstein and Pfeiffer, 1970).

CHLORDIAZEPOXIDE

The structurally related benzodiazepine, chlordiazepoxide, has many chemical and pharmacological similarities to diazepam. It also undergoes similar metabolism, *N*-demethylation to desmethylchlordiazepoxide being the major route of biotransformation, followed by hydroxylation to demoxepam. In addition, reduction of the primary metabolite to desmethyldiazepam with subsequent conversion to oxazepam and its glucuronide, and formation of the 'opened lactam' of demoxepam has also been reported (Koechlin *et al.*, 1965; Schwartz and Postma, 1966, 1972; Dixon *et al.*, 1976). Several of the metabolites have psychopharmacological properties

similar to that of the parent drug (Randall *et al.*, 1965; Coutinho, Cheripko and Carbone, 1969; Coutinho *et al.*, 1971). The available epidemiological data also indicate little difference between diazepam and chlordiazepoxide in the increased incidence of side effects with increasing age (Boston Collaborative Drug Surveillance Program, 1973). These considerations clearly raised the question of whether the disposition of chlordiazepoxide, like that of diazepam, was affected by ageing.

To investigate this possibility, a study of similar design to that described for diazepam was performed (Roberts *et al.*, 1978). In this case, 25 male volunteers (non-smokers), ranging in age from 16 to 86 years were studied. Chlordiazepoxide (0.6 mg/kg) was administered rapidly by intravenous injection and appropriate heparinised blood samples were obtained to follow the biphasic decline of the unchanged drug as well as accumulation of desmethylchlordiazepoxide. Plasma concentrations of these were measured by radioimmunoassay (Dixon, Earley and Postma, 1975) and fluorimetry (Schwartz and Postma, 1966), respectively.

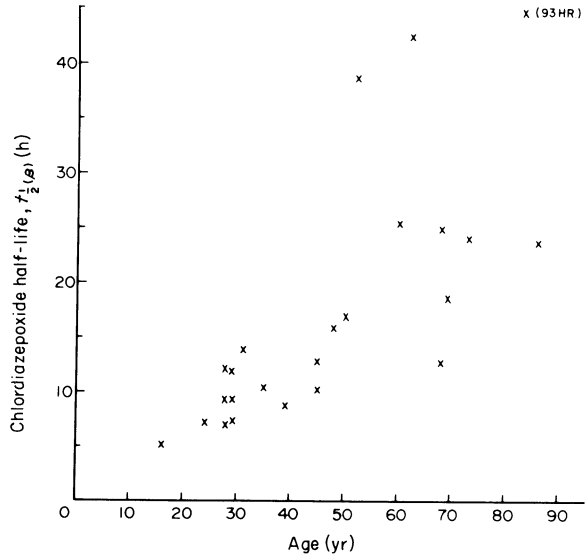

Figure 10.4 Relationship between the $t_{1/2(\beta)}$ of chlordiazepoxide and age in 25 normal, non-smoking, male subjects.

The initial results were very similar to those previously observed with diazepam. The post-distributive half-life ($t_{1/2(\beta)}$) showed a significant linear relationship with age, increasing from about 6 h at age 20 years to about 36 h at 80 years (figure 10.4). Additionally, the peak plasma levels of the primary metabolite, desmethylchlordiazepoxide, decreased significantly with age, but without alteration of the time at which these levels occurred. The explanation of the age-related prolongation of $t_{1/2\ (\beta)}$, however, differed from that with diazepam. In the case of chlordiazepoxide, the increase in $t_{1/2(\beta)}$ was associated with a highly significant reduction in

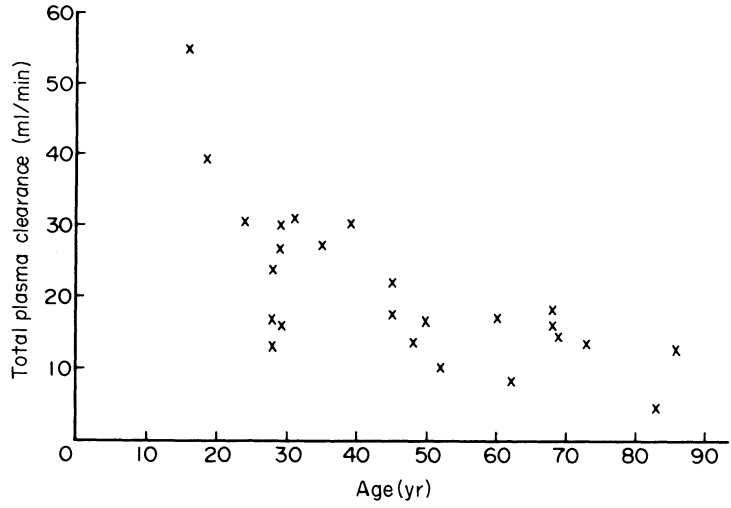

Figure 10.5 Relationship between the total plasma clearance of chlordiazepoxide and age in normal, non-smoking, male subjects.

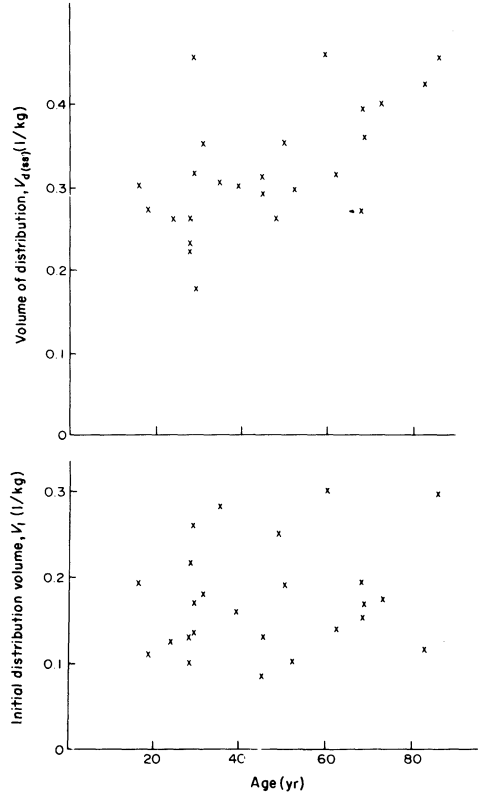

Figure 10.6 Relationship between the volumes of distribution of chlordiazepoxide and age in normal, non-smoking, male subjects.

total plasma clearance (figure 10.5) the plasma clearance decreasing, over the age range 20–80 years, from about 30 to 8 ml/min. No alteration in plasma binding or erythrocyte/plasma drug distribution occurred. In addition to the reduction in clearance, there was an increase in the distribution volume of chlordiazepoxide with ageing. In contrast to diazepam, however, this was limited to the steady state volume ($V_{d\ (ss)}$) and the initial distribution space (V_1) remained unaffected by age (figure 10.6). Thus, the increase in the $t_{1/2\,(\beta)}$ of chlordiazepoxide with ageing was attributable both to an altered distribution, of a similar magnitude to that observed with diazepam, and, in addition, to a significant reduction in the body's (and presumably the liver's) ability to remove the drug by metabolism. As a consequence, the change in $t_{1/2\,(\beta)}$ with ageing is more pronounced with chlordiazepoxide than diazepam–viz. a sixfold versus a fourfold increase over the age range 20–80 years.

LORAZEPAM

A common terminal metabolite of both diazepam and chlordiazepoxide is the active psychotropic drug oxazepam, which is predominantly eliminated from the body by conjugation with glucuronic acid and subsequent excretion in the urine (Walkenstein *et al.*, 1964; Sisenwine *et al.*, 1972). The greater polarity of this molecular relative to the parent compounds, coupled with the fact that its metabolism does not involve the mixed function oxidases, suggested that there might be differences in the effect of ageing on the disposition of this drug compared with the other benzodiazepines investigated. This hypothesis was supported by the finding, in age-matched normal volunteers serving as controls in a study of the effects of cirrhosis and acute viral hepatitis, that, following oral administration of oxazepam, there was no major difference between young and old individuals in the plasma concentration versus time profiles of either unchanged or conjugated drug (Shull *et al.*, 1976). However, since oxazepam could not be administered intravenously, it was not possible to define adequately the relevant pharmacokinetic parameters and any changes occurring in these. Accordingly, studies were undertaken with the structurally related drug, lorazepam, which is also extensively metabolised by glucuronide conjugation (Schillings, Schrader and Ruelius, 1971; Schillings *et al.*, 1975; Knowles, Comer and Ruelius, 1971; Greenblatt *et al.*, 1976), and which may be administered by the intravenous route.

To date, 10 male normal subjects, ranging in age from 15 to 74 years, have been investigated after rapid intravenous administration of lorazepam (2 mg) in a similar fashion to that previously described for the other benzodiazepines (Kraus *et al.*, 1978). A gas-liquid chromatographic method was used to determine unchanged lorazepam in the plasma and also after incubation of the plasma with β-glucuronidase. Over the age range studied, there were no apparent age-related changes in $t_{1/2\,(\beta)}$, total plasma clearance or distribution of lorazepam (figure 10.7). Furthermore, neither the plasma levels nor the urinary excretion of the conjugated metabolite showed significant alterations with age. In contrast to diazepam and chlordiazepoxide, there was considerable intersubject variability in the extent of plasma binding of lorazepam (90–95 per cent). While too few subjects have been studied to allow proper statistical analysis, there appeared to be a trend towards decreased binding with ageing. Significantly, however, even if the clearance and distribution parameters were corrected to take the binding into account–i.e. estimating the values in terms of unbound drug–there were still no discernible age-related changes.

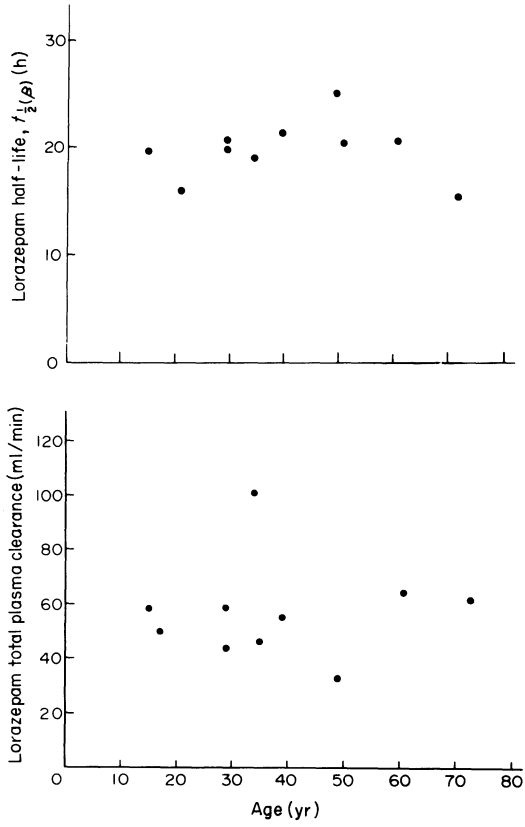

Figure 10.7 Relationships between $t_{1/2(\beta)}$ of lorazepam (upper curve) and its total plasma clearance (lower curve) and age in 10 normal, male subjects.

DISCUSSION

The increased responsiveness of the elderly and aged to the central nervous effects of both acute and chronic benzodiazepine administration appears to be now fairly clearly established. In addition to the epidemiological information previously quoted, more direct clinical studies have been recently performed. Thus, the individualised premedication dose and plasma level of diazepam necessary to achieve a uniform degree of depression prior to cardioversion was much reduced with age (Reidenberg *et al.*, 1978). Similarly, a single 10 mg oral dose of nitrazepam produced a greater number of errors during psychomotor testing in elderly subjects compared with younger individuals (Castleden *et al.*, 1977). Alterations in both disposition and pharmacodynamic aspects of the drugs' actions may be involved. However, the present studies demonstrate that, despite their close chemical and pharmacological properties, there does not appear to be any consistent pattern of change with ageing in the disposition of the benzodiazepines as a group. Depending on the particular

drug, ageing may (chlordiazepoxide) or may not (diazepam, lorazepam, oxazepam) lead to an impairment in the body's ability to remove the drug by metabolism in the liver. Similarly, the distribution of the drug may be increased (diazepam, chlordiazepoxide) or remain unaltered (lorazepam, oxazepam). Depending upon the magnitude of these changes, the elimination half-life ($t_{1/2\,(\beta)}$) may be prolonged as the age of the patient increases (diazepam, chlordiazepoxide). In spite of the limited data presently available, such a pattern of inconsistencies appears to be representative of the situation with regard to drug disposition and ageing (Triggs and Nation, 1975; Crooks, O'Malley and Stevenson, 1976). In the absence of any apparently unifying theory, such a situation will require that each drug of interest be individually investigated in relation to the effect of the ageing process on its disposition. Such studies will also require parallel pharmacodynamic investigations and an assessment of the overall clinical significance of any alterations, whether pharmacokinetic or pharmacodynamic in origin.

With few exceptions, the plasma clearances of those drugs studied are such that their values reflect drug-metabolising enzyme activity (intrinsic clearance) rather than liver blood flow, two of the determinants of hepatic clearance (Wilkinson and Shand, 1975). The third physiological determinant, binding to the blood constituents, may be altered with ageing (see Crooks *et al.*, 1976) but in the case of the benzodiazepines this does not appear to play any significant role. Expression of clearance values in terms of unbound drug can, however, correct to a certain extent for this factor. The intriguing question that is emerging in general, and for the benzodiazepines specifically, is why ageing leads to a reduction in metabolism of certain drugs but not of others. Do the findings with diazepam and chlordiazepoxide, relative to those with lorazepam and oxazepam, indicate that certain broad metabolic pathways—for example, glucuronidation—are more resistant to the ageing process than perhaps those reactions involving the mixed function oxidases? Even within such a classification there are clearly individual differences in sensitivity, since the *N*-demethylation of chlordiazepoxide is significantly affected by ageing but that of diazepam is not. The resolution of these differences may well provide valuable basic insights into the molecular aspects of the complicated processes involved in drug metabolism.

Similar puzzling differences also seem to exist with respect to the effects of ageing on drug distribution. Even after correction for changes, if any, in plasma protein-binding and in body weight, the size of the apparent volume of distribution of certain drugs (including some of the benzodiazepines) increases quite significantly as the individual ages. The fact that these changes are sometimes reflected in V_1 as well as $V_{d\,(ss)}$ probably has little physiological significance, since these volumes are purely pharmacokinetic in definition, and the inclusion of a specific organ/tissue in V_1 is highly dependent on the characteristics of the drug under consideration. The factors controlling quantitative drug distribution are complex. The rate of drug uptake into tissues depends on several parameters, including the rate of tissue perfusion with blood, the mass of tissue and the partition characteristics of the drug between blood and tissue, the latter involving such factors as membrane permeability, intracellular and extracellular pH, as well as plasma and tissue drug binding. Cardiac output and tissue perfusion are both reduced with age (Bender, 1965), but drug distributional changes due to these alterations may well be offset by changes in the tissue distribution of the cardiac output as well as by the decreases in tissue and lean body mass (Bender, 1964; Bender, 1967). Certainly, the relative increase in

body fat with ageing may well contribute to the increased volume of distribution of lipophilic drugs. However, as in the case of diazepam, the fact that distributional changes are observable almost immediately after intravenous administration suggests that other factors may well be involved. This probability is also supported by the fact that ageing in these cases leads to an increase in distribution which is contrary to expectations based on the age-related alterations in cardiovascular function. Speculatively, the factors involved might include altered tissue permeability in addition to quantitative and perhaps qualitative changes in tissue binding of the drug. However, more precise identification of the biological mechanisms and the organs involved requires additional investigation, as does the reason for the differences observed between such closely related drugs as individual benzodiazepines.

Apart from such basic questions, the present findings are clearly relevant to the use of the benzodiazepines in the elderly. Fortunately, the benzodiazepines have rather large therapeutic margins, but nevertheless the nature of both their toxicity and the population under treatment would suggest that all attempts be made to optimise the drug regimen. The major problem in such predictions is that, at the present time, no quantitative data are available regarding possible age-related alteration in the sensitivity of the central nervous system receptors. Without such information, alterations in drug dosage based only on pharmacokinetic considerations are of questionable value. For example, it is not unreasonable to assume that the depressant effect of diazepam is associated with a particular plasma level. When diazepam is used acutely as in premedication, therefore, the increase in distribution with ageing should require a larger dose of drug to attain the effective plasma concentration. In clinical practice a significantly smaller dose is required (Reidenberg *et al.*, 1978), indicating that pharmacodynamic factors completely override such pharmacokinetic considerations. Any changes in drug distribution are of lesser concern in the chronic dosing situation, where the steady state plasma levels are determined largely by the total plasma clearance. When the latter is unchanged, then extrapolation of the single-dose findings to chronic intermittent dosing would suggest that there would be no significant alteration in the average steady state plasma level. If, as is the case with diazepam and chlordiazepoxide, a distributional change leads to a prolongation in the half-life, this leads to a blunting effect on the fluctuations between the peak and trough drug levels at the beginning and end of each dosing interval, respectively. In addition, steady state will be achieved more slowly in the elderly patient than in the younger individual, since this condition is achieved in approximately four times the elimination half-life ($t_{1/2\,(\beta)}$). However, such considerations do not take into account the formation and elimination of metabolites with pharmacological activity similar to or greater than that of the parent benzodiazepine. Little pharmacokinetic information exists concerning these substances *per se*, especially with regard to their accumulation, the influence of ageing upon this and the effect that metabolite accumulation may have upon the disposition of the parent drug (Klotz, Antonin and Bieck, 1976). Such considerations suggest that the use of benzodiazepines, such as oxazepam and lorazepam, which are biotransformed to inactive metabolites, might possibly have certain advantages over those drugs which form a number of active metabolites. The fact that ageing appears to cause minimal change in the disposition of the former makes this approach additionally attractive. However, well-controlled clinical studies will be required to test this hypothesis, and, in the meantime, the clinical use of a benzodiazepine must still be guided predominantly by the response of the patient. An appreciation of

the general age-related trend in the disposition of the drug in question may nevertheless be helpful.

The studies described with the benzodiazepines also raise some points of general importance with regard to the effect of ageing upon drug disposition. The most critical aspect of such studies concerns the assessment of age. Ideally, this should correspond to the biological age of the individual, but, since the ageing process apparently proceeds at different rates according to the particular system under investigation, how may this be assessed? Perhaps the use of marker compound(s) and normalisation of the disposition of a particular drug to this might be of value. However, in the absence of any better determinant, chronological age is the only indicator that is available. Not unexpectedly, in the light of the known differences in rates of biological ageing, use of this parameter frequently leads to the observation that interindividual variability in disposition characteristics increases with ageing.

Most drug disposition/ageing studies have been performed by comparison of pharmacokinetic parameters in groups of young and old individuals. While such an approach is useful in determining whether a significant difference exists across the age range studied, it does not answer the more important question of how ageing, as a continuous variable, influences pharmacokinetics. For this, longitudinal studies are required, and again problems exist in design and interpretation of such investigations. Most studies to date, including those in animals, have for good reasons approached such a study by investigating a group of different individuals whose ages are within the range of interest. Thus, in addition to the problem of chronological versus biological ageing previously mentioned, interpretation of the findings with respect to the effects of ageing *per se* are complicated by all of the other factors contributing to the wide interindividual variability in drug disposition which exists. Longitudinal studies in individual subjects throughout their lifespan clearly have advantages in this regard. However, the difficulties of undertaking such studies probably precludes their widespread application, and even so not all of the problems concerned are overcome by this approach. It is, therefore, likely that the dependence on studies utilising different subjects within prescribed age ranges will continue. In that case, it is important to recognise that the role of the ageing process in any observed changes may be associative rather than directly causative. For example, a recent study of the effect of ageing on the intrinsic clearance of propranolol suggested that this assessment of drug-metabolising activity decreased significantly over the age range 21–73 years (Vestal *et al.*, unpublished data). Further analysis demonstrated, however, that this trend was only present in cigarette smokers and in non-smokers there was no change in metabolism with ageing. It is conceivable that smoking, either directly or indirectly (as an indicator perhaps of exposure to other environmental agents), is reflecting an age-related ability to induce propranolol's metabolism rather than an effect of the ageing process on the metabolic process itself. Such an interpretation would be consistent with the recent findings on enzyme induction of Stevenson *et al.* (see pp. 51–63). Irrespective of this, such a finding emphasises the great difficulties which exist in obtaining adequately matched individuals across a wide age range in order to determine whether an effect is solely due to ageing. It almost verges on the impossible, especially when it is realised that the elderly are likely to be considerably removed from 'normality' as defined by any criteria for the usual young volunteer. Such unrecognised differences in patient populations may well account for the discrepancies that are sometimes observed by different investigators. For example, the 'volume of distribution'

of nitrazepam after a single oral dose has been reported to be greater in older individuals than young (Iisalo, Kangas and Ruikka, 1978), in a fashion consistent with findings with diazepam and chlordiazepoxide. However, Castleden *et al.* (1976) were unable to find any significant differences in plasma levels of this drug after a single 10 mg oral dose to a young and old group of subjects. Finally, with regard to longitudinal studies, the danger of over-interpretation, especially from a statistical standpoint, must be recognised particularly as it reflects on any given individual patient. The observed data may well be described by linear regression but there is no *a priori* reason for this to be true for the underlying biological mechanism or for the trend to continue outside the age range studied. For example, despite the satisfying apparent linear decrease in the plasma clearance of chlordiazepoxide with ageing (figure 10.5), is there not a suggestion of a hyperbolic relationship? Likewise, are the few individuals whose plasma clearance of diazepam is much smaller than the majority of subjects (figure 10.2) representative of a 'biologically older' subgroup, and would all individuals eventually reach this state? Perhaps only longitudinal studies in selected individuals can answer such questions.

The increasing size of the geriatric population, the large number of medications received by the elderly and the paucity of appropriate quantitative information upon overall drug responsiveness and controlling factors at any age clearly indicate that considerable effort will be required before the age of the patient can be used in any rational fashion to guide the individualisation of drug therapy. The ageing process undoubtedly affects the pharmacodynamic aspects of any response, but before this can be adequately defined, the pharmacokinetics of the drug and any changes with age must be understood. It is also important in such future studies that more consideration be given to the actual way in which a particular drug is used in practice, and greater attempts made to separate significance from importance. The benzodiazepines will constitute a particularly challenging group of drugs in these respects.

ACKNOWLEDGEMENTS

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11

Pharmacokinetics of lignocaine and chlormethiazole in the elderly; with some preliminary observations on other drugs

E. J. Triggs (Department of Pharmacy, University of Sydney, Sydney, Australia)

INTRODUCTION

During the transition from middle to old age, important physiological changes occur, and with increase in age disease becomes more prevalent. Ageing and its associated pathophysiological changes have been shown to alter responsiveness to drugs, as a result of either altered pharmacokinetics (for review, see Crooks, O'Malley and Stevenson, 1976), or altered pharmacodynamics (Castleden *et al.*, 1977).

Examination of the pharmacokinetic disposition of chlormethiazole and lignocaine in the aged was the intention of the major portion of the work described here. These drugs were selected for two main reasons. Firstly, they are both used quite extensively in the elderly and no information was available concerning their pharmacokinetic disposition in this subject group. Secondly, they both appear to be cleared predominantly by the liver, but with different efficiencies, i.e. extraction ratios (Shand, Kornhauser and Wilkinson, 1975; Nation *et al.*, 1976).

Chlormethiazole is a sedative and hypnotic agent which possesses a marked anticonvulsant effect. It is used in treating sleep disturbances and states of confusion in geriatric subjects, delirium tremens and alcohol withdrawal states, status epilepticus and pre-eclampsia. Lignocaine is an anilide-type local anaesthetic agent used extensively in a coronary-care setting for the prevention and treatment of cardiac arrhythmias in patients who are usually middle-aged or elderly.

Preliminary observations are also reported with L-dopa and ampicillin as part of a study to ascertain whether there is any major alteration in the absorption of drugs (active and passive transport, respectively) from the gastrointestinal tract of elderly subjects.

MATERIALS AND METHODS

Lignocaine

Six elderly male subjects (residents of long stay wards, aged 61–71, mean 65 years) were selected for the study. Only those subjects whose blood chemistry was normal were included. In addition, the elderly subjects underwent a physical examination, were free of congestive heart failure and ischaemic heart disease, and were not taking any medication. Four young male subjects (aged 22–26, mean 24 years) acted as control subjects.

Each subject received lignocaine hydrochloride (50 mg, Xylocaine 0.5 per cent Plain, Astra) injected over 1 min via an antecubital vein. Venous blood samples (6 ml) were collected before injection of the lignocaine dose and then at regular intervals for 5–6 h. Blood samples were centrifuged to obtain plasma, which was then stored at −20° until assayed. Urine from each subject was collected for the 24 h prior to drug administration and for 24 h after dosing. Urine pH was not controlled.

Lignocaine in plasma and lignocaine and its metabolites in urine, monoethylglycinexylidide (MEGX), total (free and conjugated) 4-hydroxyxylidide and total xylidine, were analysed as described previously (Nation, Triggs and Selig, 1977*a*).

Graphical analysis of the logarithm of the lignocaine plasma concentration versus time data revealed polyexponential behaviour which appeared to be either bi-exponential (equation 1) or tri-exponential (equation 2) in nature:

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t} \quad (2)$$

where C_p is the plasma drug concentration at time t, A, B and C are the intercepts with the ordinate and α, β and γ are hybrid rate constants. Equations (1) and (2) were fitted in turn to the experimental plasma drug concentration versus time data using the non-linear least squares regression program NONLIN (Metzler, 1969). For the computer analysis, each point was weighted according to the reciprocal of the square of the concentration normalised to the number of data points. The goodness of fit of the equations to the experimental data for each subject was assessed using the criteria suggested by Boxenbaum, Riegelman and Elashoff (1974). The coefficients and exponents of the appropriate polyexponential equation were used to calculate estimates of the initial dilution space (V), the apparent volume of distribution at pseudo-distribution equilibrium ($V_{d(\beta)}$), the volume of distribution at steady-state, ($V_{d(ss)}$), the terminal half-life ($t_{1/2\,(\beta)}$) and the plasma clearance (V_{Cl}) (Gibaldi and Perrier, 1975).

The non-parametric Mann-Whitney U test (Goldstein, 1964) was used when statistical comparisons were made between the data for the young and aged subjects.

Chlormethiazole

Intravenous infusion study

Eight elderly subjects (6 females, 2 males) aged 69–91 (mean 75.3) years were selected for the study. Criteria for subject selection were as previously described

for lignocaine. Each subject received a constant-rate intravenous infusion via the cephalic vein of 1.2 g of chlormethiazole ethanedisulphonate (Heminevrin 0.8 per cent, Astra) over a period of approximately 90 min. A paediatric microdrip set (Metriset, McGaw) was used to meter the dose and infusion rate. All subjects were supine during the infusion and for at least 1 h thereafter. Venous blood samples (10 ml) were taken through a catheter placed in the opposite arm to that of the infusion site and collected in heparinised tubes. Blood samples were collected before the start of the infusion, at 30 and 60 min during the infusion, at cessation of the infusion and then at intervals to 22 h post-infusion. The blood/plasma concentration ratio (λ) of chlormethiazole was determined directly from a 0.67 h post-infusion sample obtained from four of the subjects. Plasma was separated by centrifugation and stored at -20° until assayed by a gas-liquid chromatographic procedure (Nation *et al.*, 1976).

Post-infusion plasma concentration versus time curves were fitted to the appropriate polyexponential equations by NONLIN as previously described (Nation *et al.*, 1976). Pharmacokinetic parameters were calculated as for lignocaine with appropriate correction for the infusion time (Loo and Riegelman, 1970).

The chlormethiazole pharmacokinetic data reported earlier for healthy young adults (Moore *et al.*, 1975*b*) were used when statistical comparisons were made between the data for young adults and aged subjects, respectively.

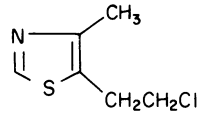
Oral study

Three elderly subjects (1 female, 2 males, aged 68–71, mean 70 years) participated in the study. Criteria for selection were as for the lignocaine study. Three young subjects (1 female, 2 males, aged 25–28, mean 27 years) were also investigated. All subjects received a single oral dose equivalent to 600 mg of chlormethiazole ethanedisulphonate as two capsules administered with 200 ml of water. Food was withheld for at least 3 h prior to and subsequent to drug dosing. Blood samples (5 ml) were collected through an indwelling cannula placed in an antecubital vein and taken into heparinised collection tubes. Blood was taken before drug administration and then at intervals thereafter for 9–10 h for the elderly subjects and 20–23 h for the young subjects. Samples were centrifuged to obtain plasma, which was then stored at -20° until assayed. Chlormethiazole (CTZ) and two of its known metabolites, 5-acetyl-4-methylthiazole (AMT) and 5-(1-hydroxyethyl)-4-methylthiazole (HEMT) (see figure 11.1), were assayed by a gas chromatographic-mass spectrometric procedure (Nation *et al.*, 1977*b*).

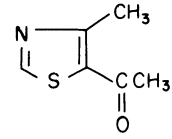
The plasma half-life values ($t_{1/2\,(\beta)}$) were estimated by linear regression analysis of the terminal phase of the logarithm of the plasma concentration versus time curves. The area under the CTZ curve (AUC_0^T) from the time of drug administration to the time of collection of the last plasma sample (T) was calculated for each subject by the trapezoidal rule. The total area under the curve (AUC_0^{∞}) was then calculated from equation (3):

$$AUC_0^{\infty} = AUC_0^T + \frac{C_T . t_{1/2\,(\beta)}}{0.693} \tag{3}$$

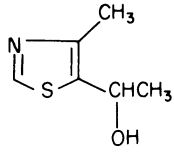
where C_T represents the plasma concentration of CTZ at time T and $t_{1/2(\beta)}$ was the half-life of CTZ for that subject. The apparent oral clearance (Cl_0) of CTZ was estimated from the ratio of the administered dose to AUC_0^{∞} (Wilkinson and Shand, 1975).



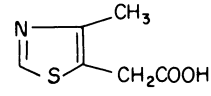
5-(2-Chloroethyl)-4-methylthiazole
chlormethiazole (CTZ)



5-Acetyl-4-methylthiazole
(AMT)



5-(1-Hydroxyethyl)-4-methylthiazole
(HEMT)



4-Methyl-5-thiazoleacetic
acid (MTAA)

Figure 11.1 Chemical structures of chlormethiazole (CTZ) and two of its known metabolites (AMT and HEMT) in human subjects. A third metabolite (MTAA) is also included.

Approximately 12-15 ml of venous blood were taken from each of 6 young (1 female, 5 males, age 25-28, mean 26, years) and 6 elderly (3 females, 3 males, age 71-86, mean 76 years) subjects who were apparently healthy. None of the subjects were currently receiving drug medication. The blood was collected in heparinised tubes and spiked with a concentrated aqueous solution of CTZ (10 μl, 24 μg/10 μl) such that the final blood concentration was either 2 μg/ml (4 young, 6 elderly subjects) or 5.5 μg/ml (2 young subjects). After incubation for 1 h at room temperature an aliquot (0.5 ml) of whole blood was retained. The remaining blood was centrifuged and subsequently 0.5 ml of the resulting plasma withdrawn. The plasma binding of CTZ was then determined using the remaining plasma and an ultrafiltration technique (Thomas *et al.*, 1976) at 37°C. A gas chromatographic method (Nation *et al.*, 1976) was used to determine the CTZ content of the retained blood, plasma and ultrafiltrate samples. The fraction of free drug in plasma (*FFP*), the blood/plasma concentration ratio (λ), the ratio of the apparent concentration of drug in erythrocytes to the plasma concentration (C_{bc}/C_p), and the fractions of drug in whole blood distributed to plasma water (*FPW*), plasma proteins (*FPP*) and blood cells (*FBC*) were determined (Nation *et al.*, 1977*b*).

L-dopa

Two elderly female Parkinsonian patients (aged 84 and 74 years) and two young healthy unmedicated normal subjects (aged 22 and 26 years) have been studied to date. Subjects were fasted overnight and were given, in the case of the young subjects, an oral dose of 300 mg of L-dopa (3 x 100 mg Larodopa tablets, Roche) or, in the case of the elderly patients, their regular morning dose (600 mg and 300 mg, respectively, as 100 mg tablets) with 200 ml of water. Food was withheld for 3 h subsequent to drug dosing. Blood samples (20 ml 'blank', otherwise 10 ml) were

collected through an indwelling venous cannula or by venepuncture into heparinised collection tubes at frequent intervals for 6 h. Samples were centrifuged to obtain plasma and stored at −20°C until assayed by a spectrofluorimetric procedure (Curzon, Bharati and Trigwell, 1972; Geissbuehler, 1973).

Ampicillin

Two elderly drug-free patients (aged 71 and 68 years) and two young healthy unmedicated normal subjects (aged 22 and 34 years) have been investigated to date. Details for the study design were similar to those described for L-dopa with the dose of ampicillin being 500 mg (one capsule as the trihydrate, Austrapen C.S.L.), and blood sampling continued for 8 h after drug administration. Ampicillin blood levels were assayed by the procedure of Yu, Nightingale and Flanagan (1977).

RESULTS

Lignocaine

The bi-exponential equation (1) was found to fit the data adequately for five of the elderly subjects and all of the young subjects. However, a tri-exponential equation was necessary to obtain a good fit to the data of the remaining aged subject (A.S.). The plasma concentrations of lignocaine following the intravenous bolus dose to one of the healthy young (J.W.) and one of the healthy aged subjects (C.P.) are plotted as a function of time in figure 11.2. Apart from the difference in half-life between these two particular subjects, it is clear that the log linear terminal portion of the curve is reached after a shorter time in the young subject compared with the elderly subject. This more rapid attainment of pseudo-distribution equilibrium in the young subjects relative to the aged subjects was a consistent trend throughout the study.

A number of pharmacokinetic parameters are presented in table 11.1 together with the age and body weights of the subjects in both age groups. The initial dilution space (V) was not significantly different between the young (0.330 ± 0.073 l/kg, mean ± s.d.) and elderly (0.354 ± 0.160 l/kg) subjects. This was not the case, however, for the other volume terms considered. Both $V_{d(\beta)}$ and $V_{d(ss)}$ were greater ($P < 0.05$) in the older age group. The mean value of $V_{d(\beta)}$ in the young group was 0.895 ± 0.276 l/kg compared with 1.586 ± 0.600 l/kg for the group of aged subjects, while the mean values of $V_{d(ss)}$ were 0.652 ± 0.167 l/kg and 1.128 ± 0.370 l/kg for the young and aged subjects, respectively. The half-life ($t_{1/2(\beta)}$) of lignocaine was prolonged ($P < 0.05$) in the aged subjects (139.60 ± 64.09 min) relative to the young individuals (80.58 ± 9.40 min). The plasma clearance of lignocaine was not different either in absolute terms (young, 543.1 ± 124.8 ml/min; elderly, 556.0 ± 150.0 ml/min) or adjusted for the body weight of the subjects (young, 7.60 ± 1.59 ml min^{-1} kg^{-1}; elderly, 8.12 ± 1.92 ml min^{-1} kg^{-1}). The value of λ for lignocaine was similar for both groups.

The percentages of the dose recovered in the 24 h urine as lignocaine, MEGX and total xylidine were not significantly different between the two age groups. The recovery of total 4-hydroxyxylidine in the same collection period, however, was less ($P < 0.05$) in the aged subjects (46.75 ± 11.22 per cent) than in the young subjects (62.74 ± 9.01 per cent).

Table 11.1 Pharmacokinetic details for bolus doses of lignocaine in young and elderly subjects*

Subject code	Age (yr)	Weight (kg)	V† (l/kg)	$V_{d(\beta)}$† (l/kg)	$V_{d(ss)}$† (l/kg)	$t_{1/2(\beta)}$† (min)	$\overline{V}_{Cl}$† (ml/min)	V_{Cl}† (ml min^{-1} kg^{-1})
Young								
J.W.	24	73	0.254	0.657	0.447	71.67	464.8	6.35
D.M.	25	73	0.369	1.277	0.848	93.27	689.7	9.49
G.W.	22	67	0.286	0.734	0.617	81.63	417.3	6.23
R.N.	26	72	0.412	0.912	0.696	75.74	600.5	8.34
Mean±s.d.			0.330	0.895	0.652	80.58	543.1	7.60
			±0.073	±0.276	±0.167	±9.40	±124.8	±1.59
Elderly								
E.L.	66	69	0.276	1.893	1.552	113.61	791.0	11.55
J.A.	61	74	0.246	1.170	0.709	102.67	582.9	7.90
C.P.	71	67	0.433	1.283	0.820	111.42	533.9	7.98
J.M.	62	55	0.421	1.003	0.863	116.28	331.2	5.98
A.S.	63	73	0.153	2.636	1.460	269.65	496.5	6.77
W.C.	67	70	0.597	1.530	1.361	123.97	600.4	8.55
Mean ±s.d.			0.354	1.586	1.128	139.60	556.0	8.12
			±0.160	±0.600	±0.370	±64.09	±150.0	±1.92
Significance level‡			N.S.	$P<0.05$	$P<0.05$	$P< 0.05$	N.S.	N.S.

*After Nation *et al.* (1977*a*). Reproduced by permission of the *British Journal of Clinical Pharmacology.*

†V = initial dilution space; $V_{d(\beta)}$ = apparent volume of distribution at pseudo-distribution equilibrium; $V_{d(ss)}$ = volume of distribution at steady state; $t_{1/2(\beta)}$ = terminal phase half-life; $\overline{V}_{Cl}$ = plasma clearance.

‡Statistical analysis was carried out using Mann–Whitney U test.
N.S. = not significant ($P > 0.05$).

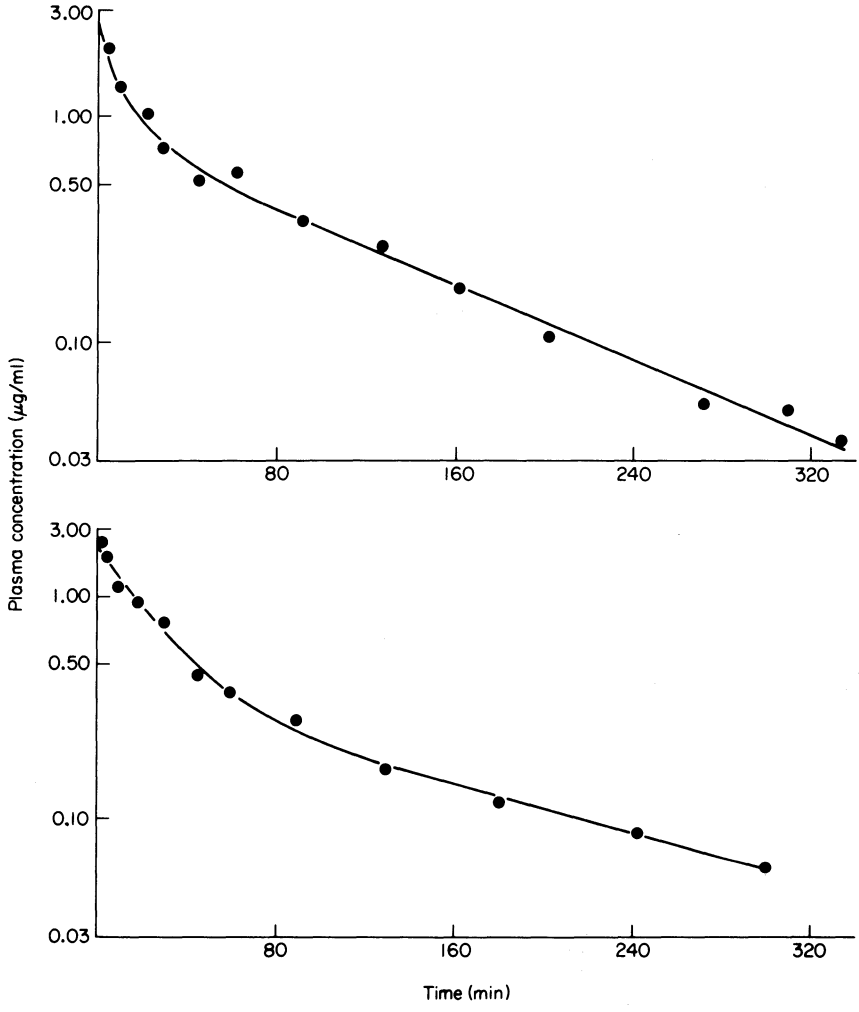


Figure 11.2 Plasma concentration versus time profiles of lignocaine after a bolus intravenous dose of lignocaine (50 mg) to young subject J. W. (top) and elderly subject C. P. (bottom). The line through the data points represents the computer generated bi-exponential fit. After Nation *et al.* (1977*a*). Reproduced by permission of the *British Journal of Clinical Pharmacology*.

Chlormethiazole

Intravenous infusion study

Post-infusion plasma concentration versus time curves of CTZ for three of the aged subjects showed bi-exponential behaviour, while a tri-exponential equation was necessary to describe data for the remaining four elderly subjects. The model-independent pharmacokinetic parameters, plasma clearance, half-life and $V_{d(\beta)}$, for CTZ

Table 11.2 Model-independent pharmacokinetic parameters for intravenously administered chlormethiazole in eight elderly subjects together with mean data previously reported for young adult subjects (Moore *et al.*, 1975*a*)*

	Age (yr)	Chlormethiazole plasma clearance (ml min^{-1} kg^{-1})	Chlormethiazole terminal phase half-life (h)	$V_{d(\beta)}$ (l/kg)
Elderly subjects				
D.W.	76	14.92	11.23	14.51
E.B.	72	23.56	6.23	12.74
J.W.	70	7.76	8.05	5.42
N.J.	72	15.40	7.41	9.83
I.H.	91	11.68	15.33	15.57
K.M.	75	16.49	7.37	10.52
D.D.	77	20.82	7.22	13.01
A.P.	69	18.47	5.10	7.97
Mean		16.14	8.49	11.20
Range		7.76–23.56	5.10–15.33	5.42–15.57
Young adult subjects†				
Mean		22.97	4.05	7.93
Range		16.30–27.80	3.07–4.95	6.42–9.82
Significance level‡		$P < 0.05$	$P < 0.005$	$P < 0.05$

*After Nation *et al.* (1976). Reproduced by permission of the *European Journal of Clinical Pharmacology.*
†Mean data for six young adults aged 20–27 (mean 22.7) years.
‡Mann–Whitney *U* test.

are presented in table 11.2. For comparative purposes data reported earlier by Moore *et al.* (1975*b*) for young adults have also been tabulated. Statistical comparisons of these parameters between the two age groups revealed significant differences in each case.

The λ values for CTZ in four of the elderly subjects were 0.83, 0.92, 0.96 and 1.12 at CTZ blood concentrations of 1.70, 1.95, 3.18 and 3.77 μg/ml, respectively.

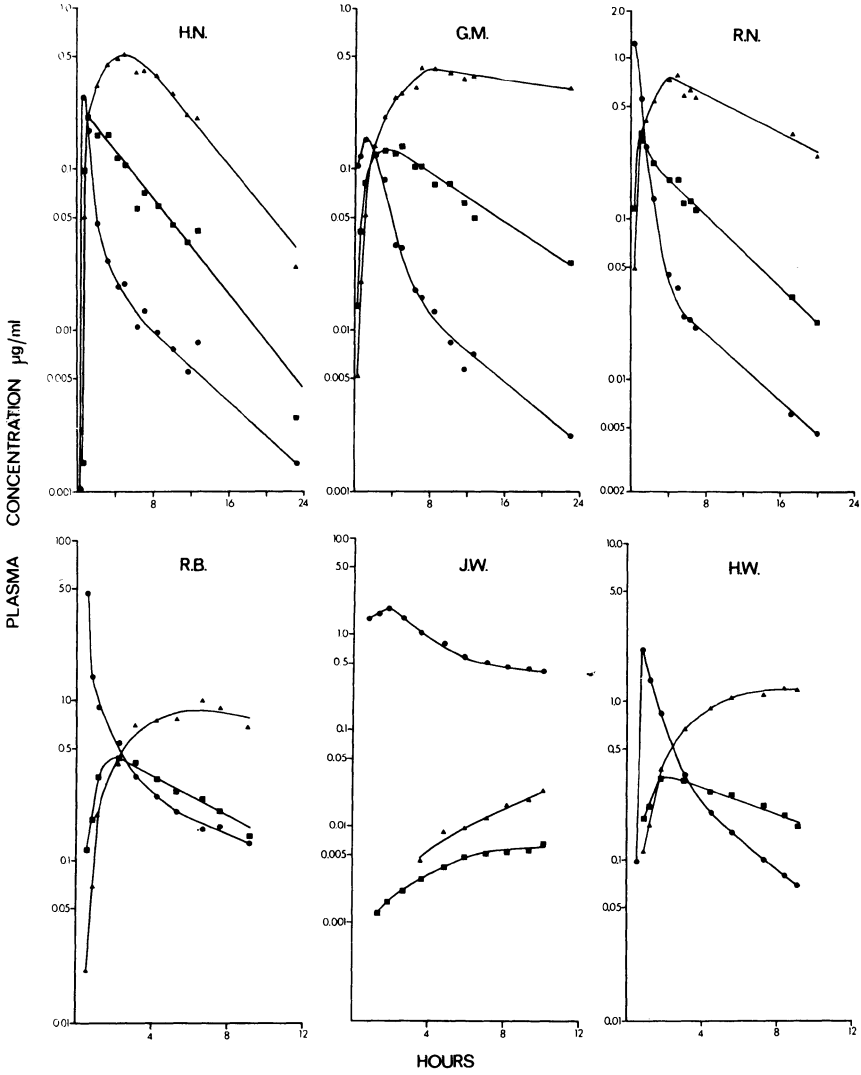


Figure 11.3 Plasma concentration versus time profiles of chlormethiazole (CTZ, •) and metabolites (AMT, ▪; HEMT, ▲) in young (top) and aged (bottom) subjects after administration of a single 600 mg oral dose of CTZ. Lines represent best visual fit to data. Note that the scales of the axes are not identical for all subjects. After Nation *et al.* (1977*b*). Reproduced by permission of the *European Journal of Clinical Pharmacology.*

Table 11.3 Pharmacokinetic details for unchanged drug and metabolites (AMT, HEMT) following oral doses of chlormethiazole (CTZ) to young and elderly subjects*

Subject code	Age (yr)	Sex	Weight (kg)	CTZ $t_{1/2(\beta)}$† (h)	AMT $t_{1/2(\beta)}$† (h)	HEMT $t_{1/2(\beta)}$† (h)	CTZ $C_{p(max)}$† (μg/ml)	CTZ t_{max}† (h)	CTZ AUC_0^∞† (μg ml^{-1} h^{-1})	CTZ Cl_0† (l/min)	CTZ Cl_0† (ml min^{-1}kg^{-1})
Young											
G.M.	28	M	75	7.08	7.84	39.60	0.154	1.02	0.635	15.75	210.0
R.N.	27	M	75	5.90	5.44	10.83	1.22	0.35	1.701	5.88	78.4
H.N.	25	F	55	5.46	3.77	4.03	0.277	0.67	0.482	20.75	377.2
Mean±s.d.				6.15	5.68	18.15	0.550	0.68	0.939	14.13	221.9
				±0.84	±2.05	±18.88	±0.583	±0.34	±0.664	±7.57	±149.8
Elderly											
H.W.	70	M	54	3.22	6.74	–	2.155	0.9	3.688	2.71	50.21
J.W.	71	M	75	9.31	–	–	1.859	1.8	13.733	0.728	9.71
R.B.	68	F	40	6.50	4.29	–	4.697	0.57	5.436	1.84	45.99
Mean±s.d.				6.34	5.51		2.904	1.09	7.619	1.76	35.3
				±3.05	±1.73		±1.560	±0.64	±5.367	±0.99	±22.3
Significance level				N.S.	N.S.		$P<0.05$	N.S.	$P<0.05$	$P<0.05$	$P<0.05$

*After Nation *et al.* (1977*b*). Reproduced by permission of the *European Journal of Clinical Pharmacology.*
†$t_{1/2(\beta)}$ = half-life; $C_{p(max)}$ = maximum plasma concentration; t_{max} = time of maximum plasma concentration; AUC_0^∞ = area under the plasma concentration time curve to infinite time; Cl_0 = apparent oral plasma clearance.
–, not possible to calculate.

Oral study

The plasma drug concentration versus time profiles of CTZ, AMT and HEMT for the young and aged subjects are shown in figure 11.3. Pertinent details of the oral studies are summarised in table 11.3. The half-lives of CTZ and AMT and the time of occurrence of the maximum CTZ plasma concentration were the same for the two age groups. However, the groups were significantly different ($P < 0.05$) with respect to the peak concentrations of CTZ. Estimates of the areas under the CTZ plasma curve (AUC_0^∞) were significantly greater ($P < 0.05$) in the aged subjects. The apparent oral clearance (Cl_0) of CTZ, both in absolute terms and adjusted for the body weight of the subjects, was significantly smaller ($P < 0.05$) in the older individuals; the mean value of Cl_0 for the elderly was only about 15 per cent that of the young subjects.

Two of the young subjects (G.M., R.N.) and one of the aged subjects (J.W.) had participated in earlier intravenous studies (Moore *et al.*, 1975*a*; Nation *et al.*, 1976) with CTZ. Thus, for these three subjects it was possible to obtain an estimate of the absolute systemic availability (F) of CTZ from the orally administered capsules by use of equation (4):

$$F = \frac{(AUC_0^\infty)_{\text{oral}}/\text{dose}_{\text{oral}}}{(AUC_0^\infty)_{\text{IV}}/\text{dose}_{\text{IV}}} \cdot \frac{t_{1/2\,(\beta),\text{IV}}}{t_{1/2\,(\beta),\text{oral}}} \tag{4}$$

where $(AUC_0^\infty)_{\text{oral}}$ and $(AUC_0^\infty)_{\text{IV}}$ are the respective areas under the plasma drug concentration versus time curves from time zero to infinity after an oral dose ($\text{dose}_{\text{oral}}$) and an intravenous dose (dose_{IV}), and $t_{1/2\,(\beta)\text{IV}}$ and $t_{1/2\,(\beta),\text{oral}}$ are the drug half-lives as measured following intravenous and oral administration, respectively.

The application of equation (4) predicted an absolute bioavailability (F) of 0.054 and 0.163 for young subjects G.M. and R.N., respectively, while for the elderly subject (J.W.) the corresponding estimate was 0.687. Mean data from the present study, together with mean data from the intravenous studies (Moore *et al.*, 1975*b*; Nation *et al.*, 1976) were also computed according to equation (4) to give approximate group estimates of F for the CTZ capsules in both the age groups. Using this approach, the values of F predicted for the groups of young and aged subjects were 0.086 and 0.897, respectively.

Details of the plasma-binding and blood cell uptake studies are summarised in table 11.4. The mean values of λ and C_{bc}/C_p were smaller in the aged subjects but not significantly so. The mean fraction of CTZ free in plasma (*FFP*) was 31 per cent greater in the elderly compared with the young individuals ($P < 0.01$) but *FPP* was not different between the groups. The fractions of CTZ distributed to plasma water (*FPW*) and blood cells (*FBC*) were significantly greater ($P < 0.01$) and smaller ($P < 0.05$), respectively, in the aged subjects relative to the young subjects. There was no apparent relationship between λ and haematocrit, λ and *FFP*, or C_{bc}/C_p and FFP.

L-dopa

Peak plasma concentrations of dopa in the young subjects were 238 and 1007 ng/ml compared with 2030 and 7128 ng/ml for the elderly patients receiving 300 mg and 600 mg doses, respectively. It was not possible to determine t_{max} accurately

Table 11.4 Distribution of chlormethiazole (CTZ) in whole blood and plasma binding *in vitro* for young and elderly subjects*

Subject code	Age (yr)	Sex	Haematocrit	Plasma albumin (g/100 ml)	Total plasma protein (g/100 ml)	CTZ blood concentration (μg/ml)	λ†	*FFP*†	C_{bc}/C_p†	Fraction CTZ in whole blood distributed to: plasma water, *FPW*	plasma protein, *FPP*	blood cells, *FBC*
Young												
A.V.	28	M	0.50	–	–	5.69	0.879	0.268	0.758	0.153	0.416	0.431
J.P.	25	M	0.46	–	–	5.69	0.828	0.355	0.626	0.232	0.420	0.348
R.A.	28	M	0.45	–	–	2.02	0.796	0.296	0.547	0.205	0.486	0.309
D.M.	25	M	0.44	–	–	1.92	0.793	0.276	0.530	0.195	0.512	0.293
H.N.	25	F	0.41	–	–	1.78	0.803	0.344	0.520	0.253	0.482	0.265
R.N.	27	M	0.51	–	–	2.03	0.827	0.307	0.661	0.182	0.410	0.408
Mean±s.d.			0.46			1.94‡	0.821	0.308	0.607	0.203	0.454	0.342
			±0.04			±0.12	±0.032	±0.035	±0.093	±0.036	±0.044	±0.066
Elderly												
J.B.	78	F	0.45	3.9	6.9	1.76	0.739	0.348	0.420	0.259	0.485	0.256
E.C.	73	F	0.42	2.9	6.2	1.52	0.769	0.465	0.450	0.351	0.404	0.245
W.F.	86	M	0.42	3.7	7.1	1.94	0.704	0.380	0.295	0.313	0.511	0.176
N.M.	71	M	0.47	4.4	7.5	1.87	0.693	0.369	0.347	0.282	0.483	0.235
F.M.	71	M	0.47	3.8	7.2	2.20	0.851	0.348	0.683	0.217	0.406	0.377
F.G.	79	F	0.34	3.3	6.3	1.99	0.876	0.506	0.635	0.381	0.372	0.247
Mean±s.d.			0.43	3.7	6.9	1.88	0.772	0.403	0.472	0.301	0.444	0.256
			±0.05	±0.5	±0.5	±0.23	±0.076	±0.067	±0.156	±0.060	±0.056	±0.066
Significance level			N.S.			N.S.	N.S.	$P<0.01$	N.S.	$P<0.01$	N.S.	$P<0.05$

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†λ = blood/plasma concentration ratio; *FFP* = fraction free drug in plasma; C_{bc}/C_p = apparent concentration in blood cells/plasma concentration.
‡Data for subjects A.V. and J.P. not included.
–, Not determined.

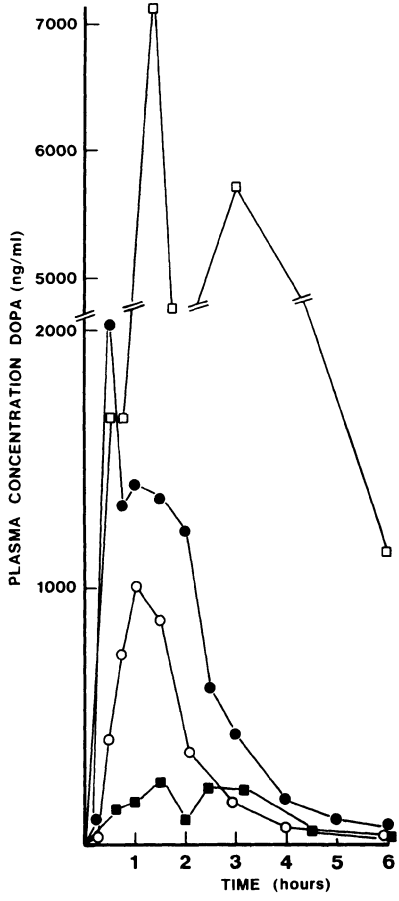

Figure 11.4 Plasma concentration versus time profiles of L-dopa in young (○,■)and elderly (●) subjects following a 300 mg oral dose, and in an elderly (□) subject following a 600 mg oral dose.

for both groups of patients, since double peaks occurred in the plasma drug concentration versus time data for three of the four subjects. The area under the plasma level versus time curve during the sampling period (AUC_0^{∞}) was substantially greater for both of the elderly patients, and this was most marked in the case of the patient receiving 600 mg of the drug (figure 11.4), even allowing for the difference in dosage.

Ampicillin

Maximum plasma levels of ampicillin and the time of their occurrence were similar ($C_{p(max)}$ range 3.4-5.0 μg/ml; t_{max} range 1.75-2.75 h) in the small number of young and aged subjects investigated. More rigorous pharmacokinetic interpretation of the plasma concentration versus time data will be pursued following intravenous studies with the drug in the same individuals.

DISCUSSION

It is evident that increasing chronological age results in some differences in the disposition of lignocaine and chlormethiazole in human subjects.

The systemic clearance of CTZ was significantly smaller in elderly subjects compared with young control subjects. The low urinary recovery of unmetabolised CTZ after intravenous (Moore *et al.*, 1975*b*) and oral (Moore *et al.*, 1975*a*) administration suggests hepatic metabolism as the major process of clearing this drug. This fact, together with the high estimated blood clearance ($\overline{V}_{Cl}/\lambda$) of 1180 ml/min, classifies CTZ as a drug with a high hepatic clearance. A reduction of liver blood flow with increasing age would be an important factor resulting in the lowered clearance, and a reduction in the intrinsic clearance of the liver was probably additionally involved. Some support for this latter assertion was gained from results obtained after oral administration of the drug when it was found that the first-pass effect was greatly reduced in elderly subjects, reflected by an increase in biological availability (F). The apparent oral clearance (Cl_o) of a drug can provide an estimate of the intrinsic ability of the liver to remove drug (Wilkinson and Shand, 1975). However, such an estimate is only valid if complete absorption into the portal circulation occurs, linear kinetics apply, and portal systemic shunting and extrahepatic clearance are absent.

The plasma binding of CTZ decreased significantly from 69 per cent in the young subjects to 60 per cent in the old subjects (table 11.4). The exact reason for such a difference is not clear, although a decrease with age of plasma albumin concentrations could be involved (Bender *et al.*, 1975). Surprisingly, in view of the lower plasma binding, there was a trend towards a reduced λ and C_{bc}/C_p in the aged. It has been demonstrated for quinidine (Hughes, Ilett and Jellett, 1975) and phenytoin (Kurata and Wilkinson, 1974) with erythrocytes and for haloperidol with total cellular components (Hughes, Jellett and Ilett, 1976), that, when cell binding is unaltered, the uptake of drug by the cells seems to be proportional to free drug concentration and an increase in the percentage of free drug in plasma leads to an increase in λ and C_{bc}/C_p. Since this did not occur with CTZ, it appears that, in the elderly, uptake by the cellular elements was reduced and to a greater extent than the reduction in binding which occurred in plasma. Haematocrits were similar for both groups and therefore should not have been a contributing factor in the result. The reduced uptake by the cellular elements in the elderly is also demonstrated by the significantly smaller fraction of CTZ in whole blood distributed to blood cells (FBC); at the same time the fraction distributed to plasma water (FPW) increased significantly. In another study, with pethidine (Chan *et al.*, 1975), it was found that although plasma binding was similar in young and old subjects, the uptake by red cells was much less in the latter group.

The significance of the decreased plasma and cell binding of CTZ in the aged is that not only will the elderly be exposed to higher total drug levels, as shown by the oral study, but also the concentrations of free drug will be relatively higher. Another implication of the reduced binding is that the AUC of total drug determined for the aged subjects after oral administration would tend to underestimate any reduction in intrinsic drug clearance in that group (Wilkinson and Shand, 1975). The age difference in binding may also be involved in the distribution and half-life differences that were evident after intravenous administration to young and old subjects (table 11.2). Finally, for the young subjects the hepatic extraction of CTZ

was greater than the free fraction of drug delivered to the liver, therefore indicating that in that group the hepatic clearance is non-restrictive.

The extraction ratio of lignocaine is lower than that of CTZ and, while an increase in half-life would be expected therefore, the systemic clearance of lignocaine should not be as readily affected by alterations in liver blood flow. Nevertheless, it was surprising to find that the systemic clearance of lignocaine was not decreased in the elderly (table 11.1). Perhaps hepatic blood flow was not decreased in the elderly subjects studied. Other possible explanations for the failure of lignocaine clearance to be decreased in the elderly are a decrease in the extent of binding of the drug in blood, thereby increasing its hepatic extraction, or the existence of some extrahepatic compensatory process in the aged subjects.

Both CTZ and lignocaine were distributed differently in the aged, compared with the young subjects. There was a trend for both drugs to have a larger apparent volume of distribution in the elderly. The volume of the initial dilution space (V) of CTZ was smaller in the aged individuals, but this was not the case for lignocaine. Intrinsic differences in the initial distribution characteristics of the two drugs would probably explain this result. The degree of equilibration of the drugs between the rapidly and slowly equilibrating tissues was different in the young and aged (figure 11.1, tables 11.1 and 11.2).

The recoveries of lignocaine, MEGX and xylidine in the urine collected for 24 h after drug administration were the same for both groups. For total 4-hydroxyxylidine, the 24 h recovery was significantly smaller in the aged subjects. The most likely explanation for these results was a decreased renal clearance of total 4-hydroxy xylidine in the aged subjects. The reduction of renal blood flow and glomerular filtration rate (Davies and Shock, 1950) have been shown to alter significantly the renal clearance of a number of drugs (Triggs and Nation, 1975).

Preliminary examination of the data obtained for ampicillin and L-dopa suggests that absorption of ampicillin may be similar in young and aged individuals, whereas in contrast, the absorption of L-dopa is likely to be increased in the aged Parkinsonian patient. The most likely explanation of this latter finding is that there is a decreased pre-systemic breakdown (decarboxylation) of L-dopa in these individuals. Further investigation of this phenomenon is warranted.

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12
Age, depression and tricyclic antidepressant levels

R. Braithwaite, S. Montgomery and S. Dawling (Poisons Unit and Department of Psychiatry, Guy's Hospital, London, UK)

INTRODUCTION

Depressive illness is a common disease in the elderly and may occur as a result of, or alongside, other organic diseases. The incidence of depressive illness increases with age, and in recurrent depressive illness, the frequency of episodes also increases. The diagnosis of a depressive illness in the elderly patient generally presents few problems, although the appearance of pseudodementia may complicate the clinical picture in a small number of cases. Treatment with a tricyclic antidepressant drug (e.g. amitriptyline, imipramine, nortriptyline) is the usual therapeutic approach. However, many patients fail to show a satisfactory response and there is a high frequency of adverse effects—postural hypotension, confusional states and cardiotoxicity being of particular concern.

Following repeated medication with a tricyclic antidepressant, plasma drug concentrations rise until a plateau, the so-called 'steady-state' level, is achieved (Hammer and Sjöqvist, 1967). Numerous studies have demonstrated that patients receiving similar doses of nortriptyline attain steady-state plasma levels which can differ by as much as 15–20-fold (Åsberg, 1974*a*). These large interpatient variations in steady-state plasma concentrations have also been reported for other tricyclic antidepressants, including imipramine (Moody, Tait and Todrick, 1967), desipramine (Sjöqvist *et al.*, 1969), amitriptyline (Braithwaite *et al.*, 1972), protriptyline (White *et al.*, 1976) and chlomipramine (Mellström and Tybring, 1977).

This phenomenon has important clinical implications because of the relationship between plasma concentrations of tricyclic antidepressants and therapeutic effects (Åsberg *et al.*, 1971; Braithwaite *et al.*, 1972; Kragh-Sørensen, Åsberg and Eggert-Hansen, 1973; White *et al.*, 1976; Ziegler *et al.*, 1976*a*,*b*; Montgomery, Braithwaite and Crammer, 1978). In addition, high plasma antidepressant levels are associated with a higher incidence of adverse effects (Åsberg, 1974*b*).

Sjöqvist *et al.* (1969) suggested that the prime determinant of the 'steady-state' plasma antidepressant concentration attained by an individual receiving a constant dosage regime was the rate at which the liver metabolised the drug. Alexanderson,

Price-Evans and Sjöqvist (1969), working with groups of fraternal and identical twins, concluded that the metabolic rate was genetically determined, although this could be modified by environmental factors such as previous drug exposure.

Age, as a factor influencing tricyclic antidepressant plasma concentrations, has been largely ignored in earlier studies. However, Nies *et al.* (1977) have recently reported a positive correlation between age and steady-state plasma levels of some tricyclic antidepressants. In order to study the influence of age in more detail, we have investigated a large group of depressed patients of varying ages using nortriptyline as a model. We have measured steady-state plasma nortriptyline concentrations following repeated medication, and at the same time assessed clinical response. In some of these patients we have administered a single oral dose of nortriptyline, prior to treatment, in order to obtain individual pharmacokinetic data such as plasma nortriptyline half-life and clearance. Similar investigations using single oral doses of nortriptyline have been carried out in a group of young, healthy volunteers. In addition, data are presented on steady-state plasma drug concentrations in relation to age in patients receiving treatment with amitriptyline.

STEADY STATE TRICYCLIC ANTIDEPRESSANT LEVELS AND AGE

Figure 12.1 shows the mean steady-state plasma nortriptyline levels in relation to age obtained in a group of 36 in-patients receiving identical daily doses of the drug (100 mg). The levels ranged from 36 to 681 μg/l. Figure 12.2 shows a similar pattern for the mean steady-state plasma amitriptyline plus nortriptyline concentrations in relation to age, measured in a group of 34 in-patients receiving the same daily dose of amitriptyline (150 mg), the range being somewhat narrower (62–341 μg/l) than that for nortriptyline. In patients receiving nortriptyline, the correlation

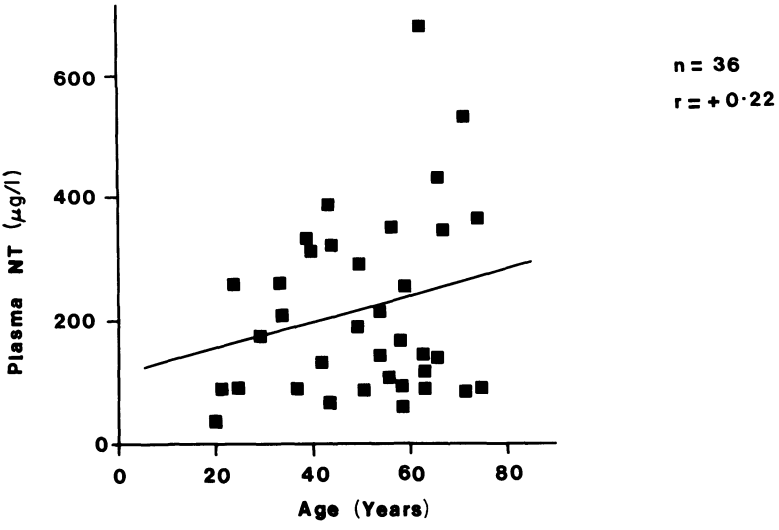

Figure 12.1 The relationship between age and mean steady-state plasma nortriptyline (NT) concentration in a group of 36 depressed in-patients receiving the same daily dose of drug.

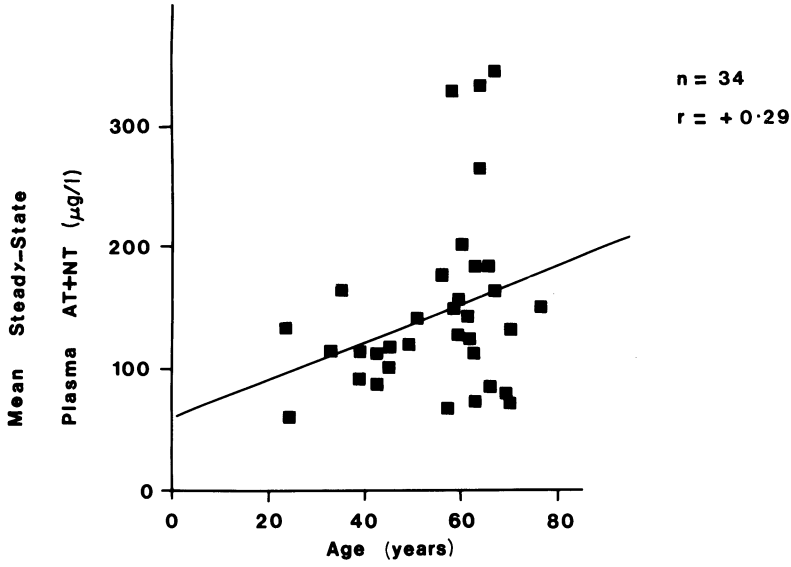

Figure 12.2 The relationship between age and mean steady-state plasma amitriptyline (AT) plus nortriptyline (NT) concentration in a group of 34 depressed in-patients receiving the same daily dose of drug.

between age and steady-state levels did not reach statistical significance. In patients receiving amitriptyline, there was a significant positive correlation between age and the parent compound, but not for its demethylated metabolite, nortriptyline (table 12.1). These findings are in agreement with those of Nies *et al.* (1977). However, there is a clear trend towards an increased *variability* in plasma antidepressant concentration with increasing age (figures 12.1 and 12.2). To compare the variability in plasma antidepressant concentrations between young and old patients, an age 'cut-off' of $\leqslant 55$ and > 55 years was chosen, 55 years being the average age of

Table 12.1 Correlation between age and mean steady-state plasma nortriptyline concentration in patients receiving amitriptyline and nortriptyline

Antidepressant	No. of patients	Correlation with age
Amitriptyline medication		
amitriptyline	34	+0.36*
nortriptyline	34	+0.17
amitriptyline + nortriptyline	34	+0.29
Nortriptyline medication		
nortriptyline	36	+0.22

*$P < 0.05$.

Table 12.2 Difference in variability of steady-state plasma antidepressant concentrations in 'young' and 'old' patients receiving standard dosage regimens

Antidepressant	'Young' patients (≤ 55 yr)			'Old' patients (> 55 yr)			Difference in variability	
	n	Steady-state plasma concentration (μg/l)		*n*	Steady-state plasma concentration (μg/l)			
		mean	s.d.		mean	s.d.	*F* ratio	*P*
Amitriptyline medication (150 mg/day)	12			22				
amitriptyline		53.3	17.9		82.4	37.2	4.7	< 0.02
nortriptyline		57.8	17.3		81.6	59.8	12.0	< 0.002
amitriptyline + nortriptyline		112.3	26.7		164.0	83.8	9.5	< 0.01
Nortriptyline medication (100 mg/day)	19			18				
nortriptyline		197.0	106.7		243.0	178.5	2.8	< 0.05

depressives seen in psychiatric practice (Post, 1976). There was a statistically significant (F test) increase in variability in plasma antidepressant concentrations in older patients receiving both amitriptyline and nortriptyline (table 12.2).

PHARMACOKINETICS OF TRICYCLIC ANTIDEPRESSANTS AND AGE

Theoretically, following the repeated administration of a fixed dose (D) of drug, at a constant dosage interval (Δt), the mean steady-state plasma concentration ($\bar{C}$) may be expressed by the equation (Wagner *et al.*, 1965; Van Rossum, 1968)

$$\bar{C} = \frac{F.D.}{V_{(d)}.k_{el}.\Delta t}$$

where F is the fraction of dose that ultimately becomes systemically 'available', V_d is the distribution volume and k_{el} is the first-order elimination rate constant.

Following the administration of a single oral dose of nortriptyline, it is possible from measurement of plasma drug concentrations to obtain important pharmacokinetic parameters that can be related to the steady-state level achieved (Alexanderson, 1972; Braithwaite, Montgomery and Dawling, 1977*a*). One of these parameters, the simplest to obtain, is plasma half-life ($t_{1/2}$), which is related to the first-order elimination rate constant (k_{el}) by the expression

$$t_{1/2} = \frac{0.693}{k_{el}}$$

However, the most important pharmacokinetic parameter which may be obtained is clearance. Following oral dosage, this parameter, correctly known as intrinsic clearance (Cl_i), may be calculated from the relationship (Wilkinson and Shand, 1975)

$$Cl_i = \frac{D}{AUC}$$

where D is the oral dose administered and AUC is the area under the plasma drug concentration versus time curve.

The mean steady-state plasma level of a drug has been shown to be related to intrinsic clearance—assuming complete oral absorption—by the expression (Wilkinson and Shand, 1975)

$$\bar{C} = \frac{D}{Cl_i.\Delta t}$$

Therefore, assuming dose (D) and dosage interval (Δt) to be constant in an individual, the steady-state plasma level should be inversely proportional to intrinsic drug plasma clearance.

Table 12.3 gives the values for plasma nortriptyline half-life and clearance that have been obtained in various studies following the administration of single oral doses of nortriptyline to both volunteers and patients. It can be seen that the results obtained in young healthy volunteers differ from those obtained either in older volunteers or in patients. In the young volunteers (aged 20–35 years) similar findings have been obtained in three separate studies (Alexanderson, 1972; Gram and

Table 12.3 Values for plasma nortriptyline half-life and clearance obtained in different studies

Study	No. of subjects	Age range (yr)	Mean age ± s.d. (yr)	Half-life range (h)	Mean half-life ± s.d. (h)	Clearance range (l/h)	Mean clearance ± s.d. (l/h)
Alexanderson (1972) (volunteers)	6	22–31	26.8 ± 3.3	18.2–35.0	26.9 ± 7.4	33.6–78.0	50.0 ± 18.2
Gram and Fredricson-Overϕ (1975) (volunteers)	6	21–28	25.5 ± 2.6	16–38	25.5 ± 7.9	37.8–85.2	63.1 ± 15.1
Braithwaite *et al.* (1977*b*) (volunteers)	12	20–35	24.9 ± 5.6	18.1–51.3	27.5 ± 8.8	15.6–63.4	44.0 ± 14.2
Alexanderson (1973) (volunteers)	22 (twins)	47–53	50.4 ± 1.9	18.3–93.3	37.6 ± 18.2	16.1–113.9	52.6 ± 24.7
Braithwaite *et al.* (1977*a*) (patients)	20	22–74	49.1 ± 14.8	21.5–88.1	43.1 ± 22.7	10.1–55.4	27.1 ± 11.9

Fredricson-Overϕ, 1975; Braithwaite, Dawling and Montgomery, 1977*b*), and both shorter half-lives and higher clearance values were observed. There was also a smaller interindividual variation in these values. In older volunteers (Alexanderson, 1973) and patients (Braithwaite *et al.*, 1978), longer half-lives and larger interindividual variations in half-life and clearance have been observed. Figure 12.3 shows the relationship between age and plasma nortriptyline half-life obtained by combining the data from all the reported studies (table 12.3). There is a significant positive correlation between age and plasma nortriptyline half-life ($r = 0.40$, $n = 66$, $P < 0.05$), a finding which supports that reported by Nies *et al.* (1977), where a positive correlation between plasma desipramine half-life and age was obtained.

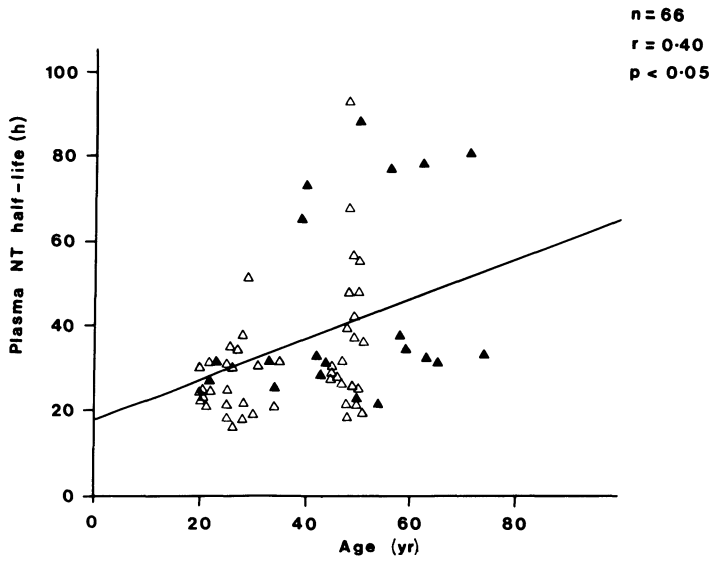

Figure 12.3 The correlation between plasma nortriptyline (NT) half-life and age in patients (▲) and healthy volunteers (△) following a single oral dose.

Taking age into account, there is no apparent difference in half-life values between healthy volunteer subjects and depressed patients. However, there is a large increase in the variability of half-life values in both older volunteer subjects and older patients. Alexanderson (1972) in a small group of volunteers and Braithwaite *et al.* (1977*b*) in a large group of patients have both shown a significant correlation between single-dose plasma nortriptyline half-lives and steady-state plasma nortriptyline levels. The achievement of higher and more variable steady-state plasma antidepressant levels in older patients (figures 12.1 and 12.2) is therefore consistent with the half-life data.

A wide but similar range of plasma nortriptyline clearance values has been obtained for both young and older volunteers (table 12.3). However, in depressed patients these values were much lower. The relationship between age and plasma nortriptyline clearance values for all volunteer subjects and patients included in

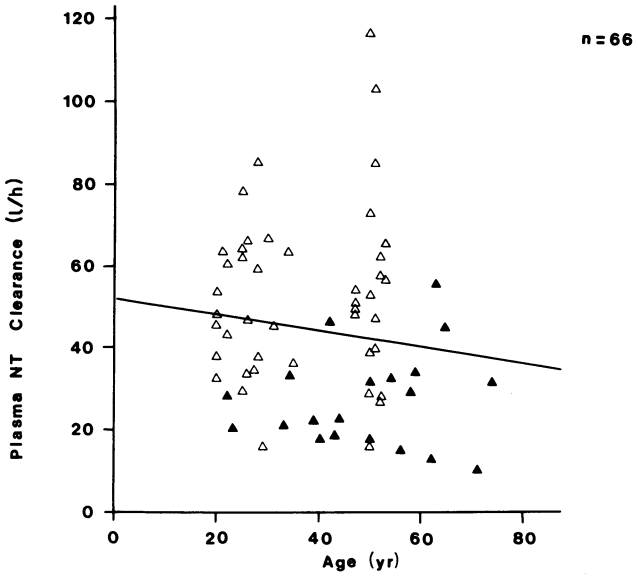

Figure 12.4 The correlation between plasma nortriptyline (NT) clearance and age in patients (▲) and healthy volunteers (△) following a single oral dose.

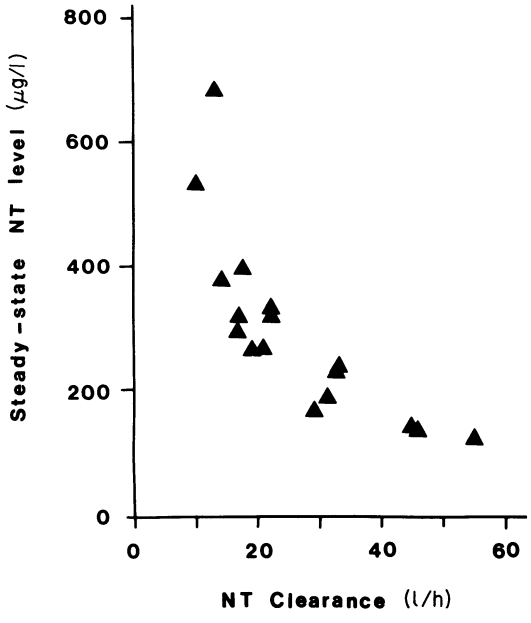

Figure 12.5 Correlation between mean steady-state plasma nortriptyline (NT) concentration and clearance in a group of patients receiving antidepressant treatment. After Braithwaite *et al.* (1977*a*).

table 12.3 is depicted in figure 12.4. Even allowing for age differences between the two groups, patients had significantly lower clearance values than volunteers ($\chi^2 = 8.0, P < 0.005$).

There are several possible explanations for this striking finding. Firstly, the volunteers were predominantly male, whereas the majority of the patients were females. Secondly, the life-style of the volunteers–e.g. diet, use of alcohol and smoking habits–may have been quite different from that of the depressed patients. Finally, it is possible that depressive illness itself in some way influences the rate of drug clearance, although this is rather speculative.

Taking the results for nortriptyline clearance as a whole (figure 12.4), there were large interindividual differences, with values ranging from 10.1 to 113.9 l/h. Figure 12.5 illustrates the inverse relationship between plasma nortriptyline clearance and steady-state plasma nortriptyline concentrations for 17 patients (Braithwaite *et al.*, 1978). The reciprocal of plasma nortriptyline clearance bears a highly significant linear correlation ($P < 0.0001$) with steady-state plasma nortriptyline levels, which suggests that this value is a closer predictor of these levels than plasma nortriptyline half-life (Braithwaite *et al.*, 1977).

STEADY STATE PLASMA ANTIDEPRESSANT CONCENTRATIONS AND CLINICAL EFFECTS

Åsberg *et al.* (1971), Kragh-Sørensen *et al.* (1973, 1976), Ziegler *et al.* (1976*a*) and, more recently, our own group (Montgomery *et al.*, 1978) have shown that the best therapeutic response with nortriptyline is obtained within an intermediate plasma level range (50–150 μg/l), patients with levels either below or above this range exhibiting a poorer therapeutic response. A relationship between plasma drug concentration and therapeutic effect has also been demonstrated for other antidepressants, namely amitriptyline (Braithwaite *et al.*, 1972; Ziegler *et al.*, 1976*b*), imipramine (Gram *et al.*, 1976) and protriptyline (White *et al.*, 1976). For nortriptyline, it appears that high plasma levels may inhibit the antidepressant action and be responsible for the persistence of depressive symptoms (Kragh-Sørensen *et al.*, 1976; Montgomery *et al.*, 1977; Montgomery *et al.*, 1978).

High plasma antidepressant levels are also associated with a higher incidence of adverse effects (Åsberg, 1974*b*). Moreover, recent work has shown a deterioration in cardiac performance in patients with high plasma nortriptyline levels, which could have serious consequences for patients with underlying cardiac disease (Burrows *et al.*, 1976; Taylor and Braithwaite, 1977).

In the recent study reported by Montgomery *et al.* (1977) the large interindividual variation in steady-state nortriptyline levels was such that the majority of patients were found to lie outside of the recommended therapeutic range. Clinical assessment disclosed a remarkably poor antidepressant response in those patients with high plasma nortriptyline levels, whereas those with levels between 50 and 150 μg/l were considerably improved. Moreover, it was difficult to identify those patients with high plasma nortriptyline levels from purely clinical examination.

This complex situation is highlighted in figure 12.6, which shows the steady-state plasma nortriptyline levels in five patients aged 44–67 years, all of whom were undergoing antidepressant medication with nortriptyline. Routine measurements of plasma nortriptyline levels and appropriate dosage adjustments were car-

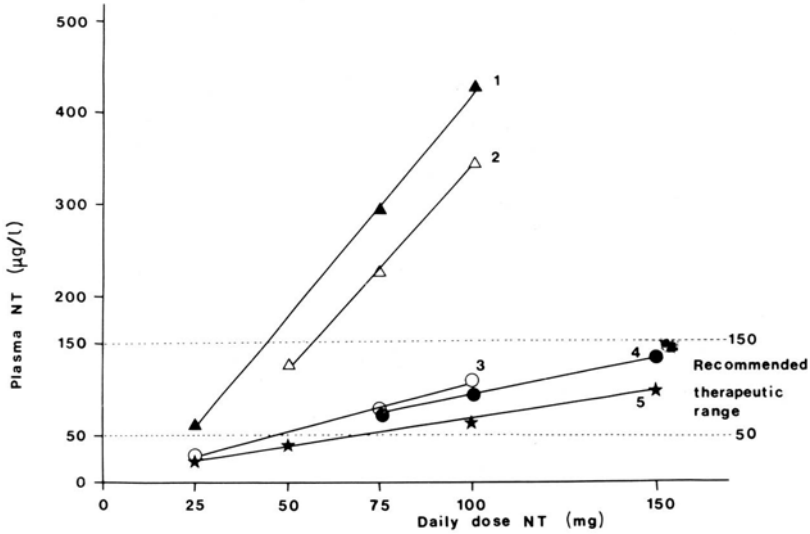

Figure 12.6 The relationship between plasma nortriptyline (NT) concentration and dosage for 5 patients undergoing antidepressant treatment.

ried out to improve the therapeutic response. Patients 1 and 2 were initially receiving 100 mg of nortriptyline daily with poor therapeutic response. Step-wise reduction of the dosage to bring the plasma nortriptyline levels to within the recommended therapeutic range had a beneficial result. This was achieved with a daily dose of 25 mg of nortriptyline in patient 1 and 50 mg in patient 2. Conversely, patients 3–5 were receiving fairly low doses initially and these had to be increased to 100–150 mg daily to raise the plasma nortriptyline levels into the optimum therapeutic range and thereby elicit an antidepressant response.

Figure 12.6 emphasises the wide variation in tricyclic antidepressant levels which may be encountered in routine practice and the value of plasma level measurements in guiding the clinician towards the optimum dosage for individual patients.

CONCLUSION

Patients over the age of 55 years represent a considerable proportion of the population who are receiving chronic antidepressant medication and it is therefore surprising that they have received so little attention in previous studies of this nature. Further, there has been a tendency to assume that pharmacokinetic data derived in young healthy volunteers can be extrapolated directly to all patients irrespective of age, and the present work shows this assumption to be erroneous. The importance of carrying out such investigations in patients for whom the drugs are actually being prescribed cannot be overstated.

It is clear from this survey that the variability in the steady-state plasma tricyclic antidepressant concentrations achieved on standard dosage regimens is considerably greater in the elderly than in young patients. Thus, a significantly higher proportion

either will fail to attain therapeutically effective antidepressant concentrations or will achieve levels in the toxic range. This might explain why tricyclic antidepressant treatment is unsuccessful in many elderly patients and also account for the reputedly high incidence of adverse reactions in these patients, who, it should be remembered, are less resilient to such effects than the young.

In summary, two simple recommendations may be put forward regarding tricyclic antidepressant medication in the elderly. Firstly, more caution should be exercised in deciding individual dosage regimens. Secondly, the introduction of routine plasma concentration measurements for patients not responding or presenting with toxic symptoms is desirable. In this way, treatment of depressive illness in the elderly could be made more effective and the risk of toxicity reduced.

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Section 3
Drug sensitivity in the elderly

CHAIRMAN: Professor K. O'Malley (Dublin)

13
Drug sensitivity in the elderly

A. D. Bender (Smith Kline and French Laboratories, Philadelphia, USA)

INTRODUCTION

The observation that the response of elderly patients to drugs differs from the response seen in younger patients is not new nor is it surprising. The effect of increasing age on drug activity was the subject of a series of early studies conducted in the 1940s by K. K. Chen and his colleagues at Eli Lilly. These investigators found that increased age in experimental animals was associated with increased sensitivity to the effects of alcohol (Chen and Robbins, 1944*a*), morphine (Henderson and Chen, 1948), picrotoxin and secobarbital (Chen and Robbins, 1944*b*) and ouabain (Chen and Robbins, 1944*c*). Interestingly, they also found that drug toxicity was not always increased in older animals. For example, the lethal dose of methadone was unaffected by age (Henderson and Chen, 1948).

At about the same time, the subject of changing drug activity with age was also investigated in other laboratories. Lillehei and Wangensteen (1948) at the Mayo Clinic observed that the incidence of histamine-induced ulcers in dogs increased with age. Previously, MacNider (1946) had noted in dogs that the toxic effects of ether and chloroform were more marked in older animals and Dearing, Barnes and Essex (1943) had reported that the frequency of digitalis-induced myocardial lesions in cats was increased with age.

On 16 March, 1949 Chauncey D. Leake (Leake, 1949) presented a paper at a symposium on geriatrics at the dedication of a new research facility of Smith Kline and French Laboratories in Philadelphia. He summarised the state of knowledge concerning drug sensitivity in the aged before the era of new drug discovery and development which began in the 1950s. Dr Leake noted in his presentation that '. . . many common drugs are apparently more toxic in old people than in adults or adolescents; alcohol, the digitalis drugs, and morphine compounds are more toxic for the aged than for the healthy adult'. Sulpha drugs are better tolerated by the young than by the old and the incidence of allergy to the cincophens increases with age. He suggested that reduced renal function in the aged suggests caution in giving drugs excreted primarily by the kidney.

Later, Lasagna (1956) stated that '. . . it seems almost ridiculous to suggest that ageing should not affect drug responses', and he pointed out the paucity of data at

that time, a situation prevailing throughout the early 1960s (Bender, 1964). In 1965 a note in the *Medical Letter* (Anon., 1965) indicated that we were then in no better position with regard to data concerning the role of age as it influenced drug response than we were at the time Lasagna published his paper—nearly 10 years earlier. Thus, the subject of geriatric pharmacology has only been approached in earnest over the past 10 years.

What we know today was predicted in large measure by Leake in 1949 and suggested by the data from studies in experimental animals published in the 1930s and 1940s. What is different is that better data regarding changes in activity of specific and widely used drugs are now available from studies of large patient populations such as those carried out as part of the Boston Collaborative Drug Surveillance Program. Also, because of the emerging discipline of pharmacokinetics, changes in drug response can be explained in terms of the effect of age on mechanisms and systems involved in the disposition of drugs. In some cases it is possible to adjust dosage to reduce the incidence and severity of adverse reaction without sacrificing efficacy.

It is not entirely correct to say that no work was conducted prior to 1965. Indeed, a considerable amount of preclinical work was carried out by two groups of investigators. On the pharmacological side, Farner and Verzar studied the effect of age on the action of a number of drugs (Verzar and Farner, 1960; Farner and Verzar, 1961; Verzar 1961). In their studies they noted that older animals were less responsive to the actions of methylphenidate and amphetamine. Further, the depressant actions of a number of centrally acting drugs were more pronounced in older animals and the appetite-depressant action of amphetamine was found to be more marked with increasing age.

Biochemical studies were undertaken by Kato and his colleagues, who showed (Kato *et al.*, 1964; Kato and Tanaka, 1968) that increasing age in the rat was associated with a reduction in microsomal enzyme activity. Meprobamate, carisoprodol, pentobarbital and hexobarbital were found to be more slowly metabolised with age and, as a consequence, plasma and tissue drug levels were increased.

As noted above, adverse reactions occur more frequently in older patients. This view has been confirmed by a number of studies. For example, Hurwitz (1969) found that adverse reactions to drugs occurred in 21.3 per cent of patients between the ages of 70 and 79 years, compared with a figure of 7.5 per cent for patients aged 40–49 and 3 per cent for those aged 20–29 years. Previously Seidl, Thornton and Smith (1966) observed adverse reactions in 24.9 per cent of patients over 80, as opposed to 11.8 per cent in patients aged 41–50 and 9.9 per cent in those aged 21–30. Side effects to specific drugs have also been reported to increase with age. Adverse reactions to phenylbutazone have been reported by Pemberton (1954) to increase sharply with advancing age, and Ayd (1961) has shown that the incidence of extrapyramidal symptoms produced by the phenothiazines is more prevalent in older patients.

There are a number of reasons why older individuals may exhibit increased incidence of adverse reactions to drugs. The first is that older patients often exhibit multiple pathology and, as a result, polypharmacy is a more prevalent practice. In a recent study by Kalchthaler, Coccaro and Lichtiger (1977), they found that in a long-term care facility the average number of drugs prescribed per patient was 3.33. The problem with polypharmacy and multiple drug administration does not lie

simply in the fact that more drugs are given, thus compounding the opportunity to exhibit side effects, but because of what has been learned over the last 10 years this obviously increases interaction potential.

Drug interactions are known to be common, and therefore the more drugs that are given, the greater the likelihood of side effects. Older patients may exhibit side effects simply because they are more sensitive to the action of a specific drug or because the body is unable to dispose of it at a rate which is comparable to that seen in younger patients. Hence, the concentration of drug in the circulation and at the receptor site is increased, and therefore the response to the drug is enhanced. One guideline that may be employed is to reduce the amount of drug administered in the elderly patient, particularly for those drugs where it is known that there is reduced metabolism or excretion.

Regarding dosage, Greenblatt, Allen and Shader (1977) recently reported the results of a study on the toxicity of high doses of the hypnotic flurazepam in patients of different ages. The frequency of adverse reactions to this drug increased from less than 2 per cent in patients under 50 years of age to approximately 7 per cent in those over 80 years of age. However, when the frequency of adverse reactions was related to the dose of the drug, it was found that age had a very marked effect on the incidence of adverse reactions at doses of 30 mg/day. At a dose of 15 mg/day the incidence of adverse reactions was essentially unaffected by age.

To explore in greater detail the relationship between drug toxicity and changes in drug disposition with age, four categories of drugs have been chosen where there appear to be sufficient data to make recommendations to reduce drug sensitivity or predisposition to adverse reactions in the older patient. They are the cardiac glycosides, the benzodiazepines, the tricyclic antidepressants and the non-steroidal anti-inflammatory agents.

CARDIAC GLYCOSIDES

The digitalis preparations are among the most commonly employed drugs in geriatric practice. Heart failure is frequently encountered and the digitalis drugs are used because of their ability to enhance cardiac contractility. The use of digitalis in the elderly is usually associated with an increased frequency of symptoms associated with digitalis toxicity, including nausea, vomiting, dizziness, visual disturbances and many types of cardiac arrhythmias (Herman, 1966; Armitage, 1973).

Since oedema is usually associated with congestive failure, digitalis is frequently prescribed along with a thiazide diuretic. The potassium loss seen with the thiazides occurs more frequently in elderly patients (Friend, 1961) and, since the toxicity of digitalis is inversely related to serum potassium levels, this is an additional area of caution when prescribing a digitalis compound.

In preclinical studies the toxicity of the cardiac glycosides has been shown to vary with age. Chen and Robbins (1944*c*) found that in rabbits the lethal dose of ouabain decreased from 197.8 μg/kg at 42 days of age to 82.9 μg/kg in animals about 5 years of age. In cats the long-term administration of relatively high doses of digitalis compounds produced more frequent and severe myocardial lesions in old animals as opposed to a younger age group (Dearing *et al.*, 1943).

An increased sensitivity of the ageing myocardium to the effects of ouabain is suggested by the work of Wollenberger, Jehl and Karsh (1953). In studies conducted

in guinea-pigs aged 20 days–6½ years the lethal concentration of ouabain for hearts perfused *in vitro* decreased with age; in addition, decreasing doses of the drug produced a greater degree of inhibition of oxygen uptake by heart slices taken from older animals.

Clinically, however, the current view is that the higher incidence of toxicity seen with digoxin in older patients is more closely related to reduced renal function, accompanied by higher and more prolonged blood levels, than to an increased sensitivity of the heart to the action of the drug (Ewy *et al.*, 1969; Chamberlain *et al.*, 1970; Taylor, Kennedy and Caird, 1974; Trounce, 1975). This conclusion, however, has not been consistently reported (Chavaz *et al.*, 1974).

Ewy *et al.* (1969) found that in normal subjects, following a single intravenous dose of digoxin, the clearance of digoxin was reduced from 83 ml/min per 1.73 m^2 in a group of subjects (average age 27 years) to 53 ml/min per 1.73 m^2 in a group of older subjects (average age 77 years). This was paralleled by a reduction in creatinine clearance with age, although there was no change with age in serum creatinine levels. Blood concentration of the drug was significantly higher in the older group and the half-life of the drug increased from 51 h in the young subjects to 73 h in the elderly subjects. The authors concluded that a decrease in the renal excretion of digoxin in the elderly may account for the sensitivity to digitalis exhibited by this age group.

Chamberlain *et al.* (1970) found no evidence for increased myocardial sensitivity to therapeutic concentrations of the drug in elderly patients but noted that the doses required to achieve a given concentration of drug in the plasma tended to be less in older subjects. They pointed also to the importance of renal function in determining plasma levels, since digoxin is excreted unchanged by the kidney. The importance of renal function and the frequency of digitalis toxicity has also been emphasised by Taylor *et al.* (1974). These authors suggest that digoxin kinetics are predictable in the elderly provided that the level of renal function has been determined. They believe that their data are consistent with the notion that the exaggerated response seen in the elderly is not due to increased sensitivity of the myocardium to digoxin.

Finally, Chavaz *et al.* (1974) concluded from their findings that, although renal failure tends to favour the retention of digoxin, the age-related increase in frequency of digitalis intoxication is more related to factors that sensitise the myocardium than simply to increased serum digoxin levels.

BENZODIAZEPINE DRUGS

The benzodiazepine class of drugs is widely used in the treatment of elderly patients. Diazepam and chlordiazepoxide are commonly used in patients exhibiting anxiety, agitation and restlessness. Flurazepam and nitrazepam are compounds which are used predominantly as hypnotics and in the treatment of insomnia.

It has been observed and reported that the elderly are more prone to exhibit toxic side effects of these drugs; for example, in patients treated with diazepam and chlordiazepoxide the frequency of drowsiness was found to be almost twice as high in patients over 70 than in patients under 40 years of age (Boston Collaborative Drug Surveillance Program, 1973), suggesting a slower level of metabolic destruction and inactivation in the older patient. As discussed previously,

Greenblatt *et al.* (1977) have shown the toxicity of flurazepam to increase with age. With nitrazepam it is recommended that reduced doses should be prescribed for patients over 65 years of age (Castleden *et al.*, 1977). It is unlikely that these changes in activity can be fully explained on the basis of alteration in the rate of elimination or metabolic destruction.

Klotz *et al.* (1975) have investigated the effect of age on the disposition and elimination of diazepam in human subjects. At 20 years of age the plasma half-life was approximately 20 h increasing linearly with age to about 90 h at 80 years of age. The prolongation of the plasma half-life appeared, however, to be due to an alteration in the distribution of the drug, since total plasma clearance was not found to be a function of age.

Castleden *et al.* (1977) compared the effects of a single 10 mg oral dose of nitrazepam with those of a placebo in healthy young and old subjects. These investigators employed a psychomotor test to assess the degree of central nervous system depression. The elderly subjects made significantly more mistakes in this test as a result of nitrazepam treatment than did the young group. Since the plasma concentration and half-life of nitrazepam were essentially the same in both groups, it would appear that the difference in response was due to an increased sensitivity of the ageing brain to the action of nitrazepam.

ANTIDEPRESSANTS

Amitriptyline and imipramine are representative of a group of compounds known as tricyclic antidepressants. These compounds have been shown to be useful in the treatment of symptoms associated with depression and depression accompanied by anxiety. Their mechanism of action appears to be related to their ability to block the re-uptake and, thus, deactivation of catecholamines in the central nervous system.

It has been recommended that lower doses be used in elderly patients. Depressed geriatric patients frequently exhibit toxic responses to tricyclic antidepressants in greater frequency than that seen in younger patients. These effects include postural hypotension, urinary retention, tachycardia and congestive heart failure. Recently Nies *et al.* (1977) have shown that older patients tend to exhibit higher plasma levels and longer plasma elimination half-lives of the commonly used tricyclic antidepressant drugs amitriptyline and imipramine. Their studies involved the establishment of steady state plasma levels following continued administration of these drugs. The mean steady state plasma levels of imipramine in young patients was 32.3 ng/ml, compared with a mean level of 83.8 ng/ml in patients over 65 years of age. For amitriptyline the corresponding plasma levels were 81.7 ng/ml and 138.7 ng/ml, respectively.

NON-STEROIDAL ANTI-INFLAMMATORY AGENTS

It has been known since the early report of Pemberton (1954) that the toxic effects of phenylbutazone are more common in older patients. In his study he showed that the incidence of adverse reactions rose from 23 per cent in patients aged 21–30 years to over 60 per cent in patients 61 years and older. In subsequent studies carried out by O'Malley *et al.* (1971) it has been shown that the mean

plasma half-life of phenylbutazone is 29 per cent greater in geriatric patients when compared with young controls. The phenylbutazone half-life in younger subjects was reported to be 81.2 h and this increased in the geriatric group to 104.6 h.

These results have been confirmed by the studies of Triggs *et al.* (1975), who reported a serum half-life for phenylbutazone of 110 h for an elderly patient population (average age 81 years), compared with a serum half-life of 87 h in young patients (average age 24 years). It has also been reported that indomethacin has a slightly longer half-life in the elderly (104 min) than in the young (92 min) (Traeger *et al.*, 1973).

SUMMARY

It is well established that the elderly exhibit a response to many drugs that is more pronounced than that usually seen in younger adult patients. The results of recent pharmacokinetic studies suggest that the enhanced response in the older patient group is the result of lower rates of excretion and metabolism. In some instances, however, the difference is unrelated to changes in plasma levels of drugs, and therefore the conclusion is that the elderly are simply more sensitive to the actions of the drug. With the data in hand, the practitioner can begin to justify the use of a lower dose in elderly patients without sacrificing efficacy. This practice, however, should be limited to situations and drugs where sufficient data are available on the relationships between age and the pharmacokinetic and therapeutic characteristics of the drug.

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14
Assessment of psychotropic drug effects

A. Elithorn, R. Cooper and R. Lennox (Institute of Neurology and the Royal Free Hospital, London, UK)

INTRODUCTION

The assessment of the effects of psychotropic drugs is a difficult problem in any age group. A recent review (Elithorn, Lunzer and Weinman, 1975) of the literature on the psychological assessment of the effects of L-dopa revealed the reports to be not only divergent but also often contradictory, some research workers finding that L-dopa had no effect on intellectual functions as such, others reporting an improvement, with a third group claiming that it produced deterioration. Some limited experimental work, using the techniques described below, combined with the review of the literature enabled these authors to conclude with some degree of certainty that the main effect of L-dopa on intellectual functions could be related to its stimulant action on mood and its arousal or alerting effect.

Although antidepressant and arousal effects are interrelated, it is useful to distinguish between them and also to distinguish both from a general stimulant effect on neurological functions as a whole. It is also useful to distinguish at least three, or possibly four, different depressant effects which occur with sedative drugs. These four effects we might call sedative or drive reduction (that is to say, the opposite of arousal), anxiolytic, hypnotic and a general depressant effect involving an overall reduction in cerebral function.

To make matters more complicated, depressant drugs with an anxiolytic action often have an antidepressant effect on the patient. These fine shades of difference in the general effects of stimulant and depressant drugs are not merely hair splitting. At a clinical, as well as at a research level, it is important that the complexities of a biochemical reality (see table 14.1) should not become blurred to the point of extinction, merely because the tools available for behavioural analysis are relatively coarse. To the behavioural changes that are produced by drugs acting on at least nine different transmitter systems we must add the effects that drugs have on intraneuronal metabolic processes and on the microcirculation of the central nervous system.

Psychologists are fond of talking in terms of intervening variables such as anxiety and depression which are essentially unobservable and immeasurable. These

Table 14.1 Drugs affecting transmitter functions

Type of receptor	Drugs acting at the neurotransmitter receptor		Drugs affecting the level of neurotransmitter available to the receptor	
	Agonists (activate receptor)	Antagonists (block receptor)	Increase levels	Decrease levels
Dopamine	apomorphine alpha-bromocriptine	phenothiazine haloperidol	L-dopa amantadine amphetamines methylphenidate	alphamethyl *p*-tyrosine
Alpha-adrenergic	phenylephrine	phentolamine	tricyclic antidepressants MAO inhibitors	reserpine alphamethyl-dopa
Beta-adrenergic	adrenaline isoproterenol isoprenaline	propranolol	amphetamines	
Serotonin	5-methoxy-*N*,*N*-dimethyltryptamine	methysergide lysergic acid diethylamide	tricyclic antidepressants tryptophan	parachlorophenylalanine
H 1	2-methyl-histamine	diphenhydramine dimenhydrinate	histidine amodiaquine	alphahydrazinohistidine brocresine
H 2	betazole	metiamide cimetidine	histidine amodiaquine	alphahydrazinohistidine brocresine
Muscarinic	pilocarpine carbachol bethanechol	scopolamine atropine propantheline	insecticides nerve gas (DFP) pyridostigmine	botulinus toxin
Nicotinic	nicotine	*d*-tubocurarine suxamethonium		
Opiate	morphine heroin methadone pethidine	naloxone		

are useful, even essential, concepts, but the fact that different meanings are attached to them by different workers often retards communication. Basically, in using psychotropic drugs we are attempting to improve our patients' powers of social adjustment and to improve one aspect of their mental competence.

Research into the behavioural effects of psychotropic drugs therefore needs to be undertaken at two levels. At a superficial level, we need studies which tell us which drugs on balance produce the most worthwhile improvement in patients with particular disabilities. At a deeper level, we need to know which aspects of behaviour a drug is affecting. This information is clinically important because it helps us to extrapolate more accurately from experimental studies to the results that we are likely to obtain in routine clinical applications. For example, it is well known that in severe depressive illness the increase in energy and activity produced by electroconvulsive therapy or stimulant drugs may precede a secondary dissipation of morbid depressing thoughts so that paradoxically the first clinically observed sign of improvement may be a successful suicidal attempt!

For the clinician, the evidence needed from experimental clinical trials is not information that a particular drug is better than an inert substance. Clinicians are by nature Bayesian in outlook and the prior probability that a new psychotropic drug is inert is virtually nil. Even if this were not so, the double-blind cross-over trial of placebo against a new psychotropic drug in patients, as opposed to volunteer normal subjects, would still be as unethical and uninformative as the comparison of a new anticonvulsant or antibiotic with a placebo. For over fifty years psychiatrists have been able to manipulate the mood and mental competence of their patients with a variety of stimulant and depressant drugs, and the information the clinician needs is whether or not a new psychotropic drug either is better than or can supplement existing treatments.

A recently published paper from the Maudsley Hospital describes a trial which has been carefully carried out and which well illustrates the value and defects of objective psychological tests. The trial (Davies *et al.*, 1977) examines the effect of cyclandelate, given either alone or in conjunction with a variety of antidepressant treatments. The results, which show clearly that cyclandelate produced on average and in their subjects an impairment rather than an improvement in intellectual functions, appear to be in direct conflict with the findings of a number of other workers, who between them have shown that cyclandelate frequently produced a marked improvement in intellectual functions in normal and in dementing subjects (e.g. Judge, Urquart and Blakemore, 1973).

The Maudsley workers express themselves at a loss to explain this contradiction. It seems to us that the totality of the evidence shows fairly clearly that cyclandelate is an active drug which alters CNS function in a variety of ways. Pare, Linford Rees and Sainsbury (1962) as well as many others have shown clearly that there are marked genetically determined differences in the ways in which psychotropic drugs are metabolised. Moreover, as with L-dopa, it would appear that cyclandelate is likely to affect different aspects of psychological test performances in different ways and that the overall effect will also be a function of individual difference in both personality and diagnostic state. It would seem arguable, therefore, that clinical trials of psychotropic drugs will inevitably be of little value unless they are able to establish the effects of the drugs on individual subjects and relate the different responses observed to differences between the subjects.

SELECTION OF PSYCHOLOGICAL TESTS

In the past, the psychological assessment of behavioural changes has played little role in the direct care of patients, mainly because the techniques of psychological testing have been more suitable to evaluating differences between individuals as opposed to measuring changes taking place within a single individual. It should not be surprising that computer technology can vastly improve the power of psychological tests. Firstly, it enables the psychologist to time both the stimuli and the subject's responses much more accurately than would otherwise be possible. In particular, by using a combination of criterion reference tests and computer-item generation, computer-based testing makes it possible to test the same subject repeatedly and, hence, to monitor treatment on a daily basis. This technology is described in greater detail elsewhere (Elithorn, Powell and Telford, 1976), but it may be helpful to describe briefly the concepts that lie behind criterion reference testing and randomised, stratified item selection. Criterion reference testing is best illustrated by a comparison between the current objective techniques used in the United States to evaluate their educational system and the 'cover-up' techniques adopted by English educationalists. The standard for an 'O' level certificate is shifting sand and the criterion adopted is purely a comparison of the individual's performance with that of other individuals. However bad the average performance may be, the top x per cent pass and the remainder fail. Criterion referenced evaluation as practised in the USA involves the assessment of the student's performance in terms of his ability to reach a definite standard in terms of writing skills, arithmetic skills, and so on.

Criterion reference tests as used in psychology, therefore, are tests which measure the individual's ability to achieve a performance in a task whose complexity is determined by measurable objective parameters. Certain examples will already be familiar, such as the measurement of an individual's short-term memory span in terms of the length of the sequence of digits which can be remembered. A more complex and less familiar example is the perceptual maze test. This test is widely used in cross-cultural studies because it is non-verbal and measures basic perceptual information processing skills. It provides a clinical test highly suitable for interactive computer testing. It has also proved to be particularly sensitive to both organic cerebral damage and the CNS effects of a wide range of stimulant and depressant drugs (Benton *et al.*, 1963; Archibald, Wepman and Jones, 1967; Avons, Cooper and Elithorn, 1974).

THE PERCEPTUAL MAZE TEST

The perceptual maze test developed from the better-known Porteus maze was designed specifically to facilitate the use of computer programs in both item design and performance analysis. The format of the test is illustrated in figure 14.1. A number of target dots are superimposed upon the intersections of a binary lattice background. The criteria which determine item difficulty are the size of the lattice and the number of target dots and the arrangement of these dots.

In this test, the subject's task is to find a path along the lattice which passes through the greatest number of target dots. In general, there is more than one pathway and the subject is said to succeed if he finds any one of these. There are two methods of presenting the test material. Under the 'with-information' condi-

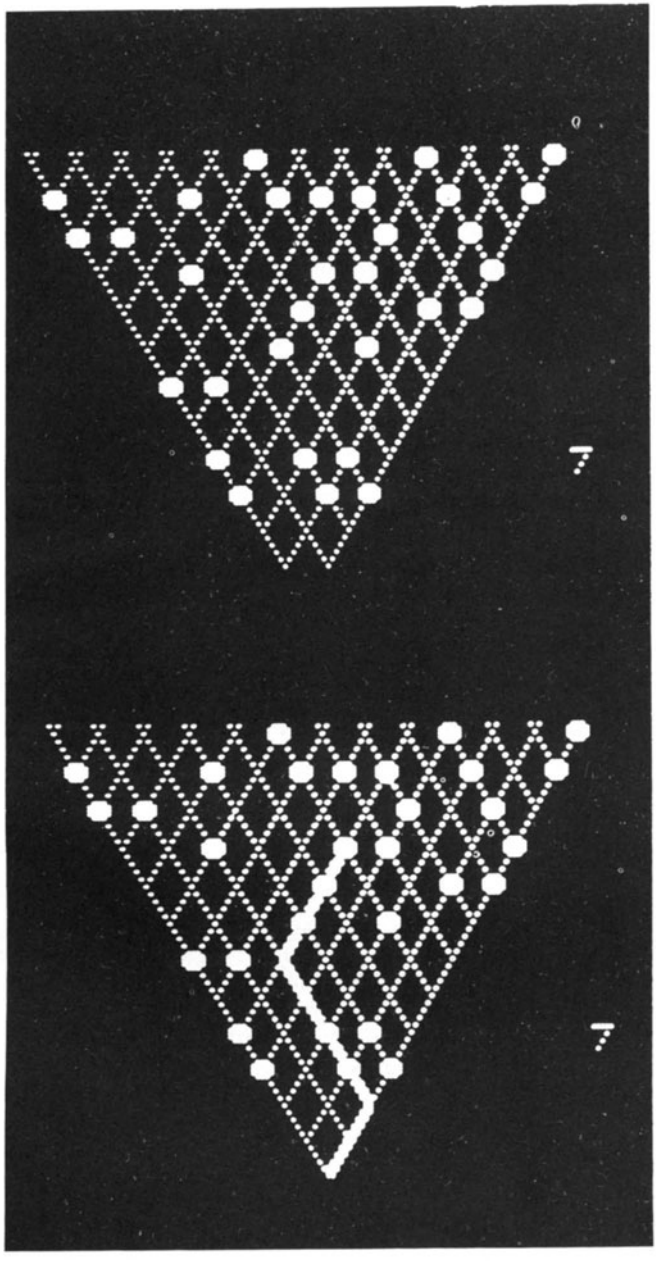


Figure 14.1 (a) Sample item for computer version of the perceptual maze test; (b) as (a) with a partly completed solution.

tion, the subject is told the maximum score which can be obtained. Under the 'without-information' condition, this information is withheld. These two methods of presentation involve fundamentally different decision mechanisms. Under the 'without-information' condition, these are in part dependent on personality as opposed to intellectual variables. Consequently, performance under the two conditions is, in general, differentially affected by psychotropic drugs.

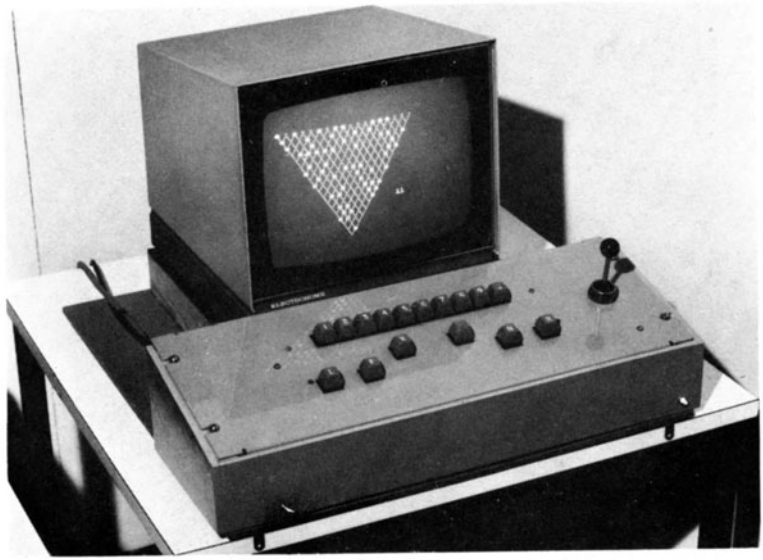


Figure 14.2 Display unit and response key board for computer-controlled psychological test procedures.

In the computer version of the test, the test patterns are presented on a CRO display or a standard TV monitor. The subject enters his solution by using left, right and erase keys (figure 14.2). Consequently, performance on the test can be broken down into three distinct phases—a preliminary search period during which no overt response is made, a tracking phase and a checking period. The tracking phase of this problem requires a series of planned sequential motor responses each of which can be timed. Some segments of the solution path are entered rapidly and thus responses are grouped as bursts of motor activity separated by periods during which renewed scanning takes place. We have found empirically that the mean time for the fastest 10 per cent of the individual key presses of the tracking phase provides a useful 'motor index' of the speed of the purely motor components of this task.

CLINICAL OBSERVATIONS

In figure 14.3 we present some results obtained with a 20 year old girl with a severe obsessional neurosis. Such patients often show a mixture of depression and anxiety symptoms, and benefit from the combination of psychotherapy with antidepressant and anxiolytic drugs. A previous admission had shown that she bene-

Table 14.2 Initial search times

	Amylobarbitone		Amylobarbitone + amphetamine	
	With information	Without information	With information	Without information
1st Day	6.6 ± 1.7	4.4 ± 0.9	4.6 ± 0.8	4.5 ±0.8
2nd Day	6.8 ± 2.2	4.7 ± 1.2	5.5 ± 1.4	5.5 ± 1.3

Means and standard deviations for initial search times. (N = 6: Days 1 and 2 of the trial have been omitted as they were not preceded by amphetamine days. Days 7 and 8 have been omitted as the amphetamine–placebo capsule was inadvertently omitted on day 7. Inclusion of these four days would have increased rather than diminished the apparent amphetamine effect.) Since these observations form an auto-regressive series, standard statistical tests are inappropriate. For the with-information condition however, a randomised test shows that if the labels day 1 and 2 and the two drug conditions are randomised, mean differences as large as those observed for day 1 occur only 3 times in 1000 random samples and for day 2 279 times in 1000 samples.

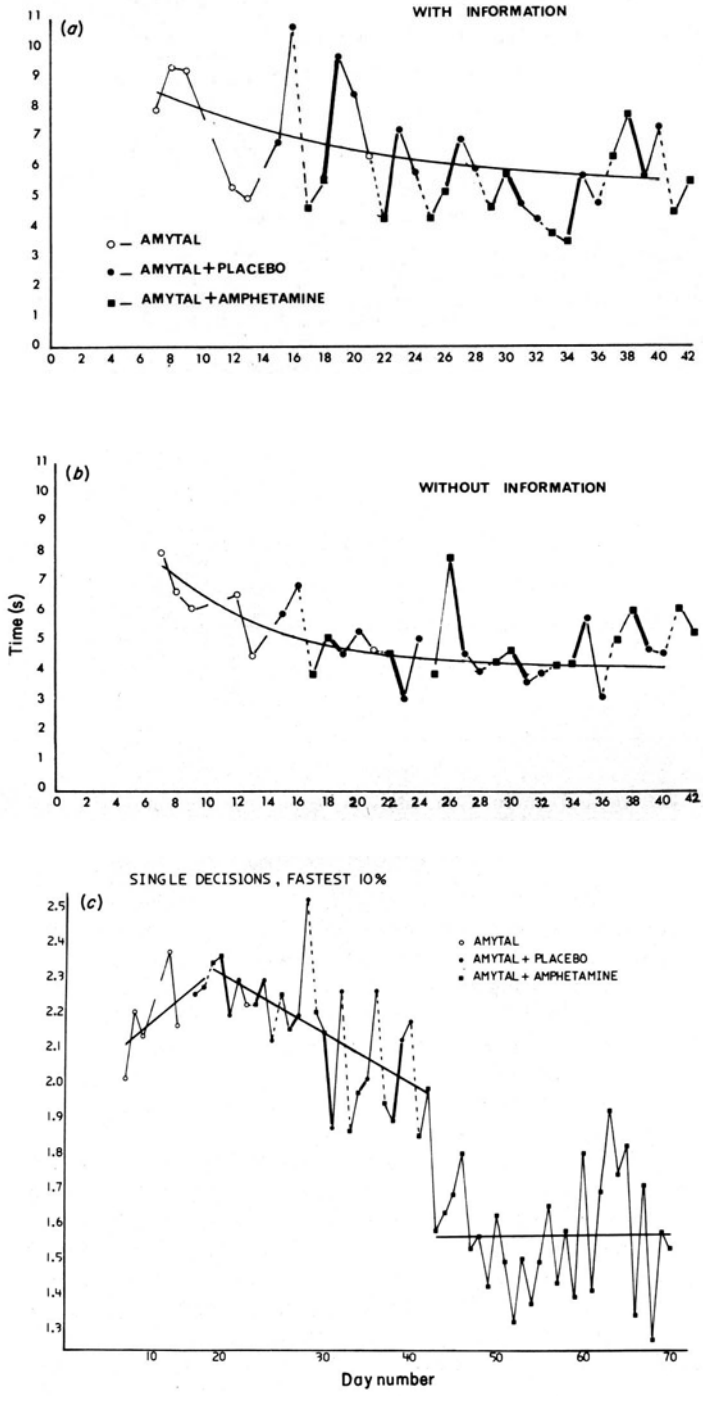
Table 14.3 Errors and corrections

	Amylobarbitone		Amylobarbitone + amphetamine	
	With information	Without information	With information	Without information
Errors	7	23	0	21
Corrections	18	33	33	27

Under the with-information condition, the addition of amphetamine increases the number of spontaneous corrections and reduces the number of errors. Under the without-information condition, the frequency of both corrections and errors is slightly reduced.

fited from sedation, and on re-admission her clinical state indicated that she again needed sedative treatment. She was at first treated with diazepam. This appeared to cause excessive disinhibition and amylobarbitone was substituted. Eight days later she started a therapeutic trial designed to determine whether the addition of a stimulant, amphetamine, to her sedative regimen would produce further improvement in her symptomatology or her accessibility to psychotherapy. The trial protocol used was based on a paradigm developed in collaboration with Laurence Freedman. In this, the patient receives two treatment regimens which alternate every second day. For a warm-up period before, and during the trial, the patient's competence on a small battery of psychological tests is assessed daily. In figure 14.3 we present plots of some of the indices derived from this patient's performance on the perceptual maze test. In figure 14.3 (a) and (b) we have plotted, for the period of the trial, the median search time under the two information conditions described above. It is immediately apparent that her performance was more variable under the with-information condition than under the without-information condition. Analysis (see table 14.2) shows that this increase in variance reflects

MEDIAN SEARCH TIMES



the effect that under the former condition the 'search' times are longer on the amylobarbitone days than on the amylobarbitone plus amphetamine days. Although the number of observations is relatively small, it was possible to conclude that this effect was most marked on the first of each pair of days.

This speeding of performance was accompanied by an increase in the number of spontaneous corrections and a marked reduction in the number of errors (table 14.3). Thus it seems reasonable to conclude that this patient was tackling the test more energetically while maintaining or perhaps increasing her ability to monitor her performance for errors. Under the without-information condition, which imposes less external constraints, her performance was not appreciably improved but neither was it appreciably impaired.

The detailed behavioural data which computer techniques enable us to collect not only allow us to look separately at a perceptual component of the subject's performance, but also we can, as described earlier, analyse the effect of treatment on the motor components. In figure 14.3 (c) we have plotted the mean motor index. Again it can be seen that the increased variance during the trial period is due to the fact that the mean times on the days on which the patient is receiving amylobarbitone alone are much slower than the times recorded on the amylobarbitone plus amphetamine days. It is also clear that there is a progressive slowing of the motor times during the pre-trial period when the subject is on amylobarbitone alone, that the addition of amphetamine reverses that trend and that, during the trial period, this reversal effect is reduced by the fact that the amphetamine is being administered on only half the days. There is also an indication which needs further investigation that the perceptual effect tends to habituate fairly rapidly, while the motor effect is initially cumulative.

On the basis of this trial it seems reasonable to conclude that in this patient a combination of stimulant and sedative treatment produced a higher level of mental competence than did treatment with a sedative alone and the combined treatment routine was therefore adopted with apparent clinical benefit. As can be seen from figure 14.3(c), the patient's motor performance during the post-trial period remained considerably faster, as indeed did her overall performance. We believe that increasing this patient's competence and self-confidence in this way enabled her to tackle more effectively her psychotherapeutic programme, which included a period of intensive 'flooding'. Subsequently the amphetamine and amylobarbitone were withdrawn blind sequentially without any subjective complaints of withdrawal

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Figure 14.3 (a,b) The mean time prior to the first motor response has been plotted during a double-blind trial (solid circles and squares). An experimental curve nas been fitted to the days on which the patient received amylobarbitone alone. It is clear that during most of the trial under the with-information condition the mean times observed on those days on which the patient also received amphetamine are faster than would have been expected for the observations made when the patient received amylobarbitone alone. This is equally clearly not the case under the without-information condition (see table 14.2). On the day during the trial with an open circle the second (amphetamine-placebo) capsule was inadvertently omitted. (c) The mean motor indices (see text) for the same patient have been plotted for the two conditions and a straight line regression fitted to the pre-trial, the trial and the post-trial periods. It is clear that much of the variance is again due to the tendency for long mean times to occur on days on which amylobarbitone was administered alone. There is also a dramatic decrease when the trial ends and the patient is placed continuously on the regimen which included daily amphetamine supplements.

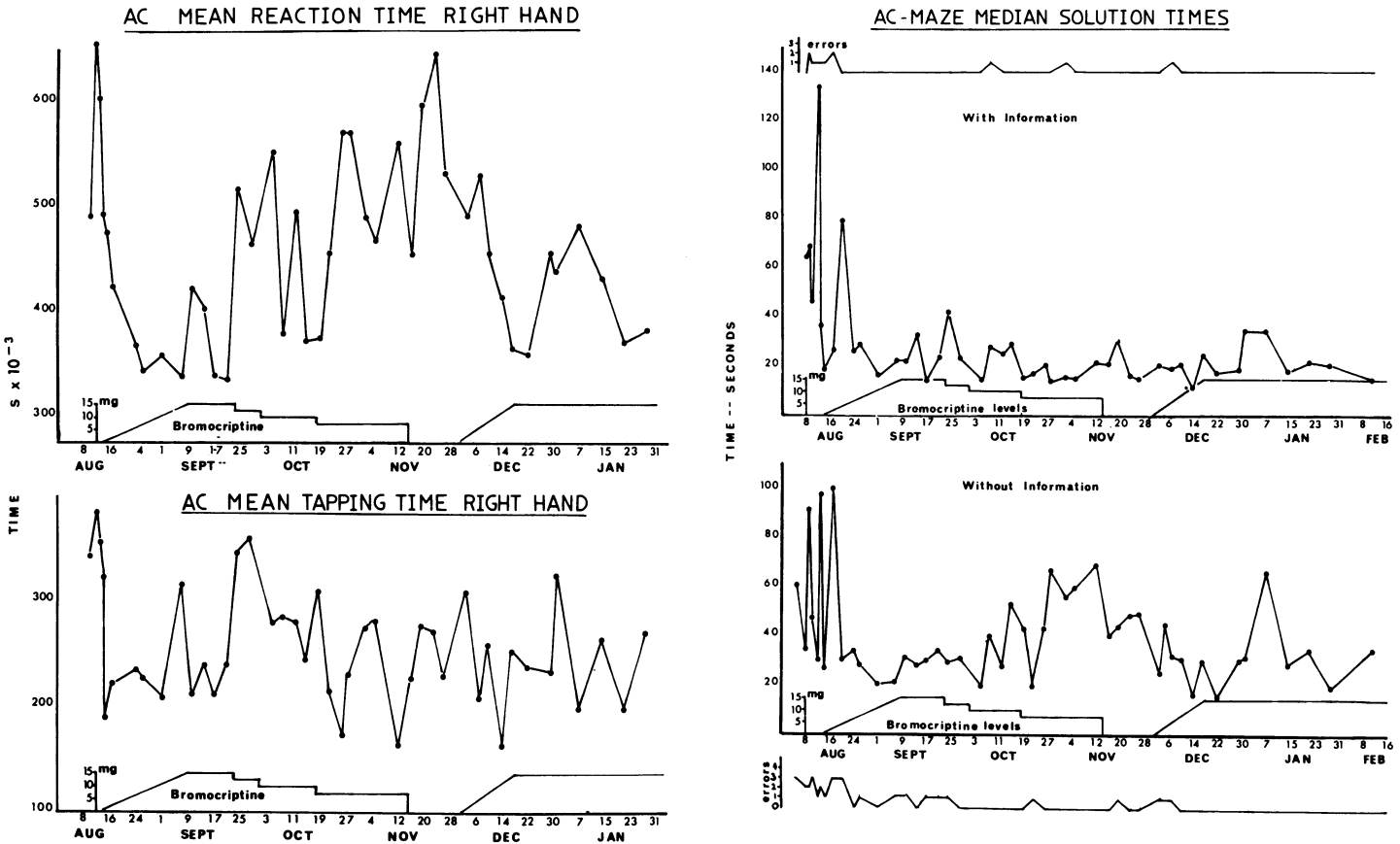

Figure 14.4 Mean reaction time and mean tapping time for the right hand and mean solution times under two information conditions for a subject receiving a trial of bromocriptine for the treatment of chronic hepatic encephalopathy. For description see text.

and with only minor transient disturbances of her test performance.

The value of being able to assess the characteristics of a patient's test performance in depth is perhaps even better illustrated by an example in which the dramatic improvement in overall performance obscured a fairly clear-cut impairment of motor skills.

In figure 14.4 we present some data from the first patient in a series of patients receiving treatment with bromocriptine for chronic hepatic encephalopathy. In figures 14.4(a) and (b) we have plotted mean daily reaction times and mean finger tapping times for the right hand. These plots show that in this subject the drug produces marked improvement in reaction time which is dose-dependent. While it would also appear that there is also improvement in finger tapping, it seems that this may be impaired at the higher dosage levels. In figures 14.4(c) and (d) the patient's performance on the more complex perceptual maze test is plotted for the two conditions of information described above. Under both conditions the administration of bromocriptine was accompanied by a marked improvement in overall performance. This was sustained well under the with-information condition, but under the without-information condition performance deteriorated as the dosage was reduced and recovered when treatment was reinstated. Examination of the subject's motor performance, however, tells a different story.

In figure 14.5 we have plotted the mean and standard deviation of our motor index for each drug dosage period of the trial. This analysis reveals that although bromocriptine produces in this patient a quite dramatic overall improvement in

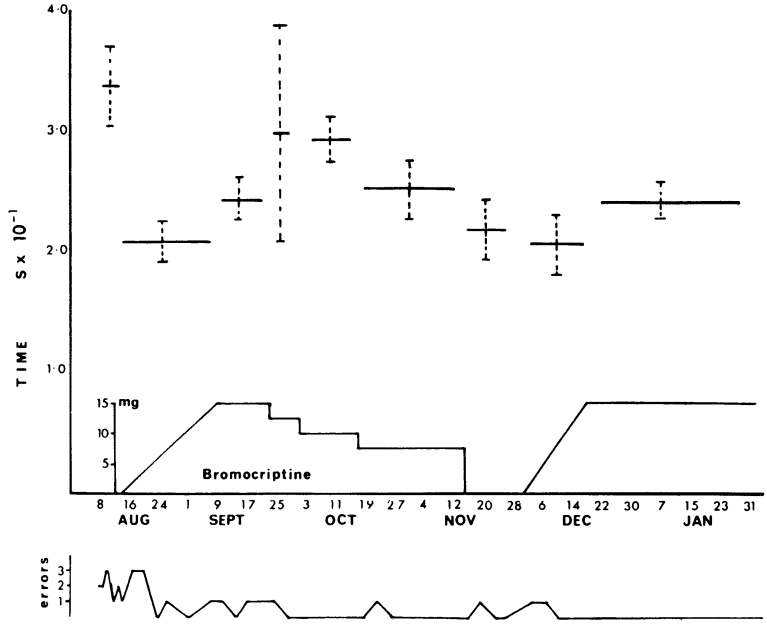

Figure 14.5 Same patient and trial as figure 14.4. Mean and standard deviations of motor indices for each drug level. (See text.)

well-being and test performance (reaction time and maze performance), it also produces quite marked motor slowing of simple motor response times. This was apparent in the finger tapping test but was most clearly recorded in the motor time analysis of the subject's performance on the maze test. It was not apparent in the reaction time recordings, presumably because the marked improvement in alertness (or arousal level) had swamped the more fundamental impairment of the motor systems.

CONCLUSIONS

We have argued that there is adequate evidence in the literature to indicate that individual subjects will respond in different ways to the same dosage of a psychotropic drug. This difference may be one of sign as well as of degree and may occur in volunteer control subjects as well as in patients (Lader, 1968; Ginsburg and Weintraub, 1976). Such differences in drug response which at times can be related to differences in the clinical diagnostic state of the subject have also been related to constitutional differences which have a genetic origin (Pare *et al.*, 1962). Papers presented in the present symposium also indicate that some individual differences which are age-dependent cannot be explained in terms of pharmacokinetic differences but must be related to individual difference in the behavioural response patterns elicited by identical chemical stimuli.

It can be concluded, therefore, that for any proper assessment of psychotropic drug effects it is essential—particularly in a clinical setting—to use methods of behavioural assessment which are sensitive to the behavioural changes produced within a single individual by the drug under investigation. Current standard psychological test procedures are not suitable for this purpose but computer techniques can greatly augment the power of psychological test procedures, and the sample protocol examples presented here suggest that these techniques will make an order of difference to our ability to monitor and evaluate the behavioural effects of a variety of psychiatric treatments.

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15
Increased sensitivity to benzodiazepines in the elderly

C. M. Castleden* and C. F. George (Department of Pharmacology, Faculty of Medicine, University of Southampton, Medical and Biological Sciences Building, Southampton, UK)

INTRODUCTION

There is a considerable body of evidence indicating that the elderly are particularly susceptible to the effects of hypnotics. Adverse reactions to these drugs not only are more common in this age group, but also may vary in quality compared with those described in the young. Thus, paradoxical excitement (Gibson, 1966), nocturnal restlessness (Exton-Smith, 1967) and imbalance following barbiturates (MacDonald and MacDonald, 1977) occur with such frequency in the elderly that their use should be restricted to the control of epilepsy; drowsiness and sedation after chlormethiazole and diazepam are more than twice as common in patients over 70 than in those under 40 years (Boston Collaborative Drug Surveillance Program, 1973); and immobility, inanition and incontinence following long-term administration of nitrazepam have been reported only in old patients (Evans and Jarvis, 1972).

However, despite this prevalence of unwanted effects, there has been little attempt to date to explain why the elderly are more prone to these reactions, or to suggest ways of avoiding them (apart from abstinence). It is known, however, that pharmacokinetic changes occur with ageing and that a decline in the efficiency of drug elimination is usual (Trounce, 1975; Triggs and Nation, 1975). Since the pharmacological action of hypnotics is related to their plasma concentration, one explanation could be that similar doses produce higher tissue concentrations in the elderly. However, Klotz *et al.* (1975) have shown that this is not the case for diazepam and, although amylobarbitone is eliminated more slowly in older patients (Irvine *et al.*, 1974), raised tissue concentrations of barbiturates in young individuals do not usually lead to excitement and restlessness. Thus, although part of the

*Present address: Leicester General Hospital, Gwendolen Road, Leicester, UK.

explanation may lie in altered pharmacokinetics, changes in pharmacodynamics are also likely.

Whatever the mechanism, one practical solution would be to recommend a reduction in dosage for the elderly. An alternative might be to prescribe an hypnotic with a short half-life, so that elimination would be virtually complete before the patient awoke the next morning. Such an hypnotic would avoid accumulation on regular treatment and suppression of normal brain activity throughout the night.

We therefore carried out two studies. The first was an attempt to demonstrate the relative importance of pharmacokinetic and pharmacodynamic variation in determining the increased action of hypnotics in the elderly. The second was designed to test the hypothesis that an hypnotic with a short half-life would cause little or no hangover the next morning.

METHODS

Study A

In the first study, the plasma concentration of nitrazepam was correlated with its pharmacological effects in healthy young and old subjects. The study was a double-blind cross-over comparison between 10 mg nitrazepam and an identical placebo. Twelve, 36 and 60 n after dosing, each subject had blood taken for plasma nitrazepam estimation, and completed a simple psychomotor test and visual analogue scales. More detailed information on subjects and methodology have been given elsewhere (Castleden *et al.*, 1977).

Study B

In the second study, the 'hangover' effect of chlormethiazole (equivalent to 2 g edisylate) was compared with that of placebo in eight young subjects. A double-blind cross-over procedure was used and the order of administration randomised and balanced by an independent observer. Each treatment was separated by at least 7 days. The subjects' mean age was 26 years and four were men. Medication was taken at 2230 h and 'hangover' effect was assessed by EEG, psychomotor performance and visual analogue scales between 0830 h and 0930 h the next day.

EEG

The EEG was recorded with the subject's eyes closed in a darkened room for 30 min on a 20-channel Van Gogh encephalograph using electrode placements according to the 10–20 system. ECG, respiration and eye movement were also monitored. A bipolar recording montage with temporal, parasagittal and transverse chains was used.

Each 10 s epoch of the recording was scored independently by two observers according to the scheme of Malpas *et al.* (1970).

Psychomotor test

The psychomotor test consisted of crossing out all the letters 'e' on a single page of prose. The same sheet of prose was used on each occasion and the time taken to complete the test and the number of mistakes made were recorded.

Visual analogue scales

Visual analogue scales assessed sleep latency (went to sleep immediately after taking the capsules–did not get to sleep at all), sleep duration (slept all night–did not sleep at all) and sedation (wide awake–almost asleep). The scales were 10 cm long and measurement was made from the left-hand side.

Statistical analysis

The results of psychomotor performance and the visual analogue scales were subjected to an analysis of variance with two treatment conditions (chlormethiazole versus placebo and order of administration).

RESULTS

Study A

Pharmacokinetics of nitrazepam

A regression of the log plasma concentration against time was plotted for each subject (figure 15.1). The mean concentration appeared slightly lower in the young at all times (table 15.1), but the differences were not statistically significant. The

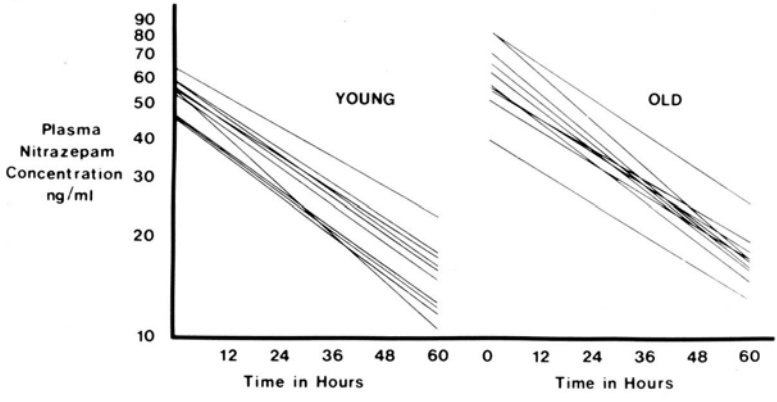

Figure 15.1 The relationship between log plasma nitrazepam concentration and time for each subject following a single 10 mg oral dose.

plasma half-life of nitrazepam was similar in both groups, as was the apparent volume of distribution and, therefore, the rate of clearance from the plasma (table 15.2).

As the mean half-life of nitrazepam was 32.0 h, 10 mg of nitrazepam would be expected to produce a steady state concentration of 104 ng/ml.

Pharmacodynamic results

After placebo, the elderly took longer to complete the test and made more mistakes than the young ($P < 0.01$ at 12, 36 and 60 h). No significant alteration in

Table 15.1 Plasma nitrazepam concentrations in old and young subjects after a single 10 mg oral dose

	Plasma nitrazepam concentration (ng/ml)		
	12 h	36 h	60 h
Old	47 ± 10	29 ± 6	17 ± 4
Young	42 ± 5	26 ± 6	15 ± 4
Probability	> 0.05	> 0.05	> 0.05

Results are given as means ± s.d. and probabilities shown relate to differences between the values for old and young subjects.

Table 15.2 Nitrazepam pharmacokinetics in old and young subjects following a single 10 mg dose of nitrazepam

	Old	Young	
Half-life (h)	31.9 ± 5.5	32.1 ± 4.6	$P > 0.05$
$V_{d(a)}$ (l/kg)	2.7 ± 0.4	3.0 ± 0.5	$P > 0.05$
Clearance (ml min^{-1} kg^{-1})	1.0 ± 0.2	1.1 ± 0.3	$P > 0.05$

Results are shown as means ± s.e.m.

the accuracy of the young occurred after nitrazepam, whereas the number of mistakes was greater at all times in the elderly, compared with placebo. At 12 and 36 h (figure 15.2) the differences were highly significant ($P < 0.01$ at both times). Although both groups took longer to complete the test after nitrazepam than after placebo, the effect of the drug on speed was not significantly greater in the elderly than in the young group (figure 15.3). The difference for both groups was significant at 12 and 36 h ($P < 0.05$ at both times).

The relationship between plasma nitrazepam concentration and its pharmacological effect

(a) Subjective assessment. The subjects' complaints following nitrazepam are tabulated in table 15.3. There was no difference between the old and the young in the type or number of complaints. No complaints were received from either group after placebo. The subjects with symptoms had higher plasma concentrations of nitrazepam (mean 44.6 ng/ml) than those without (mean 20 ng/ml) (figure 15.4). Most symptoms occurred at 12 h, when the mean plasma concentration for all

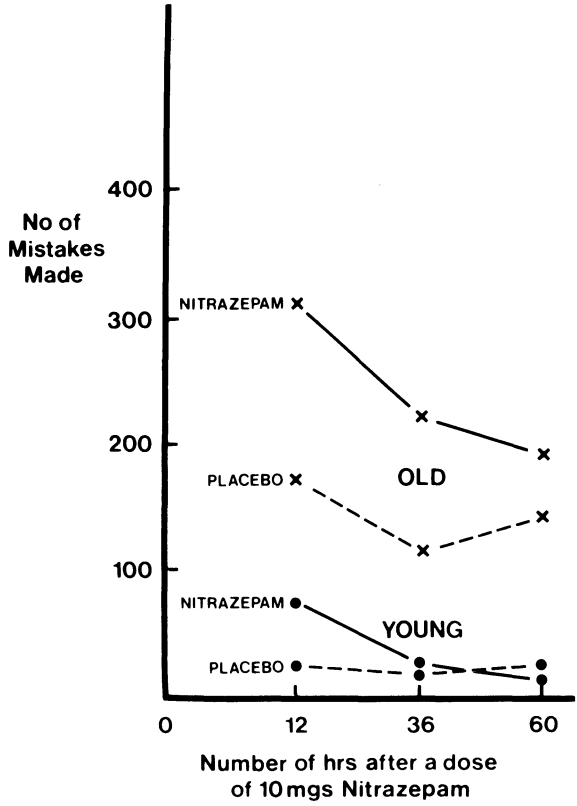

Figure 15.2 Total number of mistakes made in the psychomotor test by each age group after nitrazepam (10 mg) and placebo.

Table 15.3 Number of subjects complaining of side effects 12 h after 10 mg oral nitrazepam

	Sleepy	Unsteady/ dizzy	Nausea	Headache	Abnormal dreams	None
Old	5	5	1	1	1	2
Young	7	4	1	0	0	2
Total	12	9	2	1	1	4

subjects was 44.5 ng/ml. Only one subject reported an adverse effect at 36 h, and her plasma concentration (42 ng/ml) was the highest of all subjects at that time (mean 27.9 ng/ml). No subject complained of an adverse effect at 60 h, when the mean plasma concentration was 16.9 ng/ml.

(b) Visual analogue scales. The mean results are tabulated in table 15.4. Subjects

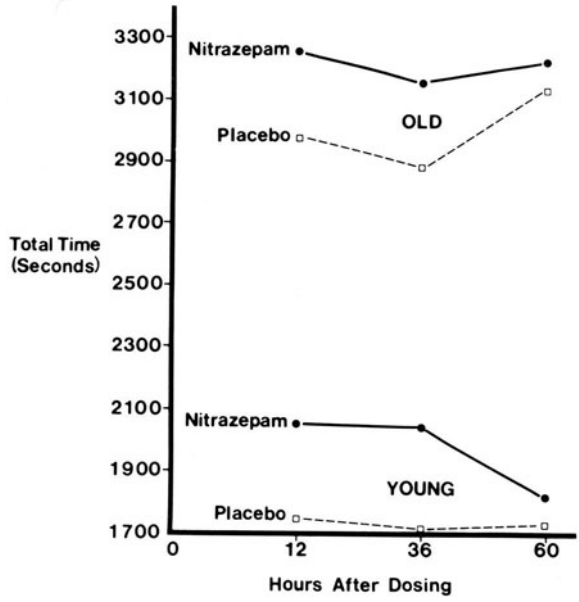

Figure 15.3 Total time taken by each age group to complete psychomotor test after 10 mg nitrazepam and placebo.

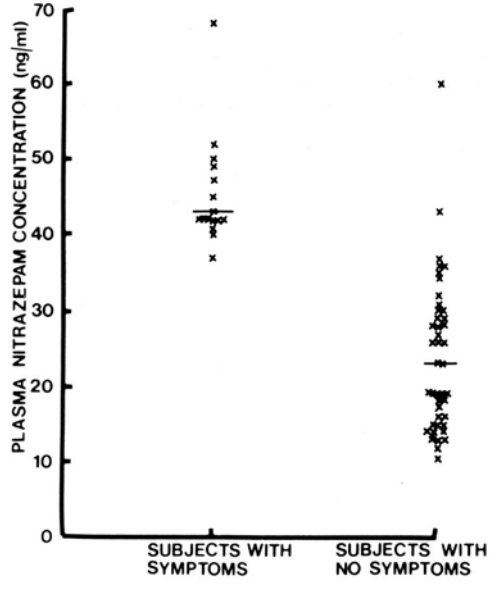

Figure 15.4 Plasma nitrazepam concentrations (ng/ml) of subjects with symptoms compared with those who had none.

Table 15.4 Mean results of all subjects in visual analogue scales for subjective assessment of sleep and alertness after 10 mg nitrazepam and placebo

		Placebo	Nitrazepam	Significant difference
Sleep	12 h	32.0	4.2	< 0.01
	36 h	21.0	9.1	< 0.01
	60 h	14.1	8.7	< 0.01
Alertness	12 h	12.9	42.2	< 0.01
	36 h	8.2	12.8	< 0.01
	60 h	8.7	14.3	> 0.05

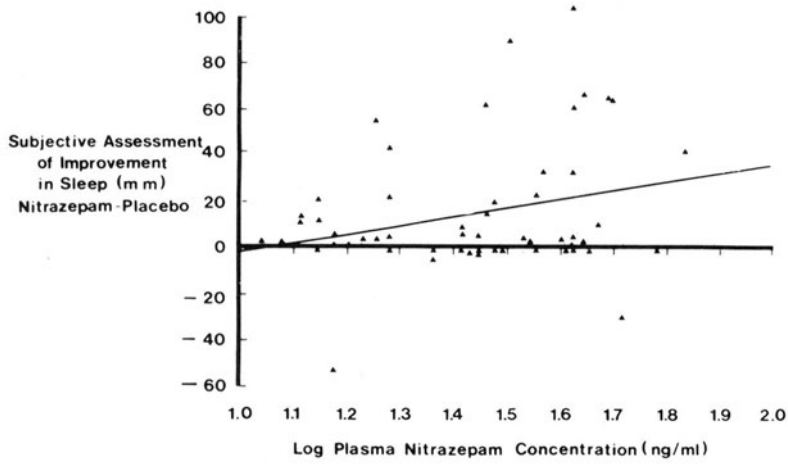

Figure 15.5 The relationship between subjective assessment of improvement in night's sleep after nitrazepam compared with that following placebo and the log plasma nitrazepam concentration. The regression was calculated by the least squares method.

slept better on all three nights after nitrazepam and a correlation was shown between subjective impression of the night's sleep and log plasma nitrazepam concentration ($P < 0.05$) (figure 15.5). However, subjects felt less awake after nitrazepam at 12 and 36 h ($P < 0.01$) than after placebo (table 15.4). Plasma nitrazepam concentration correlated again with this difference (figure 15.6) but not with the accuracy and speed of psychomotor performance.

Study B

Results of the comparison between chlormethiazole and placebo

No difference could be detected in the EEG sleep score following chlormethiazole and placebo. No subjects showed stage III or IV sleep and REM sleep did not occur.

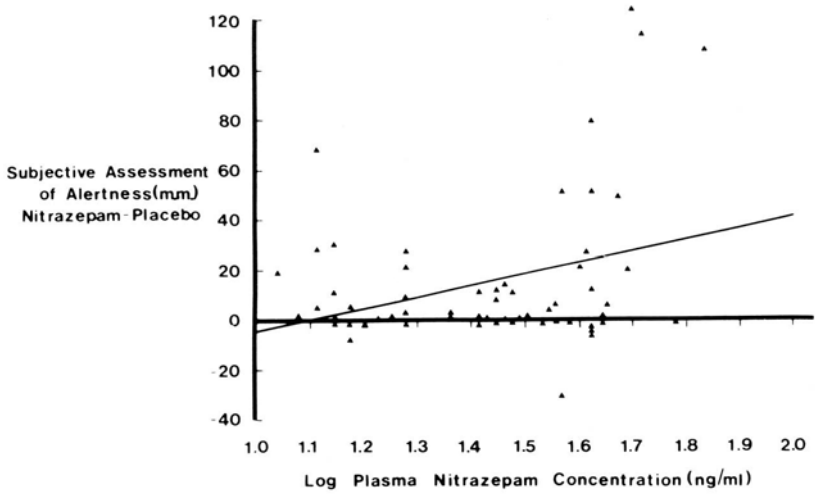

Figure 15.6 The relationship between subjective assessment of alertness after nitrazepam compared with that following placebo and the log plasma nitrazepam concentration. The regression was calculated by the least squares method.

Performance in the psychomotor test was also similar on both treatments, and visual analogue scales indicated that subjects felt equally wide awake after chlormethiazole as following placebo (table 15.5).

All eight subjects had nasal symptoms, prickling and burning in the nose, associated in some with watering of the eyes, after chlormethiazole and none following placebo.

Table 15.5 Results of all subjects in EEG sleep score, psychomotor performance and visual analogue scales following chlormethiazole and placebo

	EEG sleep score	Psychomotor test mistakes	Psychomotor test time (s)	Visual analogue scale sedation
Chlormethiazole	17 ± 14	12 ± 3	194 ± 13	25 ± 6
Placebo	32 ± 16	18 ± 5	206 ± 20	45 ± 11
Probability	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$

Results are shown as means ± s.e.m.

DISCUSSION

Evans and Jarvis (1972) reported that some elderly patients became confused, incontinent and immobile after long-term administration of nitrazepam. As the syndrome had not been reported in younger patients, a suggestion was made that

nitrazepam elimination became less efficient with ageing, so that similar doses produced higher tissue concentrations in the elderly than in the young. Despite some evidence that plasma nitrazepam concentrations were related to their pharmacological effects, we found no evidence to support the hypothesis that healthy, old subjects showed a different pharmacokinetic profile from that of healthy young subjects. Nevertheless, nitrazepam had a significant effect on the ageing brain which was not seen in younger individuals. Bond and Lader (1972) have pointed out that the speed of psychomotor tests relies largely on motor function, while the accuracy depends on cognitive factors. Thus, nitrazepam depressed motor function irrespective of age, while it affected cognitive function to a greater extent in the elderly. The fact that the elderly performed less well overall in the psychomotor test, even on placebo, reflected a general deterioration that accompanies ageing, especially when speed of performance is emphasised (Anastasi, 1958).

A number of possible explanations exist for the increased response of the elderly CNS to nitrazepam. Firstly, in view of the complex events interposed between target organ stimulation and effector organ response (Rawlins, 1974), impaired efficiency of homeostatic mechanisms in the elderly may explain the observed differences in psychomotor response. Secondly, the presence of intercurrent disease may unmask pharmacological effects of drugs which are minimal under normal circumstances; for example, bronchospasm following the administration of β-blockers to asthmatics. This might explain the abnormal effect of L-dopa in demented Parkinsonian patients and the restlessness and confusion caused by hypnotics in patients with mild chronic brain failure (Sacks *et al.*, 1970).

A third possibility is based on recent evidence that specific receptors for benzodiazepines may exist in the CNS (Squires and Braestrup, 1977). By analogy with morphine receptors and the subsequent elucidation of the action of encephalins (Snyder, 1977), such receptors would imply the presence of an unknown, endogenous neuro-transmitter chemically similar to the benzodiazepines as a natural ligand for this receptor. If production of this benzodiazepine-like transmitter fell in the elderly as a result of neuronal atrophy or decreased metabolic activity in the central nervous system analogous to that seen in the liver, an increased sensitivity of the receptor to the action of exogenous transmitter would be expected.

However, in practical terms the results of this study suggest that it would be impossible to obtain an adequate hypnotic effect with nitrazepam at any age without 'hangover' effects the next day. Furthermore, accumulation would occur on regular treatment and, as abnormal EEG sleep patterns persist throughout the night, cessation of therapy would be likely to lead to increased wakefulness, encouraging dependence (Oswald and Priest, 1965; Adam *et al.*, 1976).

These unwanted effects are not peculiar to nitrazepam but are common to most hypnotics which have half-lives in excess of 7 h; thus plasma concentrations decline only slowly, and substantial amounts of drug are present in the body the following day (Breimer, 1977).

The absence of demonstrable hangover effects following chlormethiazole showed that an hypnotic with a short half-life (less than 2 h) may provide a solution to these problems. The results were in stark contrast to the findings of other workers with the benzodiazepines, meprobamate and barbiturates and indeed to our findings in the initial study (Malpas *et al.*, 1970; Bond and Lader, 1973; Keston and Brocklehurst, 1974; Walters and Lader, 1971). However, all subjects suffered nasal symptoms which would preclude their use of this particular drug.

Such effects do not occur so frequently in the old (Pathy, 1977), for whom the drug is recommended, and further studies are in progress to assess its effectiveness in this age group. This preliminary evidence suggests, however, that chlormethiazole may be a more satisfactory hypnotic for the elderly.

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16
Response to anaesthetic drugs in the elderly

J. W. Dundee (Department of Anaesthetics, The Queen's University of Belfast, Northern Ireland)

INTRODUCTION

It is difficult to separate the effects of disease from those of the ageing process, but as far as anaesthesia is concerned, this is an academic distinction, since disease is more common in the elderly. Anaesthetists are probably more aware of drug sensitivity than are any other physicians. Not only do they use potent drugs, but also because of the intravenous and inhalational routes, the maximum effect of these occurs within a few minutes. Furthermore, the effects of a severe adverse

Table 16.1 Drugs used by anaesthetists

Pre-anaesthetic medication	
Anti-sialogogues	i.m.
Sedatives, hypnotics, narcotic analgesics	Oral; i.m.
Induction agents	
Thiobarbiturates, steroids, eugenols, ketamine	i.v.
Maintenance agents	
Nitrous oxide–oxygen, cyclopropane	Inhalation
Halothane, methoxyflurane, enflurane, trichloroethylene	Inhalation
Neuromuscular blocking drugs	
Depolarising–suxamethonium	i.v.
Non-depolarising–tubocurarine, gallamine, pancuronium	i.v.
Various adjuvants, etc.	
Neuroleptic combinations	i.v.
Narcotic analgesics, benzodiazepines	i.v.
Hypotensive drugs	i.v.
Neostigmine, pyridostigmine	i.v.
Local anaesthetics	

reaction require immediate attention. However, these routes are themselves safety factors, as they permit a fine adjustment of dosage to the patient's needs and thereby minimise the risk of overdosage with its accompanying dangers. Provided one appreciates the slower circulation time found in the elderly (Hunter, 1947), with proper adjustments of dosage and technique most anaesthetic drugs can be given safely to geriatric patients.

Although this presentation deals with drug responses, it is difficult at times to separate this from the state of 'anaesthesia'. The fact that a patient is rendered unconscious, may be paralysed and may have a multitude of physiological insults, is itself a stress which is less well tolerated by the elderly patient. However, as far as possible, an attempt has been made to look at the effects of individual drugs.

It is not out of place to remind readers of the various types of drugs used in anaesthetic practice (table 16.1). Not all of these will be referred to in this paper.

Most examples of sensitivity to anaesthetic drugs in the elderly are the result of alterations in pharmacokinetics rather than a true age-dependent difference in the type of response. Altered responsiveness of organs to drugs is also important, and it is often impossible to separate pharmacodynamic and pharmacokinetic contributions to the clinical response to anaesthetic drugs.

DIFFERING TYPE OF RESPONSE

True age-dependent differences in response to drugs used by the anaesthetist are rare and may be more anecdotal than proven. Elderly patients often develop mild restlessness and anxiety after barbiturates or hyoscine, and these should be avoided or used sparingly.

The rise in intraocular pressure induced by atropine, while of little consequence in normal subjects, may induce acute glaucoma in the elderly. Extended venous thrombosis following intravenous diazepam is much more likely to occur in elderly patients (figure 16.1). These latter two may be examples of an exaggeration of a normal response rather than a differing type of response; however, their clinical importance is obvious.

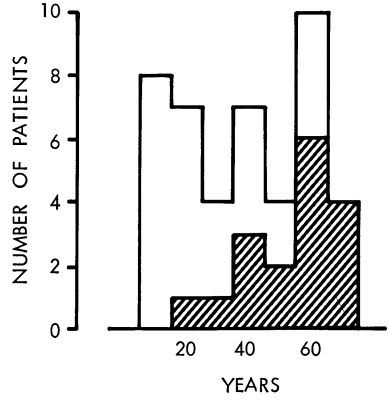

Figure 16.1 Incidence of venous thrombosis found 7–10 days after intravenous injection of 10 mg diazepam, related to the age of the patients. (After Hegarty and Dundee, 1978).

PHARMACOKINETIC ALTERATIONS

Table 16.2 lists the three important factors which may influence the rate of onset of action of anaesthetic drugs in the elderly.

There are good clinical reasons to believe that the arm-brain circulation time is frequently prolonged in the elderly. This is the main factor in determining the rate of onset of action of thiopentone and similar drugs, and, if a fixed rate of injection is used, clearly there is an increased risk of giving an overdose to the elderly patient.

Table 16.2 Factors influencing the onset of action of anaesthetic drugs in the elderly

Slow circulation time
Decreased pulmonary function
Poor absorption from injection sites

One frequently notices a marked delay in the occurrence of muscle fasciculations following suxamethonium in the elderly; this is likewise due to a slow circulation time. Since fasciculations precede relaxation , a second (unnecessary) dose of relaxant could easily be given if the importance of the prolonged circulation time is not appreciated. A slow circulation time will also affect the rate of onset of effect of opiate analgesics and of other drugs given intravenously during anaesthesia, but this is of less clinical importance than with drugs given during induction.

Although most important pulmonary functions decline with age (Briscoe, 1965; Richards, 1965), this does not markedly affect the response to inhalational anaesthetics. Increases in residual volume will result in a slower rate of change of alveolar and arterial blood levels, but this is not of great clinical importance. However, the additive effects of smoking and age (Fletcher and Peto, 1977) can make an inhalational induction both slow and stormy.

Apart from poor absorption of intramuscularly administered premedicants, which are decreasing in popularity, there are no other important factors influencing the onset of action of anaesthetic drugs in the elderly.

Recovery from the anaesthetic action of drugs such as thiopentone is due mainly to translocation to non-nervous tissues rather than detoxication (Dundee and Wyant, 1974). A reduction in total body water and lean body mass together with a less efficient circulation will interfere with redistribution, and these are common findings in the elderly. Even allowing for the smaller body mass of the elderly patient (Crooks, O'Malley and Stevenson, 1976), there is a general impression that recovery is not as prompt as in the younger age group.

A reduction in plasma proteins, which is not uncommon in the elderly, results in more unbound drug reaching target organs. This will produce not only a deeper level of narcosis, but also a more profound cardiovascular depression. A vicious circle is quickly established (table 16.3), with reduced regional blood flow and tissue perfusion further decreasing redistribution and prolonging the clinical effects. This is undoubtedly the most serious type of sensitivity to anaesthetic drugs in elderly patients. It occurs in patients who are not well able to tolerate sudden cardiovascular depression, and the eventual outcome may be disastrous.

Table 16.3 Factors which can modify the action of thiopentone in the elderly and lead to prolonged hypotension

Decreased binding to albumin
Increased free-drug concentration
Exaggerated pharmacological action
Exaggerated pharmacodynamic action
Hypotension and reduced tissue perfusion
Decreased redistribution in the body
Prolonged clinical effect
Possible cerebral hypoxia

Pharmacokinetic disturbances do not appear to affect the action of inhalational agents. In contrast, paralysis from myoneural blocking drugs may be prolonged because of decreased tissue perfusion and slower removal from their site of action. Plasma protein derangements can have a profound effect on both their intensity and their duration of action, and this will be discussed later, as will be the influence of decreased renal function.

There is one interesting pharmacokinetic finding in relation to local anaesthetics. Bromage (1954) found an inverse relationship between the dose of local anaesthetic required for epidural anaesthesia and the age of the patient. With increasing age, the intravertebral foramina becomes less permeable and so hinders the escape of solutions, so that a given volume travels further up the spinal canal and causes a wider area of block.

The altered ability of elderly patients to eliminate drugs which are entirely metabolised in the body is not of great importance in anaesthesia. The fact that patients with liver disease may be unable to detoxicate repeated doses of pethidine has led to problems in the post-operative period (Dundee and Tinckler, 1952) when its effects became exaggerated, but this analgesic is widely used in geriatric practice. For the sake of completeness, reference is made to enzyme induction, but this is not important in the present context. Renal excretion of relaxants will be discussed later.

ALTERED END ORGAN RESPONSE

Reference has already been made to the profound degree of hypotension which may follow the use of thiopentone in the elderly. This is not all due to altered pharmacokinetics but is in part due to the increased sensitivity of the myocardium to its depressant action and to the lesser ability to compensate for peripheral vasodilation. This sensitivity applies to all intravenous anaesthetics and to a lesser extent to inhalational drugs. It is also seen with some opiates, particularly pethidine, and occasionally with the histamine-releasing relaxant tubocurarine. Phenothiazines, droperidol and other vasodilator drugs may also produce marked hypotension in the elderly. The increased prevalence of postural hypotension must also be remembered in this age group.

While dysrhythmias are relatively common during anaesthesia in the elderly patient, it is difficult to say whether this is a true accompaniment of the ageing process or whether it is associated with coronary artery disease.

Altered respiratory responses to anaesthetics in the elderly may be due to disturbance of perfusion-ventilation ratio, but also in part associated with concomitant disease such as emphysema and chronic bronchitis. In addition, increased irritability of the tracheobronchial tree may occur, with tendency to breath-holding, coughing, etc. Many elderly patients have a higher $P_{a(CO_2)}$ level than normal, and difficulty may occur in re-establishing normal respiration after relaxants or opiates.

A diminshed respiratory exchange, with a decrease in tidal volume, may lead to an exaggeration of the respiratory depressant effects of opiates, particularly in the post-operative period, and minor degrees of persistent curarisation can have serious effects in the elderly.

There are two studies on the relationship between thiopentone dose requirement and age of patient. Dundee (1954*a*) reported a retrospective analysis of the total dose required for 2 h of anaesthesia (intermittent thiopentone with nitrous oxide-oxygen and tubocurarine or laudexium) in 500 patients undergoing abdominal or thoracic operations (figure 16.2). Requirements of thiopentone were fairly constant in middle age, but were increased in patients under 26 years and decreased in those aged 46 and over. Because of the small number of cases in each group, when these data were analysed for the individual types of operation, it was not possible to subject them to statistical analysis. In a similar type of analysis,

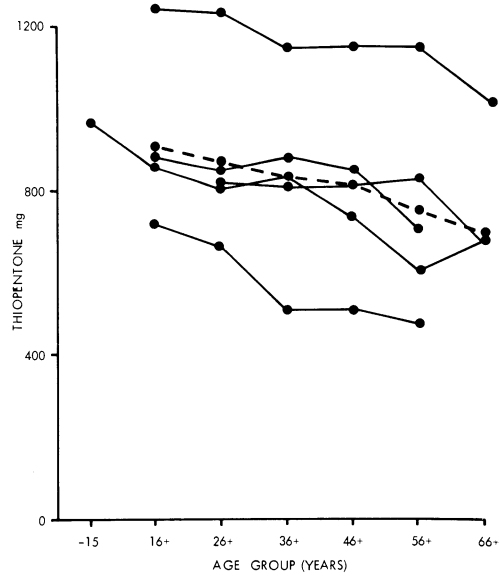

Figure 16.2 Average dose of thiopentone, adjusted on a weight basis for a 63 kg patient, required over a 2 h period in five types of thoracic and abdominal operations. Patients were anaesthetised with intermittent thiopentone–nitrous oxide–oxygen and relaxed with tubocurarine. Hatched line indicates average for all patients. (Modified from Dundee, 1954*a*.)

Dundee (1954*b*) found no relationship between age and the 2 h requirements of either tubocurarine or laudexium.

In a different type of study, Andreasen and Christensen (1977) analysed the induction dose of thiopentone in 540 patients and found a significant fall with age, although the extent of this is not stated. These reports highlight the problem of studying the dose requirements of drugs during anaesthesia. The end-point for an initial or supplementary dose is often difficult to elicit, and differing impressions as to the 'depth' of anaesthesia introduce inaccuracies. However, it is generally agreed that smaller doses of anaesthetics are required to induce and maintain sleep in the elderly, but this is not an invariable finding. Unexpected resistance does occur, and this may be associated with alcoholism or increased drug-taking. A recent survey by Skegg, Doll and Perry (1977) showed increased prescribing of psychotropic drugs in the elderly which may contribute to this.

The well-documented increase in side effects after benzodiazepines in the elderly (Greenblatt, Allen and Shader, 1977), together with persistence of depressant action, is typical of the response to most sedative and hypnotic drugs. Part of this may be due to slower removal from the body but Castleden *et al.* (1977) have suggested that increased sensitivity of the ageing brain does occur.

Hypothyroidism and hypothermia, which are not uncommon, will also induce sensitivity to depressant drugs in the elderly. From the clinical point of view, one must not forget that the aged patient is unduly susceptible to the adverse effects of hypoxia, whether this be of the hypoxic or the stagnant form. A degree of hyperventilation which will produce no adverse effects from cerebral vasoconstriction may cause persistence of minor degree of personality changes, confusion, urinary upset or other undesirable cerebral sequelae.

There are no grounds for believing that the response of the liver or kidney to exposure to general anaesthesia is *per se* altered in the elderly patient. Increased toxic action on these organs results mainly from exaggerated cardiovascular depression reducing their blood supply. This, in turn, will alter their ability to detoxicate or excrete certain drugs. However, attention is drawn to the potentially nephrotoxic action of large amounts of methoxyflurane—whether from short administration of a high concentration or long administration of a low concentration—which might have serious consequences in elderly patients who already have some impairment of renal function. Nephrotoxicity will be potentiated by tetracyclines, and this combination is better avoided in the elderly.

The action of drugs on the myoneural junction may be very different in the elderly, and this is such a major topic that the neuromuscular blocking drugs will be considered separately.

NEUROMUSCULAR BLOCKING DRUGS

Table 16.4 lists a number of factors which influence the response of the elderly to these drugs.

Since these drugs are bound to a variable degree to plasma proteins, the alteration in plasma protein levels or in the ratio of individual proteins which occurs commonly in the elderly will affect the response to neuromuscular blocking drugs. Increased sensitivity to all relaxants can be expected where there is a low level of plasma protein (Skivington, 1973). Patients with a low albumin level are particularly sensitive to alcuronium (Stovner, Theodorsen and Bjelke, 1971*a*).

Tubocurarine is bound to gamma-globulin (Aladjemoff, Dikstein and Shafrir, 1958) and studies by Baraka and Gabali (1968) and by Stovner *et al.* (1971*a*). showed a positive correlation between tubocurarine requirements during anaesthesia and plasma gamma-globulin level. This agrees with reports of resistance to tubocurarine in patients with an altered A/G ratio (Dundee and Gray, 1953; El-Hakim and Baraka, 1963). Surprisingly, one may encounter this resistance in elderly patients with liver disease or an increased gamma-globulin from other causes. Theoretically, these patients would be expected to react normally to other non-depolarising relaxants (Stovner, Theodorsen and Bjelke, 1971*b*, 1972).

Table 16.4 Factors influencing the response to myoneural blocking drugs in the elderly

Altered plasma proteins
Liver dysfunction
Hypothermia
Electrolyte and acid–base disturbance
Impaired renal excretion

Liver dysfunction, malnutrition and general debility may be accompanied by a low level of plasma pseudocholinesterase of sufficient degree to prolong the action of suxamethonium and possibly produce a 'dual' block.

Impaired temperature homeostasis is not uncommon in the elderly (Collins *et al.*, 1977). On coming to surgery, particularly for emergency operations, many elderly patients may have an undetected low body temperature. Even moderate degrees of hypothermia will decrease the effectiveness of tubocurarine and other non-depolarising relaxants (Cannard and Zaimis, 1959). This can produce problems of reversal if the patient is warmed during the operation, at the end of which they may have received a very large dose of relaxant. There is an enhancement of the action of depolarising relaxants at low body temperature.

Although the problem is not confined to the elderly, there may be difficulty in establishing adequate respiration after non-depolarising relaxants in patients with electrolyte and acid-base disturbances. Acidaemia and a low serum potassium influence the response to these drugs (Baraka, 1964; Gamstorp and Vinnars, 1961, 1963), but hypovolaemia may be a contributory factor. One must hesitate to incriminate a specific pharmacological action in this syndrome of 'neostigmine-resistant curarisation' (Hunter, 1956) in elderly patients. In the absence of relaxants, metabolic acidaemia can cause confusion or unconsciousness, and even inadequate respiration (Brooks and Feldman, 1962), and the term 'moribundity' has been applied to this situation.

Some degree of renal dysfunction is common in the elderly, and this could prolong the action of gallamine, which is solely dependent on the kidneys for removal from the body. Although tubocurarine is largely excreted in the urine, its action is seldom prolonged in patients with renal disease.

SUMMARY

With adequate knowledge of the factors which alter the response to drugs and with careful handling and prompt treatment of emergencies, the anaesthetist can safely use most of our available drugs in the elderly patient. True age-dependent differences in response to such drugs are rare.

A slower circulation time and decreased respiratory function may prolong the onset of action of injected or inhaled drugs. Impairment of normal processes of redistribution in the body can increase the toxicity of thiopentone, and this is probably the greatest problem which crops up in clinical practice. Slower detoxication is not important with most drugs used in anaesthesia.

The elderly patient is relatively sensitive to the depressant effects of most drugs given by the anaesthetist. This can be manifested by more marked and more prolonged hypotension and respiratory depression and also by a delay in return of full consciousness. The additional adverse effects of hypoxia may contribute to this. However, on occasions, elderly patients may show unexpected resistance to cerebral depressants.

The response of the geriatric patient to neuromuscular blocking drugs is complex and will be affected by reduction or alteration in plasma protein, liver dysfunction, hypothermia, electrolyte imbalance and renal impairment. With these drugs, in particular, adequate knowledge of the overall condition of the patient can prevent problems which may well endanger life.

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Monoamines and their metabolites and monoamine oxidase activity related to age and to some dementia disorders

C. G. Gottfries, R. Adolfsson, L. Oreland, B. E. Roos and B. Winblad
(From the Departments of Psychiatry (C. G. G., R. A.) and Pharmacology (L.O.) and Institute of Pathology (B. W.), University of Umeå, Sweden, and from the Department of Psychiatry (B. E. R.), University of Uppsala, Sweden)

INTRODUCTION

Most psychotropic drugs exert their effects by influencing the activity in monoaminergic systems in the human brain. It is therefore of importance, when discussing drugs and the elderly, to know whether and, in what way, age and dementia disorders influence the metabolism of monoamines in the CNS. In animal experiments, it has been shown that there is a reduced turnover of the catecholamines in the old rat brain (Finch, 1973, 1976; Algeri *et al.*, 1976). The activities of tyrosine hydroxylase (TH) as well as dopamine decarboxylase (DOD) have been examined post mortem in humans and highly significant age declines have been reported (Lloyd and Hornykiewicz, 1970; McGeer, McGeer and Wada, 1971; McGeer and McGeer, 1973; Cote and Kremzner, 1974). Post-mortem studies in man have also shown reduced levels of dopamine (DA) and noradrenaline (NA) related to age (Carlsson and Winblad, 1976; Adolfsson, Gottfries and Winblad, 1976; Robinson *et al.*, 1977). In senile dementia and Alzheimer's disease reduced levels of homovanillic acid (HVA) have been found (Gottfries, Gottfries and Roos, 1968, 1969) as well as reduced levels of DA and NA (Gottfries, Roos and Winblad, 1976) when compared with age-matched controls.

In the present investigation, monoamines, their metabolites and monoamine oxidase (MAO) activity were estimated in brain tissue in autopsy material, including cases with normal ageing. Levels of monoamines and their metabolites have also been determined in a series of patients with dementia disorders of the Alzheimer type. Furthermore, patients with Alzheimer's disease have been investigated as regards MAO activity in platelets.

MATERIAL AND METHODS

The material of cases with normal ageing was collected in the autopsy room. Samples from the brain were dissected from patients who before death had suffered no neurologic or psychiatric disease. In all, 45 cases were investigated. Chemical analyses were not made on each sample, however, and therefore the number of cases in the different series varies. Various (9–16) nuclei or regions of the brain were investigated, as is evident from the tables. The samples were removed as quickly as possible after the opening of the skull and immediately frozen at −18°C.

The brains of 19 patients with senile dementia or Alzheimer's disease were also analysed for monoamines and their metabolites. Patients with encephalomalacias were excluded, even though they sometimes were, on clinical grounds, regarded as suffering from dementia disorders of Alzheimer type.

In another study of 40 autopsy cases (including 25 schizophrenics and 15 normally aged people), the activitiy of MAO was estimated in brain tissue. There were no significant differences in the MAO activity between schizophrenics and controls. The mean age of the 40 cases was 70.0 ± 10.0 (s.d.) years, and the age variance 53–85 years.

Twelve patients (8 men, 4 women) with the clinical diagnosis of Alzheimer's disease were investigated for their platelet MAO activity. Blood samples from a control material of healthy volunteers matched for age and sex were also collected.

Variables which might influence the levels of the monoamines, their metabolites and the MAO activity were controlled as far as possible. These variables include: cause of death, medication, age, sex, brain weight, dissection technique, arteriosclerosis of basal brain vessels, encephalomalacias, time elapsed between death and autopsy, time until the samples were frozen and storage time. Time elapsed between death and autopsy seems to have a significant influence on the 5-hydroxyindoleacetic acid (5-HIAA) levels, and therefore they were corrected for this time variable. DA was determined according to the method of Carlsson and Lindqvist (1962); HVA according to Andén, Roos and Werdinius (1963) and Korf, Roos and Werdinius (1971); NA according to Bertler, Carlsson and Rosengren (1958) and Häggendahl (1963); 3-methoxy-4-hydroxy-phenylethyleneglycol (MHPG) according to Meek and Neff (1972); 5-hydroxytryptamine (5-HT) according to Andén and Magnusson (1967); and 5-HIAA according to the method of Jonsson and Levander (1970). The activity of MAO in brain tissue was estimated according to the method of Wurtman and Axelrod (1963), with serotonin, tryptamine and β-phenylethylamine as substrates, as described earlier (Ekstedt and Oreland, 1976), and the activity of MAO in platelets with tryptamine and β-phenylethylamine as substrates according to Wiberg, Gottfries and Oreland (1977).

Pearson's correlation test was applied in the study of correlations between chemical variables and age. Group differences were analysed with Student's *t*-test or Wilcoxon's matched-pairs signed-rank test. Two-sided test of significance was used if not otherwise stated.

RESULTS

Cases with normal ageing

DA was estimated in 16 nuclei or regions of the brain in a variable number of cases between 18 and 24. The mean age for the 24 cases was 61.0 ± 18.7 (s.d.) years and

Table 17.1 Product-moment correlations (r) between dopamine (DA), homovanillic acid (HVA), noradrenaline (NA), 3-methoxy-4-hydroxy-phenethyleneglycol (MHPG), 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) in brain tissue and age (one-sided test for DA/age and NA/age)

	DA/age		HVA/age		NA/age		MHPG/age		5-HT/age		5-HIAA/age	
Part of brain	r	n	r	n	r	n	r	n	r	n	r	n
Hypothalamus	−0.18	24	0.16	19	−0.14	28	−0.37	11	0.40†	21	0.29	21
Nucleus caudatus	−0.33*	23	−0.01	44	−0.19	42	−0.51*	11	0.12	41	0.32*	41
Putamen	−0.19	24	0.06	44	−0.22†	42	0.27	11	0.14	41	0.12	41
Globus pallidus	−0.41*	18	0.28	18	−0.36†	18			−0.46*	20	0.10	20
Thalamus	−0.08	18	−0.27	18	0.15	36	0.09	11	−0.02	45	0.22	45
Mesencephalon	−0.41*	18	−0.34	17	−0.20	36	−0.38	11	0.48‡	25	0.22	45
Pons	0.16	18	0.09	17	0.03	37	0.26	11	0.08	24	0.13	26
Medulla oblongata	0.34	18	0.03	18	−0.22†	37	0.16	11	0.44*	24	0.22	40
Hippocampus	−0.37*	18	−0.04	18	−0.10	34	−0.40	11	0.32	21	0.47‡	26
Cortex gyrus hippocampus	−0.38*	18	0.35	18	−0.32†	18	−0.17	11	−0.36*	36	0.18	37
Cortex gyrus cinguli	0.10	18	0.11	18	−0.29	18	−0.45	11	−0.01	42	0.35*	39
Cortex gyrus frontalis	−0.25	18	0.35	18	0.07	32	−0.19	11	0.15	38	0.16	44
Cortex gyrus occipitalis	−0.14	18	−0.01	18	−0.08	36	−0.14	11	−0.08	38	0.01	39
Cortex gyrus temporalis	−0.03	18	−0.01	19	−0.17	20			0.04	18	−0.03	18
Cortex gyrus parietalis	0.04	18	0.23	18	−0.11	17			−0.25	17	−0.13	17
Cerebellum	0.05	18	0.14	18	−0.01	38	0.02	11	−0.02	16	0.43*	18
Medulla spinalis									0.08	16	0.01	19

*$P = < 0.05$.
†$P = < 0.10$.
‡$P = < 0.01$.
n = number of cases.

Table 17.2 Product-moment correlations between different forms of MAO activity in human brain and age. One-sided test of significance

Part of brain	MAO A (serotonin)	MAO AB (tryptamine)	MAO B (β-phenylethylamine)
Hypothalamus	−0.07	0.10	0.44*
Nucleus caudatus	0.03	−0.20	0.04
Putamen	−0.10	0.24†	0.23†
Globus pallidus	0.07	0.29‡	0.50ʃ
Thalamus	−0.14	0.12	0.22†
Mesencephalon	0.19	0.28‡	0.09
Pons	0.20	0.29‡	0.15
Medulla oblongata	0.32‡	0.23†	0.14
Hippocampus	−0.15	0.19	0.25‡
Cortex gyrus hippocampus	−0.19	0.28‡	0.08
Cortex gyrus cinguli	0.02	−0.14	0.13
Cortex gyrus frontalis	−0.01	−0.07	0.15
Cortex gyrus occipitalis	0.05	0.02	0.17

*$P = < 0.01$.
†$P = < 0.10$.
‡$P = < 0.05$.
ʃ$P = < 0.001$.
n = 40.

the age variance 23–92 years. As is evident from table 17.1, there was a negative correlation between age and levels of DA in 11 of the 16 investigated areas, and 5 of the 11 negative correlations were significant ($P < 0.05$, one-sided test of significance).

The levels of HVA were estimated in 18–44 cases, and 16 nuclei or regions of the the brain were investigated. The mean age for the 44 cases was 62.3 ± 18.8 (s.d.) years, and the age variance was 18–95 years. As is evident from table 17.1 there was no correlation between HVA and age.

The levels of NA were estimated in 17–42 cases, and 16 nuclei or regions of the brain were investigated. The mean age for the 42 cases was 61.4 ± 18.3 (s.d.) years and the age variance was 22–92 years. As is evident from table 17.1, the correlation between NA and age was negative in 13 of the 16 analyses and with four of these borders on significance.

The levels of MHPG were estimated in 10–11 cases, and 14 nuclei or regions of the brain were investigated. The mean age for the 11 cases was 59.1 ± 18.8 (s.d.) years and the age variance was 22–81 years. As is evident from table 17.1, the correlation between age and MHPG was negative in 9 of the 14 regions investigated, and one of the negative correlations was significant ($P < 0.05$; one-sided test of significance).

5-HT was determined in 16–41 cases, and 16 nuclei or regions of the brain and the spinal cord were investigated. The mean age for the 41 cases was 51.6 ± 19.8 (s.d.) years and the age variance was 18–95 years. The correlations between 5-HT and age were not consistent. In 10 areas there was a positive correlation which was significant in the case of the mesencephalon and the medulla oblongata ($P < 0.05$) and which borders on significance with the data on the hypothalamus. In 7 areas the correlation between 5-HT and age was negative, and in the globus pallidus and the cortex gyrus hippocampus the negative correlation was significant ($P < 0.05$).

5-HIAA was determined in 17–45 cases and 16 nuclei or areas of the brain and the spinal cord were investigated. The mean age for the 45 cases was 56.6 ± 19.8 (s.d.) years and the age variance was 18–95 years. As is evident from table 17.1, there was a positive correlation between 5-HIAA and age in 15 of the 17 areas investigated. The positive correlation was on a significant level in three areas—the caudate nucleus, the hippocampus and the cortex gyrus cinguli ($P < 0.05$)—and borders on significance for the data on the cerebellum.

As is evident from table 17.2, there is a positive correlation between age and MAO (β-phenylethylamine as substrate). With tryptamine and particularly with serotonin as substrate, there was a weaker positive correlation between age and MAO.

Cases with dementia disorders

In the group of 18 cases with senile dementia or Alzheimer's disease, the DA levels were compared with age-matched controls. As is evident from table 17.3, the mean DA value was lower in the dementia group in seven of the ten regions investigated and in two of these the difference was significant ($P < 0.05$). In table 17.4 the results from the NA determinations are presented. In all of the ten areas investigated the dementia group had lower mean values of NA than age-matched controls and in two areas the difference was significant. In table 17.5 the results from the de-

Table 17.3 Dopamine levels in different parts of the human brain in controls and in patients with senile dementia

Part of brain	Controls			Senile dementia		
	m	s.d.	*n*	*m*	s.d.	*n*
Nucleus caudatus	1.36	± 0.54	11	1.03	± 0.70	16
Putamen	1.23	± 0.82	12	1.57	± 1.41	16
Hypothalamus	0.06	± 0.12	11	0.09	± 0.11	18
Thalamus	0.04	± 0.04	10	0.01	± 0.01*	17
Hippocampus	0.04	± 0.07	10	0.02	± 0.02	15
Mesencephalon	0.34	± 0.03	10	0.04	± 0.03	17
Pons	0.05	± 0.05	10	0.02	± 0.02*	18
Cortex gyrus frontalis	0.03	± 0.05	10	0.02	± 0.02	17
Cortex gyrus hippocampus	0.02	± 0.03	10	0.01	± 0.01	17
Cortex gyrus cinguli	0.03	± 0.03	10	0.02	± 0.03	16

m = mean; s.d. = standard deviation; *n* = number of cases.
Differences between group means were tested by Student's *t* test.
* = $P < 0.05$, compared with corresponding value in controls.

termination of HVA are presented and in the caudate nucleus and the putamen there were significantly lower levels of HVA in the dementia group compared with age-matched controls ($P < 0.005$ and $P < 0.05$, respectively).

In a preliminary investigation, the MAO activity in platelets from 12 patients with Alzheimer's disease was compared with an age-matched control group. The results indicate that the MAO activity was higher in patients with Alzheimer's disease. With tryptamine as substrate, (figure 17.1a), the increase was significant (Wilcoxon test, $P < 0.05$), and with β-phenylethylamine (figure 17.1b), the difference bordered on significance.

Table 17.4 Noradrenaline levels in different parts of the human brain in controls and in patients with senile dementia

Part of brain	Controls			Senile dementia		
	m	s.d.	*n*	*m*	s.d.	*n*
Nucleus caudatus	0.02	± 0.01	21	0.02	± 0.01	17
Putamen	0.04	± 0.03	21	0.01	± 0.02*	16
Hypothalamus	0.75	± 0.40	13	0.44	± 0.51	18
Thalamus	0.71	± 0.05	19	0.08	± 0.10	18
Hippocampus	0.01	± 0.02	18	0.01	± 0.01	15
Mesencephalon	0.12	± 0.06	19	0.09	± 0.05	17
Pons	0.05	± 0.10	20	0.02	± 0.01	18
Cortex gyrus frontalis	0.02	± 0.02	18	0.01	± 0.01*	17
Cortex gyrus hippocampus	0.01	± 0.02	10	0.01	± 0.01	17
Cortex gyrus cinguli	0.02	± 0.02	10	0.01	± 0.02	16

m = mean; s.d. = standard deviation; *n* = number of cases.
Differences between group means were tested with Student's *t* test.
* = $P < 0.05$, compared with corresponding value in controls.

Table 17.5 Homovanillic acid in different parts of the human brain in controls and in patients with senile dementia

Part of brain	Controls			Senile dementia		
	m	s.d.	*n*	*m*	s.d.	*n*
Nucleus caudatus	3.24	± 1.34	24	2.00	± 0.63*	14
Putamen	7.20	± 2.60	24	5.05	± 2.56†	15
Cortex frontalis	0.04	± 0.04	10	0.05	± 0.07	12

m = mean; s.d. = standard deviation; *n* = number of cases.
Differences between group means were tested with Student's *t* test.
*$P < 0.005$, compared with corresponding value in controls.
†$P < 0.05$, compared with corresponding value in controls.

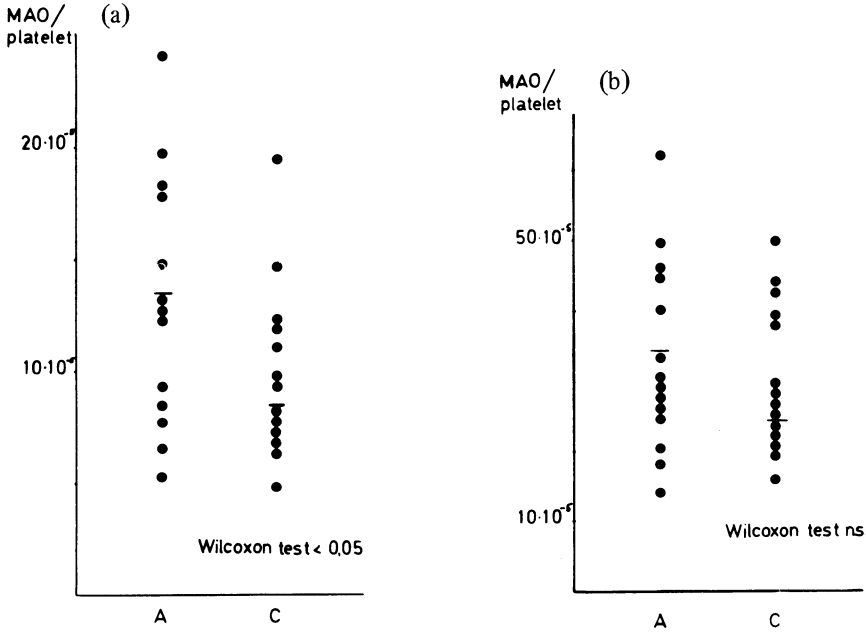

Figure 17.1 Activity of MAO in platelets in Alzheimer's disease and in age-matched controls: (a) with tryptamine as substrate; (b) with Fβ-phenylethylamine as substrate. Abbreviations: A, Alzheimer's disease; C, age-matched controls.

DISCUSSION

In post-mortem investigations of normal human brains, we have found a trend towards a negative correlation between DA, NA and MHPG levels on one side and age on the other, while the correlation for 5-HT and age varied in different parts of the brain. It may be assumed that there is a decline in the activity of catechol-

aminergic pathways in old age, which is in agreement with other post-mortem investigations (Robinson *et al.*, 1977; Carlsson and Winblad, 1976) and with animal experiments (Finch, 1973; Algeri *et al.*, 1976). There were, however, no reduced levels of HVA and the levels of 5-HIAA were significantly increased with age. In the cerebrospinal fluid it has been demonstrated in previous investigations (Bowers and Gerbode, 1968; Gottfries *et al.*, 1971) that the levels of both HVA and 5-HIAA increase with age. One interpretation of the findings of low levels of catecholamines in brain tissue and of high levels of the acid metabolites HVA and 5-HIAA may be that in old age there is a reduced rate of metabolism of DA and NA but that the 'out-transport' of the acid metabolites is reduced.

As reported previously by Robinson, Davies and Nies (1972), we also have found an increasing activity of MAO with age in brain tissue. Such a correlation, however, was only found for the B-type of MAO (β-phenylethylamine as substrate). Further investigation is needed to see whether the lack of correlation for the A-type MAO (serotonin as substrate) was due to a less reliable estimation method for this enzyme.

The non-vascular form of senile dementia has many features in common with Alzheimer's disease and often these two disorders are grouped together. In our investigation 18 patients with senile dementia (which included two cases of Alzheimer's disease) were investigated for their levels of monoamines and their metabolites in the brain. There seemed to be reduced levels of catecholamines and HVA when the group of dementia disorders were compared with age-matched controls.

Our findings indicate that there is an age-dependent decline in the metabolism of catecholamines in the human brain. In patients with dementia disorders of the Alzheimer type, there is a greater disturbance of the metabolism of catecholamines.

Of great interest is our preliminary finding that platelet MAO activity in Alzheimer patients is increased when compared with age-matched controls. Previously we have put forward indices for a positive correlation between platelet and brain MAO activities (Wiberg, 1977). If the increased platelet MAO activity reflects an increased activity of brain MAO in patients with Alzheimer's disease, it would mean that in this disease there is not merely an accelerated decrease in catecholaminergic functions, due to, for example, an increased rate of cell loss, but also an accelerated change in those processes normally increasing with age, for example MAO activity. Since, in addition, the platelet MAO activity, which should not be affected by changes in the CNS, is increased, it may be assumed that Alzheimer's disease is more generalized than just an increased rate of ageing of the CNS.

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18
Warfarin sensitivity in the elderly

A. M. M. Shepherd, N. Wilson and I. H. Stevenson (Department of Pharmacology and Therapeutics, Ninewells Hospital Medical School, University of Dundee, Dundee, UK)

INTRODUCTION

Drug prescription is particularly high in the elderly population (Office of Health Economics, 1968) and is associated with an increased incidence of adverse drug reactions (Seidl *et al.*, 1966; Hurwitz, 1969). While there are many possible causes of this high incidence of adverse reaction, Ogilvie and Ruedy (1967) suggested that a large proportion was due to excessive drug effect. Drugs with a low therapeutic ratio, or with a narrow range of effective plasma concentration, might therefore be expected to be particularly liable to cause adverse effects in the elderly age group. One such group of drugs is that of the oral anticoagulant drugs, which carry the risk of haemorrhage when administered in excessive amounts and which may allow thrombotic episodes when given in subtherapeutic amounts.

Interest in the response of the elderly to oral anticoagulant drugs first started in this department in 1974. A retrospective, epidemiological survey (O'Malley, Stevenson and Ward, 1974) of the factors influencing anticoagulant control in a hospital in-patient population revealed, among other things, that increasing age appeared to be associated with an increased sensitivity to warfarin. The elderly were more effectively anticoagulated, with lower Thrombotest (TT) levels, than were the younger groups, despite receiving a lower daily dose of warfarin (figure 18.1). A further prospective study in a hospital anticoagulant out-patient population (Shepherd *et al.*, 1978) has confirmed this effect, although less dramatically than in the first retrospective study of O'Malley *et al.*

In order to determine whether this apparent age increase in sensitivity could be demonstrated under more closely defined conditions, the anticoagulant response to a single dose of racemic warfarin was observed in a group of young and a group of elderly patients. Four young (mean age 31 years) and four elderly (mean age 76 years) patients, who were to be anticoagulated against deep venous thrombosis, were each given a single oral dose of racemic warfarin and the anticoagulant response, measured by TT, was observed over the next 120 h. The warfarin dose, decided by the clinician in charge, averaged 0.94 mg/kg in the young and 0.55 mg/kg

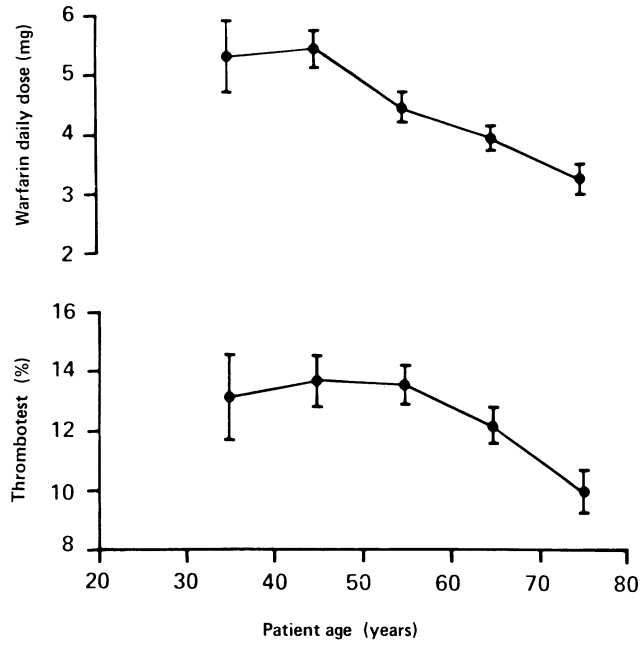

Figure 18.1 The effect of age on warfarin dose and effect in a hospital in-patient population. From O'Malley *et al.* (1974). Reproduced with permission from Raven Press.

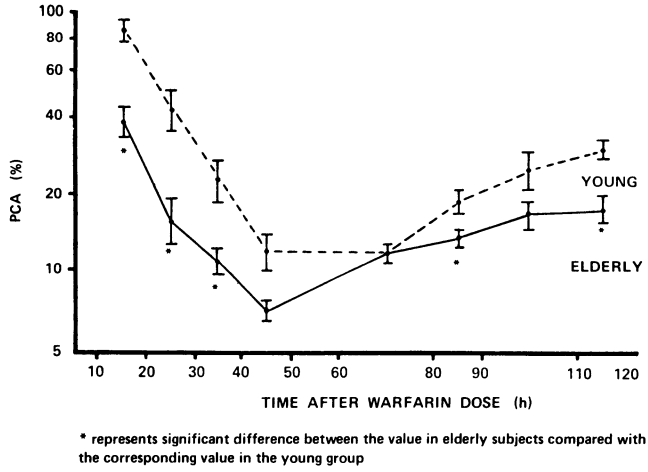

Figure 18.2 The anticoagulant response of young and elderly patients to a single dose of warfarin. For explanation of PCA measurement, see text.

in the elderly. The anticoagulant response is recorded in figure 18.2.The rate of decline of TT (hereafter called PCA) was approximately log-linear and the slopes of the lines were similar in the two age groups. PCA, however, was depressed for longer in the elderly, and the mean values for the 80–90 and the 110–120 h periods were significantly lower in the elderly. This more prolonged anticoagulant

response occurred in the elderly despite their receiving only approximately half the weight-related dose of warfarin that the young received. From this study it appeared that the elderly were indeed more sensitive to warfarin than their younger counterparts.

Further studies were therefore undertaken to elucidate the mechanism of this effect. These investigations were undertaken in the light of the present understanding of the mechanism of anticoagulant action of warfarin. Warfarin acts by preventing the formation in the liver of the blood coagulation factors, II, VII, IX and X, which depend on the presence of vitamin K_1 for their synthesis. They are formed (figure 18.3) by carboxylation of their precursor proteins during which vitamin K_1 is oxidised to vitamin K_1 2,3-epoxide. This oxide is subsequently reduced by a NADH-dependent system to vitamin K_1, allowing further carboxylation to occur. The coumarin anticoagulants, including warfarin, prevent this reduction step, causing accumulation of the oxide, depletion of vitamin K_1 and reduced rate of formation of the clotting factors. For ease of explanation in subsequent studies, the site of these reactions in the liver is called the 'receptor site'.

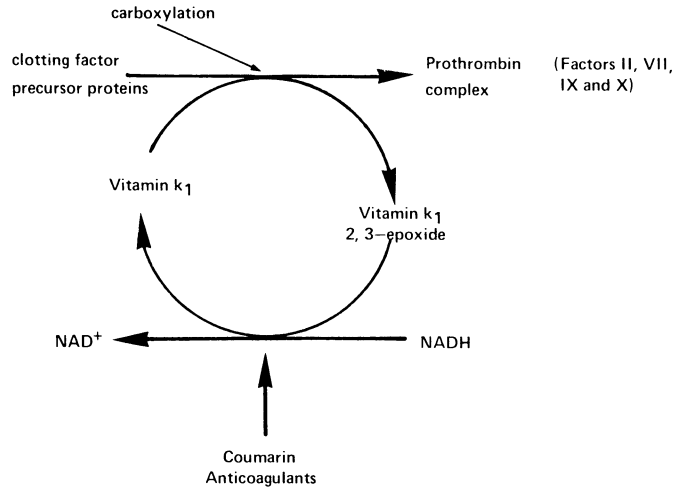

Figure 18.3 Proposed mechanism of the warfarin–vitamin K_1 interaction. Modified from O'Reilly (1976).

The increased sensitivity of the elderly to warfarin could arise from altered amounts of warfarin or vitamin K_1 reaching this receptor site or from altered receptor sensitivity to either warfarin or vitamin K_1. The first of these possibilities could result from alteration in kinetics, in other words change in absorption, distribution, or elimination of either compound. The second possibility–altered receptor sensitivity–could result from altered PCA response to the same pharmacologically active levels of warfarin or vitamin K presented at the receptor site. The possible mechanisms operating in the age-related increase in sensitivity therefore include

Altered warfarin kinetics
Increased receptor sensitivity to warfarin

Altered vitamin K kinetics
Decreased receptor sensitivity to vitamin K.

The objective of subsequent studies was to examine each of these possibilities in turn.

WARFARIN KINETICS

In order to compare warfarin handling in young and elderly, groups of 18 young (mean age 24 years) and 20 elderly (mean age 82 years) subjects were each given a single weight-related oral dose of racemic warfarin and venous blood samples taken at intervals for the following 72 h. Plasma warfarin and warfarin alcohol (warfarin metabolites with weak anticoagulant activity) concentrations were measured by a modification (Shepherd, 1978) of the method of Lewis, Ilnicki and Carlstrom (1970). From the plasma levels obtained, the following parameters were calculated–plasma warfarin elimination half-life ($t_{1/2}$), apparent volume of distribution of warfarin (*AVD*), plasma warfarin clearance (*Cl*) and, for the 11 young and 11 elderly subjects given the same dose of warfarin, the area under the plasma warfarin alcohol versus time curve for 72 h after warfarin administration.

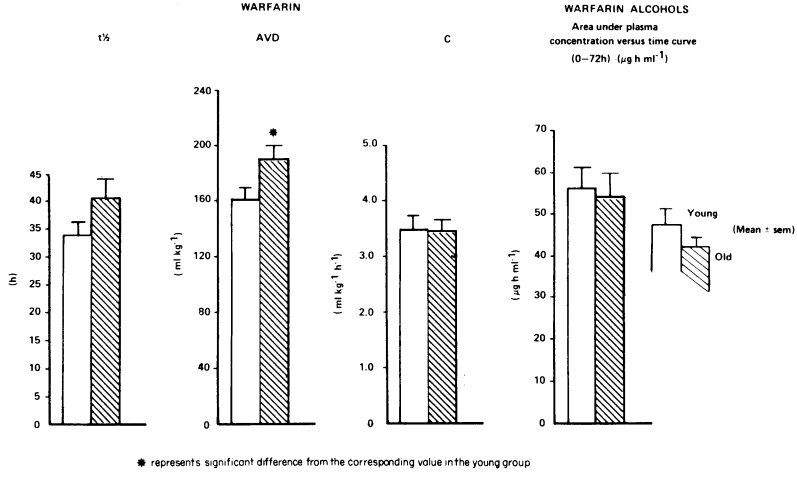

Figure 18.4 Warfarin kinetics in young and elderly subjects.

The group mean results obtained are shown in figure 18.4. It may be seen that although the plasma half-life was greater in the elderly, the distribution volume was also significantly higher in this group. Because of this alteration in the distribution of warfarin, the plasma clearance, which is the most valid measure of the rate of drug elimination from the plasma, was almost identical in young (3.45 ± 0.21 ml kg^{-1} h^{-1}, mean ± s.e.m.) and elderly (3.4 ± 0.26/ml kg^{-1} h^{-1}) groups.

Since the warfarin alcohols have been shown to have weak anticoagulant effect, a greatly increased accumulation of the alcohols, if it occurred in the elderly, could be partly responsible for their increased sensitivity to warfarin. The similar

areas under the plasma warfarin alcohol concentration versus time curves in the two age groups after a single dose of warfarin, however, makes this unlikely. Furthermore, to achieve significant anticoagulant effect, plasma warfarin alcohol levels of between 4 and 7 μg/ml are required (Lewis *et al.*, 1973). The levels achieved in our studies were approximately one-tenth of these concentrations, and it is therefore most unlikely that the warfarin alcohol levels achieved in this study could affect anticoagulant control in young or elderly patients.

In the studies described above, the kinetic parameters measured have been related to total plasma warfarin, of which part is bound to plasma albumin and part is free in the plasma. Only the free portion is available for pharmacological effect, and alteration in the free/bound ratio could change the free, effective, warfarin concentration at the receptor site without changing the total plasma warfarin concentration. In order to determine whether this was the case in the elderly, the percentage protein binding of warfarin was measured by equilibrium dialysis in fresh, undiluted plasma from 10 young (mean age 23 years) and 8 elderly (mean age 70 years) subjects. The method of measurement and calculation of the extent of binding was as described previously (Shepherd, 1978). Warfarin binds exclusively to albumin (O'Reilly and Kowitz, 1967) and plasma albumin concentration therefore might be expected to affect the extent of the binding. Plasma albumin concentration has been shown to fall with increasing age (Rafsky *et al.*, 1952) and this effect was also seen in the subjects in the present study, the plasma albumin being significantly higher in the young group (613 ± 10 μmol/l, mean ± s.e.m.) than in the elderly group (555 ± 22 μmol/l). Despite this however, no significant differences in extent of plasma protein binding of warfarin were seen between the two groups (young 97.5 ± 0.1 per cent; elderly, 97.4 ± 0.1 per cent).

From these studies, it is apparent that there are no major differences in warfarin handling with ageing. Such age-related differences as are present are relatively small compared with the inter-individual differences found in both young and elderly subjects in these studies and in young subjects by O'Reilly *et al.* (1963) and Breckenridge (1973).

RECEPTOR SENSITIVITY TO WARFARIN

This was compared in young and elderly subjects by measuring the rate of synthesis of the vitamin K-dependent clotting factors (PCA) at a range of plasma warfarin concentrations in each age group. The rate of synthesis of PCA was measured by the method of Nagashima, O'Reilly and Levy (1969), which states that the net rate of change of PCA (R_{net}) is a balance between the rate of synthesis (R_{syn}) and the rate of spontaneous degradation of PCA (R_{deg}). This may be expressed as the equation

$$R_{net} = R_{syn} - R_{deg}$$

R_{deg} may be calculated from the rate of decline of PCA (measured by TT per cent) following an inhibitory dose of warfarin and R_{net} from the rate of change of PCA during the phase of recovery of PCA. R_{syn} may therefore be calculated by difference for any plasma warfarin concentration. When the relationship between R_{syn} and plasma warfarin concentration was investigated in groups of six young (mean

age 31 years) and six elderly (mean age 76 years) subjects, it was found that the data best fitted a straight line when calculated from the double logarithmic plot of R_{syn} against plasma warfarin concentration (figure 18.5). The values obtained in the young group occupy the upper and right portions of the plot, while those of the elderly group occupy the lower and left portions. In other words, PCA synthesis appeared to be inhibited to a greater degree by warfarin in the elderly. The following relationships were obtained: in the young, $\log R_{syn} = 0.249 - 0.729 \log$ warfarin concentration; and in the elderly, $\log R_{syn} = -0.052 - 0.669 \log$ warfarin concentration. These relationships explained 71 per cent of the variability in the logged data in the young and 66 per cent of the variability in the elderly group. The slopes of these lines (young, −0.729; elderly, −0.669) did not differ significantly but the position of the lines themselves were significantly different ($P < 0.001$).

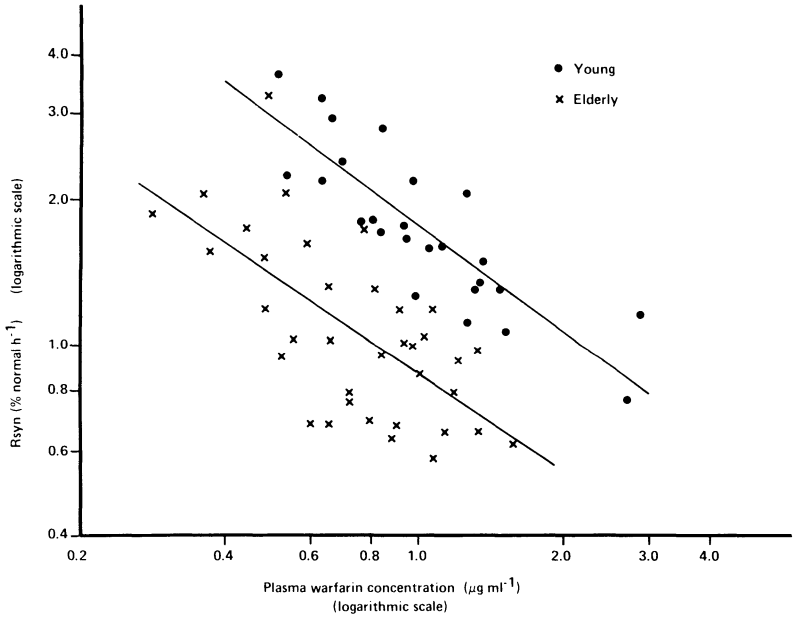

Figure 18.5 Double logarithmic plot of the relationship between clotting factor synthesis (R_{syn}) and plasma warfarin concentration in young and elderly subjects. For explanation of determination of R_{syn}, see text.

From this plot it may be seen that over the range of therapeutic plasma warfarin concentration the R_{syn} is depressed to approximately twice as great a degree by the same warfarin concentrations in the elderly as in the young. For example, when the plasma warfarin concentration is 1.0 μg/ml in both age groups, R_{syn} is 1.8 per cent normal per hour in the young but only 0.9 per cent normal per hour in the elderly. It therefore seemed possible that the receptor site was twice as sensitive to warfarin in the elderly as in the young. If this were so, it would be expected that the rate of synthesis of PCA required to maintain the resting TT level in the

absence of warfarin ($R_{syn(0)}$) would be the same in both groups and the difference in R_{syn} would only appear when warfarin was introduced into the system. To determine whether this was the case, $R_{syn(0)}$ was compared in groups of seven young (mean age 26 years) and ten elderly (mean age 80 years) subjects by the method of Nagashima *et al.* (1969). The mean value of 6.7 per cent normal per hour in the young group was approximately twice that of the elderly group (3.4 per cent normal per hour), the difference between the means being highly significant ($P < 0.001$).

It is apparent, therefore, that the ratio of the values of $R_{syn(0)}$ and R_{syn} in the young groups to those in the elderly groups is approximately 2 to 1, both in the presence and in the absence of warfarin. The implication of this is that warfarin is not responsible for the difference in R_{syn} and that some other mechanism is responsible. Among the possible mechanisms are those already outlined, that is alteration in vitamin K intake or handling or in receptor sensitivity to vitamin K_1 in the elderly. These possibilities have been examined in subsequent studies.

[^{3}H]-VITAMIN K_1 KINETICS AND RECEPTOR SENSITIVITY TO VITAMIN K_1

The handling of [^{3}H]-vitamin K_1 was compared in a group of three young (mean age 20 years) and three elderly (mean age 84 years) subjects both while anticoagulated with warfarin and in the absence of warfarin. The PCA response to a weight-related dose of [^{3}H]-vitamin K_1 was also measured in the same patients when anticoagulated with warfarin as a means of measuring receptor sensitivity to vitamin K_1. The study design is as shown in figure 18.6.

Each subject was given a single oral inhibitory dose of racemic warfarin and subsequent maintenance doses of oral warfarin to maintain a therapeutic level of anticoagulation (TT level between 5 and 15 per cent of normal). At least 8 days after starting warfarin, each subject was given 10 μg/kg of intravenous [^{3}H]-vitamin K_1 and plasma [^{3}H]-vitamin K_1 and vitamin K_1 oxide levels were measured by a

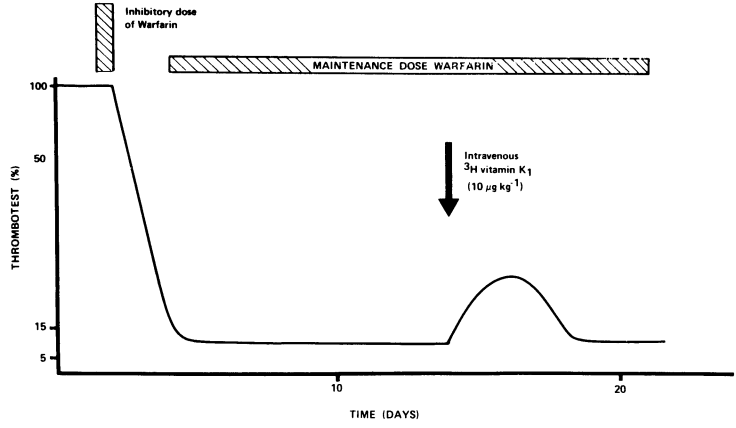

Figure 18.6 Schematic representation of study to determine PCA response to vitamin K in anticoagulated patients.

Table 18.1 [^{3}H]-Vitamin K_1 and [^{3}H]-vitamin K_1 oxide handling in young and elderly subjects

	[^{3}H]-Vitamin K_1			[^{3}H]-Vitamin K_1 oxide
	Plasma $t_{1/2}$ (h)	AVD ml kg^{-1}	Plasma clearance (ml kg^{-1} h^{-1})	Area under plasma concentration versus time 0–6 h (μg ml^{-1} h) x 10^{-3}
Vitamin K_1 alone				
Young	9.3	1,313	98	16.3 ± 2.8[a]
Elderly	10.1	1,950	134	13.3 ± 1.7[b]
Vitamin K_1 + warfarin				
Young	4.3	1,153	187	29.7 ± 3.4[a, c]
Elderly	7.6	1,689	155	43.8 ± 3.4[b,c]

[^{3}H]-Vitamin K_1 parameters are calculated from composite data in each group.
[^{3}H]-Vitamin K_1 oxide data are presented as means ± s.e.m. There was significant difference between the vitamin K_1 oxide mean values coded with the same letters.

modification (Shepherd, 1978) of the method of Shearer, Barkhan and Webster (1970) in venous blood samples taken at intervals following administration. At least 8 weeks after stopping anticoagulant therapy, the same subjects were again given the same dose of [^{3}H]-vitamin K_1 and venous blood samples were taken for analysis. From the plasma levels obtained in each study, plasma half-life, apparent volume of distribution and plasma clearance of [^{3}H]-vitamin K_1 were calculated for each subject along with the area under the plasma concentration of [^{3}H]-vitamin K_1 oxide versus time curve (*AUC*). A measure of [^{3}H]-vitamin K_1 handling and of the accumulation of its plasma metabolite, [^{3}H]-vitamin K_1 oxide, was therefore obtained in young and elderly subjects both in the absence and in the presence of warfarin. To measure the receptor sensitivity to injected vitamin K_1, the TT response (PCA) to [^{3}H]-vitamin K_1 was obtained when the subjects were anticoagulated with warfarin by calculating the areas under the TT per cent versus time curve and under the R_{syn} versus time curve for 48 h after injection of [^{3}H]-vitamin K_1 as shown in figure 18.6.

The plasma kinetic parameters for [^{3}H]-vitamin K_1 were calculated from the composite data obtained in each age group and are presented in table 18.1. In the absence of warfarin, the plasma half-lives were similar in each group but the distribution volume appeared to be greater, and consequently the plasma clearance higher, in the elderly group. In the presence of warfarin, plasma half-lives were shorter, more so in the young group. Distribution volumes were not substantially altered and plasma clearances were increased, markedly so in the young group. Because composite data were used for the calculation of these parameters, statistical comparison could not be undertaken. The *AUC* data for [^{3}H]-vitamin K_1 oxide for each group are also contained in table 18.1. The *AUC*, which was similar in the absence of warfarin, was significantly increased in both age groups in the presence of a therapeutic plasma concentration of warfarin. In the presence of warfarin, the mean *AUC* was significantly higher in the elderly group than the comparable value in the young group. The PCA response to the injected [^{3}H]-vitamin K_1 appeared to be greater in the young group when measured both as area under the TT versus time curve (young, 776 ± 17 per cent per h, mean ± s.e.m.; elderly, 456 ± 91 per cent per h) and as area under the R_{syn} versus time curve (young, 61.5 ± 9.1 per cent h^{-1} h; elderly, 38.9 ± 8.3 per cent h^{-1} h). In each case, the difference just failed to reach statistical significance and may well have done so had it been possible to study larger groups of subjects.

In summary, therefore, there was evidence of age-related alteration in three of the measured parameters of [^{3}H]-vitamin K_1 handling and receptor sensitivity. Firstly, [^{3}H]-vitamin K_1 clearance appeared to be greater in the elderly in the absence of warfarin. Secondly, there was a significantly greater accumulation of [^{3}H]-vitamin K_1 oxide in the elderly than in the young, when both groups were anticoagulated with warfarin. Finally, there was probably a reduced PCA response to [^{3}H]-vitamin K_1 in the elderly, perhaps indicating reduced receptor sensitivity to vitamin K_1.

DISCUSSION

The first of the four possible sources of the age-related difference in sensitivity which were investigated was warfarin kinetics. There was no significant difference

in warfarin clearance between the two age groups. Warfarin, however, exists in two enantiomeric forms, since there is an asymmetric carbon atom in the molecule. The two isomers have both differing anticoagulant properties (Hewick and McEwen, 1973) with the S isomer being more potent than the R isomer, and differing rates (Hewick, 1972) and routes (Lewis *et al.*, 1974) of metabolism. Prior administration of phenylbutazone quantitatively affects the metabolism of each of the isomers to a differing degree, the decreased clearance of S-warfarin masking the increased clearance of R-warfarin. The net effect is that there is greater anticoagulant effect because of higher S-warfarin concentration without alteration in the total warfarin concentration. Racemic warfarin, an equimolar mixture of the two isomers, was used in the studies of warfarin kinetics and this work, therefore, does not exclude the possibility that the elderly group behave as if they had been pre-treated with phenylbutazone. Reduction in plasma protein binding of warfarin in the elderly would increase the pharmacologically active concentration at the receptor site with no alteration in total plasma concentration. No alteration in binding was demonstrated in these studies, initiating a similar proportion of free warfarin in each age group. The wide variation in the free proportion of warfarin, however, from less than 0.4 per cent (Lewis *et al.*, 1974) up to 3 per cent of the total concentration (depending on the method of measurment) must cast doubt on the ability of each method to measure small alterations in the free concentration.

Receptor sensitivity to warfarin was studied by measuring the relationship between plasma warfarin concentration and the rate of synthesis (R_{syn}) of vitamin K-dependent clotting factors. Initially, it appeared that warfarin caused greater inhibition of R_{syn} in the elderly. Subsequent investigation showed that this was probably not related to warfarin sensitivity, since the difference was also present in the absence of warfarin, $R_{syn(0)}$ also being lower in the elderly. The indications were, therefore, that the increase in sensitivity was related more to differences in PCA synthesis or in vitamin K metabolism/effect than to differences in warfarin handling/effect.

Plasma [^{3}H]-vitamin K_1 elimination appeared to be more rapid in the elderly and, while no excretion studies were undertaken, it could indicate more rapid removal from the body, causing a relative deficiency of vitamin K_1 to be presented at the receptor site. On the basis of the PCA response to injected [^{3}H]-vitamin K_1, it appeared that there could also be reduced receptor sensitivity to vitamin K_1 in the elderly. This might indicate reduced efficiency of the carboxylation of the precursor proteins, or lower concentrations of the precursor proteins in the livers of the elderly. The increased concentration of [^{3}H]-vitamin K_1 oxide in the elderly might indicate a reduced efficiency of the NADH-dependent reduction of the oxide to vitamin K_1, although impaired elimination of the oxide in the elderly is another possible explanation.

There are several other causes of the age-related difference in warfarin sensitivity which have not been considered here. For example, there is some indication (Shepherd, 1978) that the elderly may have higher plasma concentrations of endogenous inhibitors of clotting factor activity than do the young. What is apparent, however, is that the observed increase in sensitivity to warfarin in the elderly is complex and perhaps is multifactorial in origin.

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19
Barbiturate sensitivity in ageing animals

D. S. Hewick (Department of Pharmacology and Therapeutics, Ninewells Hospital Medical School, Dundee, UK)

Two types of barbiturate response will be considered: the central nervous system (CNS) depressant effect associated with acute dosage, and the induction of hepatic drug-metabolising enzymes occurring with chronic barbiturate treatment.

CNS DEPRESSANT EFFECT OF BARBITURATES IN OLD ANIMALS

One of the earliest studies on the effect of age on barbiturate response was carried out by Streicher and Garbus (1955). They reported that hexobarbitone sleeping times were markedly prolonged in very old male rats (approximately 840 days old) but that ageing reduced sleeping times in female rats. Subsequent studies have not confirmed such an age-related sex difference; irrespective of sex, elderly rats have prolonged hexobarbitone sleeping times. This is shown in figure 19.1, which has been assembled from hexobarbitone sleeping-time data published over the last ten years (Kato and Takanaka, 1968*a*; Kuhlmann *et al.*, 1970; Lal *et al.*, 1973; Baird *et al.*, 1975). The categories 'young', 'middle-aged' and 'old' shown in figure 19.1 have been arbitrarily assigned on the basis of published rat lifespan data (Hollander, 1976). Taking a 100-day-old rat ('young', fully sexually mature) as the baseline, it is seen that hexobarbitone sleeping times progressively lengthen throughout middle and old age. Kuhlmann, Oduah and Coper (1970) showed that the age-related increase in sleeping time could be linked with reduced hexobarbitone elimination from the brain and plasma, and with reduced drug oxidation by hepatic microsomes. On the other hand, no such link between effect *in vivo* and metabolism *in vitro* has been demonstrated in mice. Kato, Takanaka and Onoda (1970), comparing 35, 105 and 350-day-old mice, found that hexobarbitone sleeping times increased with increasing age but that the rates of hexobarbitone hydroxylation in hepatic microsomes were similar in all three age groups.

Kato and Takanaka (1968*a*) carried out more detailed studies in rats on another extensively metabolised barbiturate, pentobarbitone, a comparison being made between 100 and 600-day-old Wistar rats. Sleeping times were prolonged by about

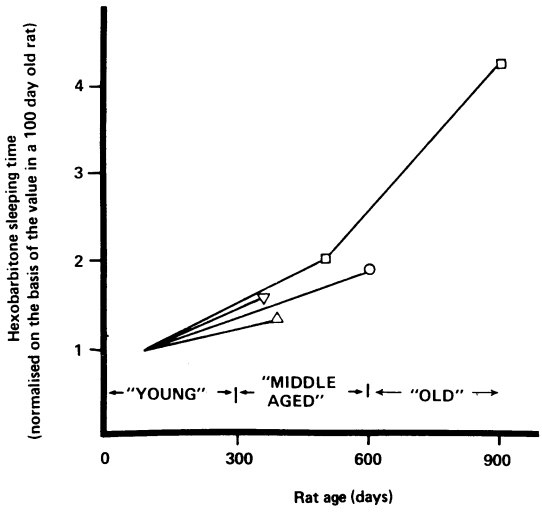

Figure 19.1 Increase in hexobarbitone sleeping times with increasing age. The data are from Kato and Takanaka, 1968*b* (○); Kuhlmann *et al.*, 1970 (▽); Lal *et al.*, 1973 (△); Baird *et al.*, 1975 (□). In all studies, male rats were used except for Kato and Takanaka (1968*a*). To facilitate comparison between the different publications, sleeping times have been normalised using the values for 'young' 100-day-old rats as a baseline. The categories of 'young', 'middle-aged' and 'old' have been arbitrarily assigned on the basis of published rat lifespan data (Hollander, 1976).

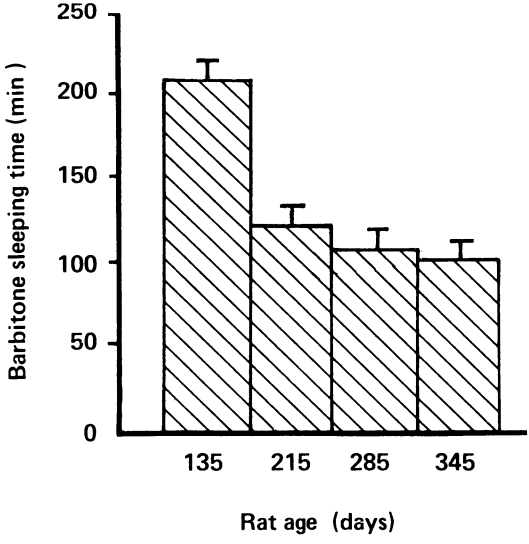

Figure 19.2 The reported decrease in barbitone sleeping times (means ± s.e.m.) with increasing age (from Lal *et al.*, 1973). Male Sprague–Dawley rats (20 per group) were each given 200 mg/kg barbitone intraperitoneally.

300 and 100 per cent in old male and female rats, respectively. The brain pentobarbitone levels on recovery from anaesthesia were similar in young and old animals, indicating no change in brain sensitivity to pentobarbitone with increasing age. The change in response seemed entirely attributable to age-related changes in drug handling and, in particular, drug oxidation. The rate of pentobarbitone metabolism *in vivo* (calculated from plasma pentobarbitone half-lives) was approximately halved in the old rats of both sexes, while the rate of hepatic pentobarbitone metabolism *in vitro* was reduced by about 65 per cent.

Where, as with barbitone, the drug is only minimally metabolised, there is some evidence that there is no age-related increase in sensitivity to barbiturates. For instance, Kuhlmann *et al.* (1970) compared two groups of rats aged about 100 and 350 days, respectively, and found that, although hexobarbitone sleeping times were longer in the older rats (figure 19.1), the barbitone sleeping times in both groups were similar. A more surprising result was reported by Lal *et al.* (1973), who determined barbitone sleeping times in 135, 215, 285 and 345-day-old male Sprague-Dawley rats. These workers recorded a progressive decrease in barbitone sensitivity with increasing age (figure 19.2); the sleeping times of the 345-day-old rats were about half those of the youngest rats.

To ascertain if such a decrease in sensitivity is continued into old age and to clarify the situation regarding a possible differential age-related effect of minimally and extensively metabolised barbiturates, the response to intraperitoneally injected pentobarbitone and barbitone was compared in 100 and 600-day-old male Wistar rats.

Comparison of response to pentobarbitone and barbitone in young and old rats: a preliminary study

To assess the relative agility of the young and old rats before barbiturate injection, 'righting times' (time between the rat being placed on its back and regaining its feet) were determined. In young rats the righting times were too fast to measure accurately with a stop watch, but were about 0.4 s. In ten old rats the righting times ranged from 0.4 to 2 s, with the times being greater than 1 s in five rats.

After intraperitoneal injection, the time for the onset of barbitone-induced anaesthesia (time between injection and loss of righting reflex) was three to four times as long as that for pentobarbitone, but for each barbiturate the onset time was similar in young and old rats (table 19.1). During the onset of anaesthesia and before loss of the righting reflex, the rats showed, in spite of increasing ataxia, typical hyperactivity ('excitement phase' of anaesthesia), both young and old rats appearing to be similarly affected. In contrast, the duration of anaesthesia (time between loss and regain of righting reflex) was markedly longer in old rats with 80 per cent and 140 per cent increases in pentobarbitone and barbitone sleeping times, respectively (table 19.1).

To determine the tissue barbiturate levels on awakening from anaesthesia, smaller groups of rats were injected with either [^{14}C]-pentobarbitone or [^{14}C]-barbitone. The sleeping times in these animals (table 19.2) were similar to those obtained in corresponding groups injected with unlabelled barbiturates (table 19.1). The respective brain or plasma levels on awakening were not significantly different in the young and old rats (table 19.2).

Table 19.1 The effect of old age on the hypnotic response to barbiturates in the rat

	Pentobarbitone (30 mg/kg)		Barbitone (175 mg/kg)	
	Young	Old	Young	Old
Number of rats	9	10	10	7
Rat weight (g)	378.5 ± 7.8*	510 ± 22.4	384.5 ± 8.2*	539.2 ± 23.5
Time for onset of anaesthesia (min)	6.5 ± 1.2	5.6 ± 0.6	21.5 ± 1.0	19.0 ± 1.0
Duration of sleep (min)	51.4 ± 1.7*	93.2 ± 3.6	79 ± 4.2*	189 ± 12.5

The animals used were male Wistar rats aged about 100 days (young) or 600 days (old). The barbiturates were injected intraperitoneally. The figures given are means ± s.e.m.
*The value is significantly different ($P < 0.05$) from that for old rats.

Table 19.2 Tissue [^{14}C]-barbiturate levels in young and old rats on awakening from anaesthesia

	[^{14}C]-Pentobarbitone (30 mg/kg)		[^{14}C]-Barbitone (175 mg/kg)	
	Young	Old	Young	Old
Number of rats	4	5	5	4
Duration of sleep (min)	49.3 ± 3.0*	89.8 ± 4.5	86.2 ± 7.1*	175 ± 9.9
[^{14}C]-Barbiturate level† on awakening in:				
brain (μg/g)	20.2 ± 1.2	23.1 ± 2.1	215.8 ± 33.9	219.7 ± 10.7
plasma (μg/ml)	23.6 ± 1.8	26.4 ± 2.0	335.9 ± 10.4	319.5 ± 5.9

The animals used were male Wistar rats aged about 100 days (young) or 600 days (old). [^{14}C]-Pentobarbitone (10 μCi/kg) or [^{14}C]-barbitone (5 μCi/kg) was injected intraperitoneally. The figures are given as means ± s.e.m.
*The value is significantly different ($P < 0.05$) from that for old rats.
†Unmetabolised [^{14}C]-pentobarbitone was extracted for measurement by the method of Kuntzman *et al.* (1967).

Discussion of preliminary study

Although, without treatment, the righting times were longer in the older rats, it is unlikely that such a prolongation (measured in seconds) would alter the end-point of a sleeping-time determination (measured in minutes) to any marked extent. The time for the onset of anaesthesia was similar in the young and old rats, even when it was quite prolonged, as in the case of the more polar barbiturate, barbitone. This indicates that the respective rates of access to the brain of the barbiturates tested were similar in young and old rats. This, in turn, suggests that in the elderly animals (1) absorption from the peritoneal cavity was not impaired and (2) the ability of the barbiturates to penetrate the blood–brain barrier was not altered.

The main effect of old age on barbiturate response was to prolong markedly the duration of hypnosis, irrespective of whether the drug was minimally or extensively metabolised. The results with pentobarbitone resemble those of Kato and Takanaka (1968*a*) in that the young and old rats appear to have a similar brain sensitivity to the drug. The present data do not indicate that old rats develop a tolerance to barbitone, as might have been suggested by the study of Lal *et al.* (1973). Since barbitone is negligibly metabolised, the greater effect in old rats found in the present study may be due to a reduced renal clearance.

Unfortunately, in this cursory study, the limited supply of old rats precluded further investigation on barbitone elimination. Future studies comparing young and old rats should involve a detailed analysis of plasma and brain barbitone elimination rates, measurement of renal function and rate of drug excretion in the urine.

The CNS effect of barbiturates–relationship between animal and clinical reports

When barbiturates were more commonly used clinically, they were traditionally avoided in elderly patients because of the reported higher incidence of adverse or paradoxical reactions such as disorientation, confusion, agitation, restlessness and delirium (Dawson-Butterworth, 1970; Gibson, 1966). The widespread subjective impression among clinicians was that the stimulatory/excitement component of the barbiturate response became more marked in the elderly, and it had been suggested that CNS centres stimulated by the barbiturates are less affected by age than those which are depressed (Jacobsen, 1964). However, as can be seen from earlier discussion, this trend cannot be readily confirmed in animal experiments, where, if anything, most of the data indicate a more marked depressant effect with increasing age.

There are a number of possible reasons for this apparent discrepancy between human and animal data, the most obvious being that the ageing human brain responds to barbiturates differently from that of an ageing laboratory animal. It is also possible that some of the 'atypical' responses to barbiturates in patients could have been explained on a pharmacokinetic rather than a pharmacodynamic basis. For example, it is conceivable that on some occasions elderly patients (with reduced drug-eliminating ability) were receiving relative overdoses or were suffering from prolonged barbiturate 'hangover' effects.

A general factor that must be considered is that the original clinical data were mainly from uncontrolled studies. For example, drug compliance was not routinely checked, no comparison was made with young patients as controls and there was no adequate record of other drugs being taken concurrently. A further complication that makes comparison of animal and human data difficult on the basis of

published reports is the difference in barbiturate usage in animals and humans. In a laboratory animal, the usual procedure was to administer the drug intraperitoneally in order to measure the sleeping time (time between loss and regain of righting reflex). In patients the barbiturate was used as a daytime sedative or in larger doses as a hypnotic. In the latter case drug-induced sleep progresses into natural sleep and, obviously, no precise measurement of drug effect can be made. Furthermore, in animal studies the drug was usually given acutely, while in patients barbiturates may have been given chronically, often over prolonged periods. Therefore, in the human situation, barbiturate tolerance (both by induction of hepatic drug-metabolising enzymes and by direct CNS cellular mechanisms) could have developed. In such circumstances, if drug compliance were poor (as is likely in elderly patients), side effects such as 'rebound' insomnia or even withdrawal symptoms could occur. It is perhaps significant that more recent clinical investigations do not support the idea that there is a greater incidence of paradoxical barbiturate side effects in the elderly (Miller and Greenblatt, 1976), and, furthermore, it has even been suggested that, as far as elderly patients are concerned, side effects associated with barbiturates are no worse than with any other hypnotic (Stotsky, 1975).

Unfortunately, contributions from animal experiments have been infrequent and often limited owing to the problems and expense of raising suitably aged laboratory animals in sufficient numbers. Another limitation of animal work to date is that only the readily measured CNS depressant effect of barbiturates has been studied; the transient excitatory effect of these drugs, which is much more difficult to measure, has not been examined. However, during the preliminary experiments described, there seemed no obvious difference in the degree of excitement between young and old rats during the onset of anaesthesia.

As a final comment on the current clinical situation, it must be made clear that, irrespective of paradoxical side effects in elderly patients, the overall consensus of clinical opinion is that barbiturates should be avoided where possible in young and old patients alike. This view is based on the availability of alternative, safer hypnotics and sedatives such as the benzodiazepines, which largely avoid the possible problems associated with barbiturates (dependence, dangers of overdosage) in patients of all ages (Editorial, 1974, 1975, 1976).

PHENOBARBITONE INDUCTION OF HEPATIC DRUG-METABOLISING ENZYMES IN OLD ANIMALS

Many lipid-soluble drugs and chemicals on repeated administration will increase levels of hepatic drug-metabolising enzymes and thus cause a wide variety of drug substrates to be metabolised more rapidly (Conney, 1967). The most commonly used inducing agent for experimental purposes is phenobarbitone and it is this drug which has been exclusively used as such in the limited number of studies published to date on induction in old animals.

The first investigations were carried out by Kato and Takanaka (1968*b*) using 100 and 600-day-old Wistar rats. The following measures of hepatic microsomal drug-metabolising activity were assessed: NADPH oxidase, NADPH-cytochrome c reductase, NADPH-neotetrazolium reductase, cytochrome P-450, aminopyrine *N*-demethylation, hexobarbitone hydroxylation, aniline hydroxylation and *p*-nitrobenzoic acid nitro reduction. In the older rats these parameters were initially lower and were less affected by phenobarbitone pretreatment (60 mg/kg per day

for 3 days). The measurement of hexobarbitone sleeping times seemed to indicate that this trend was paralleled *in vivo* (Kato and Takanaka, 1968*a*). The marked difference in sleeping times observed between young phenobarbitone-treated and young control rats was progressively reduced with increasing age until, in 600-day-old rats, phenobarbitone pretreatment had no significant effect on sleeping times.

The situation in mice (Kato *et al.*, 1970), however, seemed completely different, in that levels of the enzymes measured *in vitro* as above were essentially identical in 35, 105 and 350-day-old mice and were similarly affected by phenobarbitone pretreatment (80 mg/kg per day for 3 days).

The inducibility of NADPH-cytochrome c reductase by phenobarbitone in old rats was examined in more detail by Adelman (1971). He compared 2-month-old rats with 2-year-old rats and found that it was possible to attain the same maximally induced enyzme levels in the older rats but that a longer pretreatment period was required (96 h as opposed to 72 h; figure 19.3). After 72 h of phenobarbitone pre-

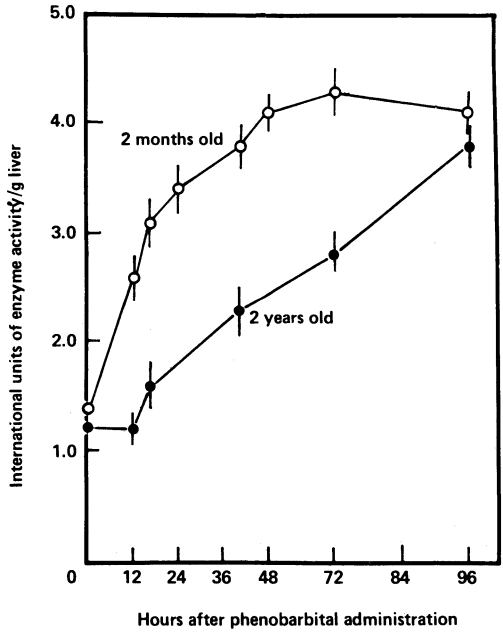

Figure 19.3 Age-dependent induction of NADPH-cytochrome c reductase by phenobarbitone (60 mg/kg per 24 h intraperitoneally) in rats. Each value represents the mean ± s.e.m. from at least four rats. After Adelman (1971). Reproduced with permission of *Experimental Gerontology*.

treatment (as used by Kato and Takanaka, 1968*b*) only about half maximal induction was obtained in old rats (figure 19.3). A further point to notice regarding these data is that, in contrast to Kato and Takanaka (1968*b*) and Baird *et al.* (1975), the basal levels of NADPH-cytochrome c reductase were similar in young and old rats.

Baird *et al.* (1975) have challenged the concept of an age-related lag period in hepatic microsomal drug metabolic enzyme induction. They claim that components of the NADPH-dependent cytochrome P-450 mediated drug-metabolising enzyme

system can be induced to the same maximal levels and as readily in old as in young rats. This is in spite of their reported finding that basal levels of NADPH-cytochrome c reductase and zoxazolamine hydroxylase are lower in old animals.

Thus, on the basis of published data to date, the situation regarding enzyme induction by phenobarbitone in old animals is confused. Depending on data source it can be concluded that in old animals, in comparison with young animals, lower or similar basal enzyme levels are found, the time taken for maximal phenobarbitone induction is prolonged or similar, and maximal inducible enzyme levels are lower or similar!

At present it is not possible to make any extrapolations from animal work on induction to the human situation. However, it has been recently suggested, on the basis of plasma antipyrine and quinine half-life data, that elderly human subjects are less induced by dichloralphenazone than their younger counterparts (Stevenson, Salem and Shepherd, 1978).

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Section 4
Clinical aspects of drug use in the elderly

Chairman: Dr O. T. Brown (Dundee)

20

Drug-prescribing patterns in the elderly— A general practice study

G. K. Freeman (Primary Medical Care, University of Southampton Medical School, Aldermoor Health Centre, Southampton, UK)

INTRODUCTION

Most surveys of primary care prescribing have examined prescriptions without reference to the clinical situation. This is because prescription forms (EC10/FP10) have been examined after dispensing by the retail pharmacist. This includes the notable work of Parish and his colleagues (Parish *et al.*, 1976). Our data are practice-based and linked to the relevant clinical information within our computerised record system CLINICS (Clark, 1977). Skegg and his colleagues have shown (Skegg, Doll and Perry, 1977) that psychotropic drug prescribing rises sharply with age. In this survey I briefly review our total prescribing for patients aged over 65 years and give some examples linking our psychotropic prescribing for the elderly to the relevant clinical indication.

METHOD

Setting

At Aldermoor Health Centre in Southampton we have a practice population which is typical of the city as a whole – a mixture of recently registered patients in new housing and well-established patients who have been with the practice for many years. The practice population on 30 June 1975 was 6432, of whom 941 (14.6 per cent) were aged 65 years or more.

Data collection

We have developed our computerised information system since 1973 using problem-oriented records modified from Weed's system (Weed, 1969). Details of all consultations since mid-December 1974 are held on computer file. Our data are taken from routine clinical care, 'warts and all', and are not a specific study of prescribing for the elderly. Data for the year 1975 have been used for this survey.

	Episode 1	Episode 2	Episode 3
Consultation 1	Encounter		
Consultation 2	Encounter	Encounter	
Consultation 3		Encounter	Encounter
Consultation 4		Encounter	
Consultation 5	Encounter	Encounter	Encounter

Figure 20.1

Two terms in our problem-oriented system need definition – *episode* and *encounter*. 'Episode' means an individual problem–it may be acute or chronic and may be medical, psychological or social. Each time an episode is actively managed at a consultation, the process is termed an 'encounter'. Active management implies prescription, investigation, referral, collection of new data or clinical reassessment of the episode. Figure 20.1 illustrates the relationship between episodes, encounters and consultations in a hypothetical patient with three concurrent episodes. Note that an episode may not generate an encounter at every consultation.

RESULTS

Of the 941 patients aged 65 or more, 659 (70 per cent) consulted during 1975. They presented 2455 illness episodes (3.7 per patient) during the year which were managed by 8769 encounters (13.3 per patient).

Referral to hospital colleagues

A total of 124 patients were referred for consultant opinion during the year and, as a few patients were referred more than once, the total number of referrals was 150, or 6.1 per cent of all episodes–thus, referral was not a very frequent management decision even in this relatively vulnerable age group. The 150 referrals comprised 99 to out-patient clinics, 17 for domiciliary consultation and 34 direct admissions to in-patient care.

Number of drugs per episode

Although referring patients for consultant opinion is a significant function of the primary care physician, a more important one is that of prescribing. Table 20.1 shows that prescribing need not be excessive, over 60 per cent of episodes being handled with the prescription of either no drugs or only one drug, and only 5.1 per

Table 20.1

No. of different drugs prescribed	Episodes	
	No.	%
0	749	30.5
1	839	34.2
2	474	19.3
3	165	6.7
4	101	4.1
5 or more	127	5.2
	Total 2455	100.0

cent of episodes requiring more than four different drugs. Thus, 'multiple' prescribing for a single problem was rare, particularly as the different drugs would often not have been given together.

Therapeutic class of drugs prescribed

Table 20.2 shows the number of 'drug encounters' for the main therapeutic classes. The first group consisted of almost equal parts of cardiovascular drugs and diuretics, while the second consisted almost entirely of analgesics. Corticosteroids (systemic and topical) accounted for a full third of the metabolic and endocrine group; more than half the respiratory drugs were cough suppressants and expectorants; similarly, over half the alimentary group were antacids.

It should be no surprise that our prescribing for the elderly was dominated by drugs for heart failure and hypertension, while analgesics and psychotropics vied for second place. However, Parish's 1970 sample of 116 principals new to general practice showed a greater use of psychotropic drugs than any other class (Parish *et al.*, 1976).

Table 20.3 shows that, of the psychotropic drugs, the benzodiazepines were used more than any other group (nearly 50 per cent). By contrast, the antidepressants (almost all of which were tricyclic agents) accounted for only 12 per cent of

Table 20.2 Therapeutic class of drugs

Drug class	Drug encounters	
	No.	%
CVS/diuretics	1741	25.6
Analgesics/CNS	1123	16.5
Psychotropic	1101	16.2
Metabolic/endocrine	917	13.5
Antimicrobials	583	8.6
Respiratory	526	7.7
Alimentary	463	6.8
Other	358	5.1
All Classes	6812	100.0

Table 20.3

Psychotropic drugs	Drug encounters	
	No.	%
Antidepressants	133	12.1
Neuroleptics	178	16.2
Benzodiazepines	529	48.0
Barbiturates	101	9.2
Other sedatives and hypnotics	115	10.4
Miscellaneous, including combined preparations	45	4.1
	Total 1101	100.0

Table 20.4

Psychotropic drugs	Total encounters	Repeat prescriptions	
	No.	No.	% of total encounters
Antidepressants	133	16	12.0
Neuroleptics	178	40	22.5
Benzodiazepines	529	146	27.6
Barbiturates	101	52	51.5
Other sedatives and hypnotics	115	30	26.1
Miscellaneous, including combined preparations	45	20	44.4
All psychotropics	1101	304	27.6

our psychotropic prescribing. The barbiturates were relatively few at 9 per cent, but this figure alone gives an incomplete picture.

Table 20.4 shows repeat prescriptions as a proportion of the total encounters for each psychotropic drug group. The highest proportion (at just over 50 per cent) occurred with the barbiturates. Taken with the small total number of encounters, this is consistent with our policy of discouraging new prescriptions for barbiturates. On the other hand, antidepressants are closely supervised, with only 12 per cent being given as repeat prescriptions. Repeat prescriptions of benzodiazepines were at the average level for psychotropic drugs as a whole.

Clinical indications for benzodiazepines

This group of drugs has only been in common use for the past decade and yet by 1975 it accounted for nearly half of our psychotropic prescribing for the elderly and is therefore a good example for analysis of clinical indications. Table 20.5 shows that episodes defined as primarily psychological accounted for less than half (40 per cent) of benzodiazepines used. Almost as many episodes were defined

Table 20.5

Use of benzodiazepines	Episodes No.	%
Psychological	87	40.5
Organic	85	39.5
Non-specific	28	13.0
Social	15	7.0
	Total 215	100.0

Table 20.6 Use of benzodiazepines: organic system

Episode	No.
Cardiovascular	24
Alimentary	21
Respiratory	16
Musculo-skeletal	14
Cerebrovascular	5
Other	5
	Total 85

as primarily organic, and there was also a significant number of non-specific symptoms. Although many episodes had an undefined social component, in 7 per cent the problem was defined as primarily social by the prescriber; these included bereavement, marital breakdown and hemiplegic spouse. Non-specific symptoms treated with benzodiazepines included dizziness, malaise, pallor and headache (note that prescription of benzodiazepines did not necessarily exclude efforts towards more precise diagnosis).

Table 20.6 details the organic systems treated. All the main organ systems are named here except genito-urinary and skins.

Table 20.7 details the primary psychological episodes. Anxiety included both acute and chronic anxiety states as well as tension states and the hybrid 'anxiety/depression'. Drug habituation included both primary benzodiazepine habituation

Table 20.7 Use of benzodiazepines: primary psychological

Episode	No.
Anxiety	32
Insomnia	29
Depression	15
Drug habituation	8
Other	3
	Total 87

and attempts to treat barbiturate habituation. We use the term 'insomnia' when sleeplessness is not thought to be a symptom of a more specific condition such as depression.

This variety of indications is remarkable and might suggest to the outsider that benzodiazepines either have many different actions or are being used as non-specific placebos. An alternative view is that prescribers are responding to the element of stress present in many different conditions. Of course, benzodiazepines should not be considered in isolation, and when deciding to use a drug, the prescriber will choose from a number of alternatives.

Drugs for insomnia

Table 20.8 shows the small list of drugs we used for insomnia. A benzodiazepine, usually nitrazepam, was used at 37 of the 69 encounters (54 per cent), but chlormethiazole was also popular, probably owing to the influence of our local geriatric department.

Table 20.8 Drugs for insomnia: encounters at consultations

Drug	No.
Nitrazepam	31
Other benzodiazepines	6
Chlormethiazole	20
Barbiturates	2
Other	10
Total	69

SUMMARY

The number of drugs prescribed for the elderly in an urban general practice is related to the number of episodes of illness presented and the number of specialist referrals. More than half the episodes were managed with either no drug therapy or only one drug, and only 6 per cent of episodes involved specialist referral. Cardiovascular and diuretic drugs were used most often, followed by analgesics and psychotropics. Nearly half of the psychotropics used were benzodiazepines. Analysis of the clinical indications showed that benzodiazepines were used for a very wide variety of problems less than half of which were defined as primarily psychological.

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21
A survey of hospital prescribing for the elderly

L. J. Christopher, B. R. Ballinger, A. M. M. Shepherd, A. Ramsay and G. Crooks
(Aberdeen-Dundee Medicines Evaluation and Monitoring Group, Ninewells Hospital, Dundee, and Royal Liff Hospital, Dundee, UK)

INTRODUCTION

The elderly population is increasing and the over 65s now comprise over 13 per cent of the total population in Great Britain, compared with 5 per cent early this century (Office of Population Censuses and Surveys, 1971).

At present, there is little available information on prescribing patterns in the elderly and this study describes the findings in an in-patient population of 873 in Dundee hospitals, examines potential problems of prescribing that emerged and suggests ways in which they may be minimised.

PATIENTS AND METHODS

The study covered one 24 h period in July 1975 and all patients 65 years and over in Dundee hospitals were included in the study. Patient data were—name, case reference number, ward, age, sex, all drugs currently prescribed, their dose, route and frequency of administration. Data extraction in all hospitals was facilitated by the use of standard forms for drug prescription and administration recording (Crooks *et al.*, 1967).

For convenience, patients were categorised into the following groups: psychiatric (301), geriatric (279), medical (158), surgical (100) and mentally subnormal (35).

Two hundred and sixty-six (43 per cent) of the females were over 80 years old and the majority of them occupied geriatric (128) and psychiatric (78) beds. While the female population increased with age from 81 in the 65-69 age band to 266 in the 80+ group, males were fairly evenly distributed, with a range of 52-69 patients in each group.

RESULTS

The average number of prescriptions issued per patient was 3.3 during the 24 h period of observation. Patients in geriatric wards were prescribed most drugs, with an average of 4.0 drugs per patient. Fifty-two per cent of all patients had from one

Table 21.1 Prescribing patterns of the most commonly used drug groups, shown as percentage of patients within each category

Drug group	158 = 100% Medical	100 = 100% Surgical	279 = 100% Geriatric	301 = 100% Psychiatric	35 = 100% Mentally subnormal	873 = 100% All patients
Neuroleptics	12	19	36	48	6	286 (33%)
Chloral derivatives	16	17	61	23	3	280 (32%)
Diuretics	40	24	35	22	17	257 (29%)
Laxatives	10	7	42	30	17	235 (27%)
Mineral supplements	35	21	23	15	14	192 (22%)
Analgesics	22	61	22	9	17	189 (22%)
Benzodiazepines	17	23	11	18		135 (16%)
Iron preparations	15	14	17	9	6	114 (13%)
Cardiac drugs	27	14	13	7	3	111 (13%)
Antibiotics / Anti-infectives	24	22	11	5	3	106 (12%)
Anticholinergics	10	7	13	3		67 (8%)
Antidepressants	5	1	9	10	11	86 (8%)
Vitamins	5	7	10	4	3	58 (7%)
Anti-Parkinson's	2		4	10		45 (5%)
Other sedatives and hypnotics (excluding barbiturates)	11	7	1	4		37 (4%)

If a patient is prescribed one or more drugs in a given group, this is counted once.

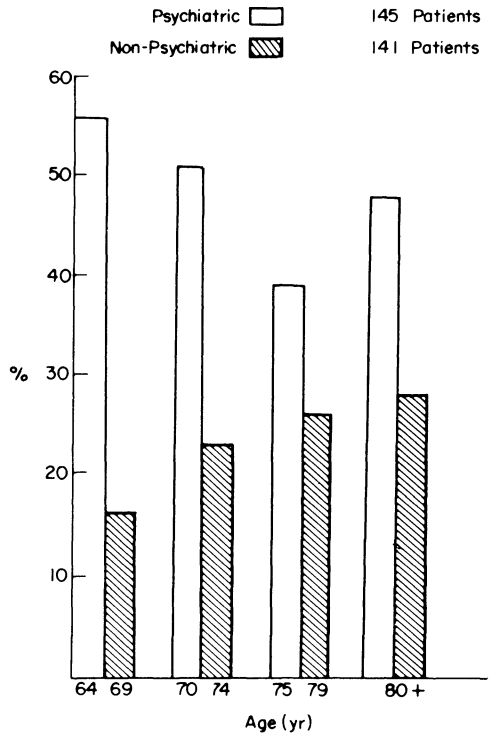

Figure 21.1 Neuroleptic drug prescribing by age groups, psychiatric versus non-psychiatric.

to six drug doses administered, 33 per cent had seven or more and 15 per cent ten or more. On the other hand, 15 per cent (128) patients did not receive any drug.

Some 67 per cent of patients in geriatric wards were prescribed one or more 'as required' medicine, compared with 31 per cent of those in the medical category. On the study day only 21 per cent of 'as required' was given, the proportion of given to not-given being similar between patient categories.

Phenothiazines (see table 21.1; figures 21.1 and 21.2), chloral derivatives, diuretics and laxatives were the most frequently prescribed drug groups, each being used in more than 200 patients. While popular drugs tended to be widely prescribed between patient categories, certain features stand out. Diuretics and mineral supplements were most used by medical patients, probably reflecting a high incidence of cardiac disease (see table 21.2). Analgesics were most frequently prescribed for surgical cases, chloral derivatives for geriatric patients and, as expected, phenothiazines for psychiatric patients. The mentally subnormal represented only a small sector of the study (35 patients) and no drug group was particularly favoured.

The use of hypnotics was high in the four main patient categories and ranged from over 40 per cent in medical to more than 70 per cent in geriatric wards. The most commonly prescribed hypnotic was the chloral derivative triclofos, particularly in geriatric wards.

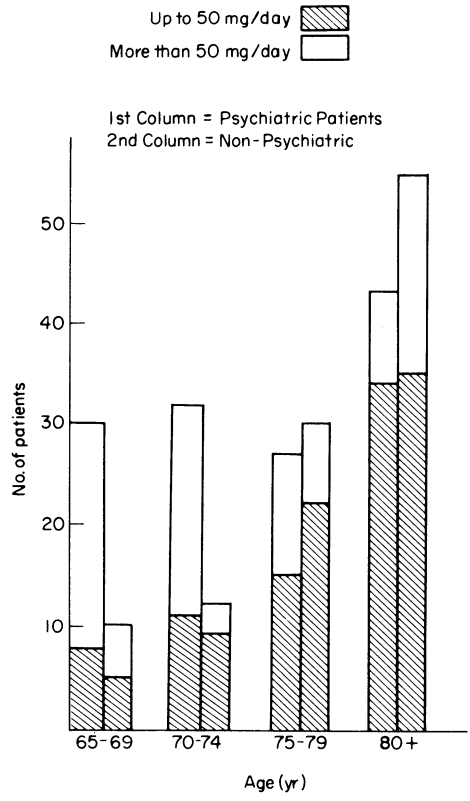

Figure 21.2 Phenothiazine daily dosage by age groups (257 patients).

Of the cardiac drugs (111 patients), digoxin was prescribed most frequently (89 patients), the main users being medical (34) and geriatric (27) patients; 44 per cent of all patients on digoxin were 80 years old or over.

Of 66 patients who received antidepressants, 29 were in the psychiatric and 24 in the geriatric groups, respectively. The most popular antidepressant sub-group, the tricyclics, accounted for 80 per cent of all antidepressant prescriptions.

DISCUSSION

The study method was simple in that drug prescription sheets in each ward are normally held in one place—the drug Kardex folder and all items needed contained therein (Crooks *et al.*, 1967). Two of the study group collected all data required over a period of 2 weeks.

In a 'one-day' cross-sectional study, it is not possible to comment on an individual patient's course of treatment which unfolds over the whole period of hospitalisation. It follows that information such as the number of drugs prescribed per patient in this survey is not comparable with the number of drugs prescribed per patient when this figure is derived from hospital discharge records.

Table 21.2 Diuretic prescribing/potassium supplementation

Drug	Medical 158 cases	Surgical 100 cases	Geriatric 279 cases	Psychiatric 301 cases	Mentally subnormal 35 cases	Total
Bendrofluazide	12	6	43	43	1	105 (39%)
Frusemide	37	12	23	11	4	87 (33%)
Others	19	9	32	13	2	75 (28%)
Total	68	27	98	67	7	267 (100%)
No. of different diuretics	6	7	9	8	3	13
Separately prescribed potassium supplement	51	21	57	46	5	180
Diuretic and potassium supplement combined	8	4	15	4	0	31
Total	59	25	72	50	5	211

Since about half of the patients were prescribed one or more drugs to be given 'as required', this probably produced some exaggeration of the true picture of drug use. Apart from continuing intermittent need for certain prescribed drugs, factors such as low doctor to patient or nurse to patient ratios in geriatric wards could contribute to this picture (Ballinger and Ramsay, 1974).

It is notable that 120 patients were prescribed six drugs or more and 132 patients received ten or more drug doses on the study day. Whether such drug regimens, particularly those requiring many administrations per day, can be effectively complied with by elderly patients at home is debatable and simplification of the regimen prior to discharge would be advantageous (Parkin *et al.*, 1976).

Laxatives were high on the list of prescribed drugs. Evidence is accumulating that the addition of roughage to the diet could achieve the same objective (Burkitt, 1972). With encouragement from the nursing staff, one geriatric ward has almost managed to eliminate the use of laxatives by adding bran to the patients' morning cereal. While the cost of laxatives is relatively small, the gain in nurses' and pharmacists' time should be considerable.

The use of diuretics and potassium supplements was high in all patient categories in this survey and comprised 33 per cent of all diuretic use (see table 21.2). Since the therapeutic result for the chronic sick would probably be no worse if a less potent (and often cheaper) diuretic were used, it is not easy to explain the common use of a powerful diuretic such as frusemide which may produce over-flow incontinence or aggravate urinary retention in elderly males. Without joining in the current debate, the need for potassium supplementation should at least be investigated further, especially in the light of recent evidence which questions its usefulness as a routine measure (Lawson *et al.*, 1976).

Neuroleptics were prescribed for 286 (33 per cent) patients, with psychiatric patients accounting for the major share. While patient age was independent of frequency of use in psychiatric patients, in non-psychiatric patients drug use increased with age, and of the 65-69 age group 16 per cent were prescribed a neuroleptic, in contrast to 28 per cent of the over 80s (figure 21.1). This probably reflects the increasing frequency of psychiatric problems in the ageing in-patient population occupying general and geriatric beds. (χ_1^2 for linear trend = 4.7; $P < 0.05$.)

The most widely used drugs were hypnotics, which accounted for over 400 prescriptions. Even though frequently prescribed on an 'as required' basis, their actual use was high. While some patients benefit from a short course during their early hospitalisation, continued hypnotic use, although common, is not easy to justify on medical grounds. Many patients (150) were prescribed concomitantly both a hypnotic and neuroleptic with the attendant risks of both over-sedation and disorientation.

Of 204 prescriptions for analgesics, the two most popular were paracetamol (44 patients) and distalgesic (35 patients). In the USA there have been reports of habituation to dextropropoxyphene, a constituent of distalgesic, leading to stricter controls of its use (Editorial, 1977). At present, it would be prudent, therefore, to limit prescribing of distalgesic to short-term, self-limiting situations where paracetamol or soluble aspirin is unsuccessful or unsuitable.

Of the antibiotics, the most popular were ampicillin (27) and co-trimoxazole (25), followed by cephalexin (12). Omitting topical use, 106 patients received them and 17 different antibiotics were used; 9 for the 35 medical cases treated and 11 for the

22 surgical cases. While comment on appropriateness of choice of antibiotic cannot be made from the survey data, it would appear that the range of drugs used might be reduced by the adoption of a uniform approach to prescribing.

Increasing age may modify response to certain drugs—e.g. digoxin and psychotropics (Bender, 1974). Phenothiazine doses were therefore examined to determine whether a correlation between daily dose and age was apparent (figure 21.2). Only the most commonly used phenothiazines were considered—chlorpromazine, promazine and thioridazine—and patients were grouped according to whether they received a daily dose of up to 50 mg (low dose) or greater (high dose). The high dose was used in 30 per cent (33) of patients 80 years old or more, compared with 50 per cent (73) of those less than 80. However, while the proportion of low to high daily dose increased with age in the psychiatric patients, this was not apparent in the case of non-psychiatric patients. Increasing age, therefore, did not appear to be a major factor in determining dose level in the latter group. (χ_1^2 for linear trend = 23.4; $P < 0.001$.)

The benzodiazepine hypnotic, nitrazepam, was prescribed 96 times. While a dose of up to 10 mg is common for younger patients, the official data sheet recommends up to 5 mg per day for elderly patients. In this survey 42 (44 per cent) of those on nitrazepam were prescribed the 10 mg dose.

With regard to frequency of doses, it is known that the clinical effects of a drug may persist for a considerable time beyond that at which it may be detected in the blood. Evidence is accumulating that this is the case with tricyclic antidepressants and that a single dose could achieve the same result as divided daily doses, provided that undesirable side effects do not occur (Mendels and DiGiacomo, 1973; Hussain and Chaudry, 1973). In this drug group, there was a diversity of prescribing patterns and, of 53 patients treated, 14 had been prescribed a once-daily regimen, 10 twice-daily, 28 three-times daily and 1 'as required' (table 21.3). Should a once-daily regime prove effective, there is a possible added advantage—the sedative effect of amitriptyline, which, if taken late in the evening, could eliminate the need for night sedation.

Table 21.3 Dundee elderly in-patient survey

	Tricyclic antidepressants (times per day prescribed)				
Drug	Once	Twice	Three times	As required	Total
Amitriptyline	7	5	11	1	24
Imipramine	6	4	16	–	26
Others (3)	1	1	1	–	3
Total	14	10	28	1	53

CONCLUSIONS

This review of drug prescription on a single day to a geriatric in-patient population was based on data collected simply by reviewing ward-level, drug recording sheets. On average, prescribing was not particularly heavy, although one patient in seven was receiving six or more drugs per day. The use of certain drug groups, particularly

the hypnotics, appeared to be excessive and little dose reduction was apparent with increasing age. Tricyclic antidepressants, a drug group with prolonged pharmacological effect, were commonly prescribed twice or even thrice daily, when a single daily dose could frequently be sufficient.

The study, therefore, revealed possible problems of hospital drug prescribing in an elderly population which deserve further investigation. It would appear that appropriate modification of regimens could lead to improved response and fewer adverse effects.

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22
Adverse reactions to prescribed drugs in the elderly

J. Williamson (University Department of Geriatric Medicine, City Hospital, Greenbank Drive, Edinburgh, UK)

INTRODUCTION

The medical profession and the lay public are increasingly aware of the problem of adverse drug reactions which the elderly are specially prone to suffer. There are many reasons for their proclivity—they metabolise drugs less effectively and excrete them with greater difficulty, and there is evidence that the sensitivity of target cells to some drugs is increased in old age (Castleden *et al.*, 1977). In addition, old people, because of mental impairment, poor vision, poor hearing and difficulty in opening containers, have a greater tendency towards non-compliance with prescriber's instructions. These factors together with the steady increase in numbers of aged persons readily account for the growing problem.

The continuing publicity of the ill-effects of drugs may have a boomerang effect in that old people may be denied the benefits of drug therapy because their medical attendants have felt discouraged. Old people can be among the major beneficiaries of carefully used drug therapy, as evidenced by the remarkable efficacy of drug treatment of congestive cardiac failure, thyroid dysfunction, Parkinsonism and depression, to name but a few common afflictions of the elderly. Thus we have the paradox that old people are most at risk from drugs and most at risk of being denied drugs.

For these reasons, the Research Committee of the British Geriatrics Society planned and executed a multi-centre inquiry. Fifty established departments of geriatric medicine in the UK were approached and 48 agreed to collaborate. Because of problems arising from the industrial action of junior doctors in the Health Service, 6 withdrew, leaving 42 participating departments. Pilot studies had been done to devise a suitable pro forma and collaborators were asked to make a return for each of 50 consecutive patients admitted. Thirty-three complete returns were made and nine others relating to fewer than 50 patients yielded a total of 1998 records.

Data comprised age, sex, diagnoses, drugs taken, whether an adverse reaction had taken place, outcome of reactions and whether adverse reactions had contri-

Table 22.1 Numbers in sample receiving prescribed drugs and with adverse reactions

	Males	Females	Both sexes
Number in sample	677	1321	1998
No. taking prescribed drugs	547 (80.8%)	1078 (81.6%)	1625 (81.3%)
No. with adverse reactions	82 (12.1%)	166 (12.6%)	248 (12.4%)
Proportion of drug takers with adverse effects	15.0%	15.4%	15.3%
Total no. of drugs causing reactions	101	211	312
Total no. of drugs taken	1528 (2.3 per male)	3148 (2.4 per female)	4676 (2.3 per person)

No significant difference between male and female groups in respect of proportion taking drugs or prevalence of adverse effects.

buted to the need for admission to hospital. Results were transferred to magnetic disc and analysed by computer.

RESULTS

There were 677 men and 1321 women; 259 (38.3 per cent) of men and 282 (21.3 per cent) of women were aged less than 75 years.

Participants were allowed up to six diagnoses and 1532 (76.7 per cent) had one to three diseases while the rest had four or more. The proportion of males and females with one to three or four and more diagnoses was equal, and likewise for the younger and older groups (under-75s and 75 +).

Table 22.1 gives a summary of the numbers of each sex who were receiving prescribed drugs and of those with adverse reactions.

Table 22.2 shows the numbers receiving different numbers of prescribed drugs.

Table 22.2 Numbers receiving no drugs, 1–3 drugs and 4–6 drugs*

	Age		
	Under 75	75 and over	Totals
Men			
No drugs	56 (21.6)	74 (17.7)	130 (19.2)
1–3 drugs	142 (54.8)	238 (56.9)	380 (56.1)
4–6 drugs	61 (23.6)	106 (25.4)	167 (24.7)
Totals	259 (100.0)	418 (100.0)	677 (100.0)
Women			
No drugs	41 (14.6)	202 (19.4)	243 (18.4)
1–3 drugs	171 (60.6)	556 (53.6)	727 (55.0)
4–6 drugs	70 (24.8)	281 (27.0)	351 (26.6)
Totals	282 (100.0)	1039 (100.0)	1321 (100.0)
Totals			
No drugs	97 (17.9)	276 (18.9)	373 (18.7)
1–3 drugs	313 (57.9)	794 (54.5)	1107 (55.4)
4–6 drugs	131 (24.2)	387 (26.6)	518 (25.9)
Totals	541 (100.0)	1457 (100.0)	1998 (100.0)

*Note: 7 men and 12 women were receiving 7–12 drugs. No significant differences between males and females or between those aged less than 75 or 75 years or more with regard to numbers receiving different numbers of prescribed drugs. Figures given in parentheses are percentages of the total in the group under study.

PRINCIPAL PRESCRIBED DRUG GROUPS

Table 22.3 gives a list of the most commonly prescribed drugs.

It will be seen that diuretics were by far the most widely prescribed drugs (37.4 per cent) but they were by no means the most likely to cause adverse reactions, as will be seen from Table 22.4.

Table 22.3 Main prescribed drug groups

	Male	Female	Total
Diuretics	243 (35.9)	504 (38.2)	747 (37.4)
Analgesics and antipyretics	157 (23.2)	391 (29.6)	548 (27.4)
Antidepressives, tranquillisers and psychomimetics	144 (21.3)	329 (24.9)	473 (23.7)
Hypnotics, sedatives and anticonvulsants	153 (22.6)	291 (22.0)	444 (22.2)
Digitalis	124 (18.3)	277 (21.0)	401 (20.1)
Salts (K)	102 (15.1)	211 (16.0)	313 (15.7)
Haematinics	60 (8.9)	191 (14.5)	251 (12.6)
Antibiotics and other anti-bacterials	97 (14.3)	132 (10.0)	229 (11.5)
Laxatives	47 (6.9)	89 (6.7)	136 (6.8)
Vasodilators	51 (7.5)	57 (4.3)	108 (5.4)
Hypotensives	32 (4.7)	75 (5.7)	107 (5.4)
Bronchodilators	58 (8.6)	43 (3.3)	101 (5.1)
Rigidity and tremor controllers	39 (5.8)	61 (4.6)	100 (5.0)
Miscellaneous nervous system	22 (3.2)	73 (5.5)	95 (4.8)
Vitamins and related substances	31 (4.6)	63 (4.8)	94 (4.7)
Insulin and hypoglycaemics	27 (4.0)	60 (4.5)	87 (4.4)
Corticosteroids	20 (3.0)	45 (3.4)	65 (3.3)
Antacids	14 (2.1)	36 (2.7)	50 (2.5)
Thyroid and antithyroid preparations	3 (0.4)	46 (3.5)	49 (2.5)
Antihistamines	13 (1.9)	22 (1.7)	35 (1.8)
Oestrogens	19 (2.8)	8 (0.6)	27 (1.4)
Propranolol	5 (0.7)	15 (1.1)	20 (1.0)

Figures in parentheses are percentages of the total number of patients (677 males and 1321 females).

Table 22.4 Principal drug groups associated with adverse reactions

	Males	Females	Total
Diuretics	24 (9.9)	36 (7.1)	60 (8.0)
Antidepressives, tranquillisers and psychomimetics	14 (9.7)	43 (13.1)	57 (12.1)
Digitalis	20 (16.1*)	26 (9.4)	46 (11.5)
Hypnotics, sedatives and anticonvulsants	10 (6.5)	23 (7.9)	33 (7.4)
Analgesics and antipyretics	5 (3.2)	20 (5.1)	25 (4.6)
Hypotensives	3 (9.4)	11 (14.7)	14 (13.1)
Rigidity and tremor controllers	5 (12.8)	8 (13.1)	13 (13.0)
Antibiotics and other antibacterials	3 (3.1)	7 (5.3)	10 (4.4)
Corticosteroids	3 (15.0)	5 (11.1)	8 (12.3)
Insulin and hypoglycaemics	2 (7.4)	6 (10.0)	8 (9.2)

Figures in parentheses are percentages of the total numbers of patients taking each individual drug. See Table 22.3.
*There was a significantly higher proportion of adverse reactions in men ($\chi^2 = 4.4$; $P < 0.05$).

From the figures in parentheses, it is evident from table 22.4 that several drugs were particularly associated with adverse reactions. Thus the greatest proportion of reactions (13.1 per cent) occurred with hypotensive agents, followed by anti-

Parkinsonian drugs (13.0 per cent) and psychotropics (12.1 per cent), while reactions were much less evident with diuretics (8.0 per cent). A sex difference in prevalence was only apparent for digitalis reactions, with males having a significantly higher rate.

EFFECT OF AGE

Most other studies (Hurwitz, 1969) have shown that old patients were more apt to have adverse reactions. In this study, comparison of the rates in the under-75s and 75+ groups showed no difference for either sex. This is probably due to the greater 'biological' (or pathological') similarity in the patients studied in the present survey, all admissions to geriatric wards tending to be very 'deteriorated', thus obscuring any purely chronological effects.

EFFECT OF NUMBER OF PRESCRIBED DRUGS

Figure 22.1 shows the prevalence of adverse reactions in relation to numbers of prescribed drugs and shows a step-wise increase from 10.8 per cent in those receiving one drug to 27 per cent in those receiving six drugs.

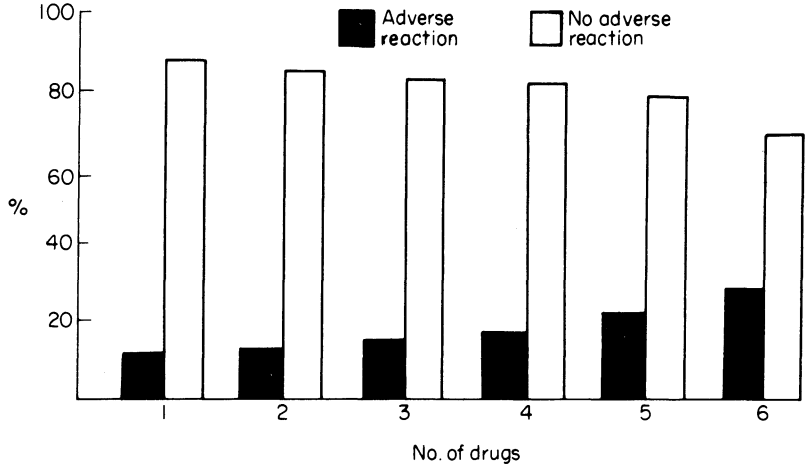

Figure 22.1 Adverse reactions to drugs in the elderly.

ADVERSE REACTIONS AS A CONTRIBUTORY CAUSE OF ADMISSION

Collaborators were asked to judge whether observed mactions had contributed to the need for hospital admission. In 209 patients (65 malea and 144 females) it was thought that this was so. This represents 9.6 per cent of males and 10.9 per cent of females in the sample.

Table 22.5 shows the contribution of the principal drug groups to the need for admission.

Table 22.5 Adverse reactions as a contributory cause for admission

	Not a cause	Sole cause	Contributory cause	Totals
Diuretics	18 (30.0)	4 (6.7)	38 (63.3)	60 (100.0)
Antidepressives, tranquillisers and psychomimetics	9 (15.8)	11 (19.3)	37 (64.9)	57 (100.0)
Digitalis	7 (15.2)	9 (19.6)	30 (65.2)	46 (100.0)
Hypnotics, sedatives and anticonvulsants	2 (6.1)	18 (54.5)	13 (39.4)	33 (100.0)
Hypotensives	0 (0.0)	5 (35.7)	9 (64.3)	14 (100.0)
Rigidity and tremor controllers	2 (15.4)	7 (53.8)	4 (30.8)	13 (100.0)

Figures given in parentheses are the % of the total patients prescribed drugs of that group.

It is seen that reactions to hypotensives were very likely to have led to hospital admission (100 per cent), with hypnotics (93.9 per cent) a close second.

OUTCOME OF ADVERSE REACTIONS

Full recovery occurred in 169 patients who had had adverse reactions, or 68.7 per cent of all with reactions. The proportion who recovered or failed to recover differed with different drug groups. Thus 80.4 per cent of patients with digitalis reactions made a full recovery, 73.3 per cent for diuretics, 71.4 per cent for hypotensives, 63.1 per cent for psychotropics, 53.5 per cent for hypnotics, but only 46.2 per cent of patients recovered fully from adverse reactions to 'rigidity and tremor controllers'.

Two patients died in this study from adverse reactions. One, an old woman on many drugs, from digitalis effects and the other, a patient on paracetamol, aspirin and ibuprofen, from perforated duodenal ulcer.

Inevitably, there were examples of extreme drug overuse, as in the 88 year old woman who was supposed to be taking 30 tablets per day including two hypnotics, four analgesics and two compound tablets each containing a different barbiturate. She recovered fully from her adverse reactions—a beneficiary of non-compliance perhaps?

DISCUSSION

These findings relate to a highly selected group of old people—admissions to British geriatric wards—and it is not justifiable to attempt to relate them to the general population of elderly persons. Nevertheless, they do give an idea of prescribing habits and adverse reactions in a sick elderly group and they represent the 140 000 or so who are admitted annually to geriatric wards.

It is legitimate to question the accuracy of these findings, recorded as they were

by so many observers. It should be pointed out, however, that judgements were all made by thoroughly experienced physicians, all of whom were senior specialists in geriatric medicine and capable of clinical judgements at least as good as any other group of doctors.

The findings confirm the general level of 15 per cent with adverse reactions (Hurwitz, 1969), but not the expected higher prevalance in the oldest patients. There was a clear correlation, which was not influenced by age, between number of drugs being taken and prevalence of adverse reactions. The groups of drugs most liable to produce adverse reactions were hypotensives and rigidity controllers.

Hospital admission was solely due to adverse reactions in 55 cases (2.8 per cent of sample) and partly so in 154 cases (7.7 per cent of sample). Thus, in more than 1 in 10 admissions, a drug was solely or partly responsible. Extrapolated to the 140 000 yearly admissions, this means that in one year some 3900 would be admitted solely and some 10 800 partly because of adverse reactions. In addition, of the 14 700 admitted solely or partly for adverse reactions, about 4700 would not recover fully.

There is no easy solution to these serious problems but significant improvement cannot occur until medical students receive adequate instruction in clinical pharmacology and geriatric medicine, and it is up to medical schools to see that this is done.

Efforts in the postgraduate field must continue meanwhile and the following general rules are advocated when prescribing drugs for the elderly.

(1) Give a drug only when a positive indication exists and use a completely inert substance when prescribing a placebo.

(2) Make a correct diagnosis. This may seem obvious, but in geriatric care it is commonplace to find systolic blood pressure being unnecessarily (and even dangerously) lowered by powerful hypotensives; non-existent Parkinsonism being treated by powerful 'tremor and rigidity controllers'; and vague 'giddiness' receiving the treatment which is only effective in labyrinthine disease.

(3) Give as few drugs as possible. Avoid repeat prescriptions. Use drugs which are well known and whose adverse reactions are familiar.

(4) Make sure patients understand prescriber's intentions. Use large, clear writing and rehearse with patient (and relatives, neighbours or home helps where relevant). Many geriatric departments routinely have relatives of patients along to the ward, rehabilitation department or day hospital in order to explain details of management. Similar pains should be taken with prescribing (Atkinson, Gibson and Andrews, 1977).

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23
Treatment of hypertension in the elderly

Jan Koch-Weser (Centre de Recherche Merrell International, Strasbourg, France)

INTRODUCTION

Many articles during recent years have discussed the pharmacotherapy of hypertension in old age. Their counsels for elderly hypertensives run the gamut from '. . . hypotensive drugs . . . should hardly ever be used' (Wedgwood, 1973) and '. . . diastolic pressures up to 120 mmHg . . . are not an indication for therapy' (Jackson *et al.*, 1976) to '. . . management of hypertension above 150/90 should vary with the individual' (Burch, 1975) and '. . . regardless of the patient's age, systolic pressure above 160 mmHg and diastolic pressure above 95 mmHg should be treated' (Chrysant, Frohlich and Papper, 1976). The one common feature of all these recommendations is their impressionistic nature. Although they tend to sound authoritative, such articles merely express the authors' opinions and are not based on any positive knowledge. They cannot possibly be, because the benefits and risks of pharmacological reduction of blood pressure in elderly hypertensives have not been established through controlled studies.

ABSENCE OF THE ELDERLY FROM ANTIHYPERTENSIVE TRIALS

One of the earliest controlled studies (Hamilton, Thompson and Wisniewski, 1964) which established the benefits of blood pressure control for preventing complications of non-malignant hypertension included only patients under 60. The mean age of the 143 patients with diastolic pressures between 115 and 129 mmHg followed by the Veterans Administration Cooperative Study Group on Antihypertensive Agents (1967) was 50.7 years, and all patients suffering morbid events were under 70. Of the 380 patients with diastolic pressures averaging 90–114 mmHg studied by the same group (1970), none were over 75 and only 30 were over 69 years old. The Hypertension-Stroke Cooperative Study Group (1974) investigated the effect of antihypertensive treatment on stroke recurrence in 452 stroke survivors. Only patients under 75 were included and only 9 per cent were at least 70 years old. The US Public Health Service Intervention Trial in Mild Hypertension (Smith, 1977) included nobody over the age of 55 years among their 389 patients. All completed trials on the effectiveness of antihypertensive therapy have been

characterised by absence or gross under-representation of the elderly.

The Hypertension Detection and Follow-Up Program of the US National Institutes of Health, which is presently being carried out to test the efficacy of antihypertensive therapy in reducing morbidity and mortality of patients with diastolic pressures above 89 mmHg, has enrolled 10 940 patients of both sexes, of all races, and 'younger as well as middle-age ranges' (Hypertension Detection and Follow-Up Program Cooperative Group, 1977). Hypertensives over 69 years of age have been omitted. Another on-going multi-centre trial of treatment in mild hypertension includes only male patients up to 55 years of age (Perry, 1977).

Controlled trials of specific antihypertensive drugs or drug combinations ignore elderly hypertensives even more strikingly. The age distribution of 1000 hypertensive patients included in 41 such studies randomly selected from the medical literature is shown in figure 23.1. Only seven of these patients were over 69 years

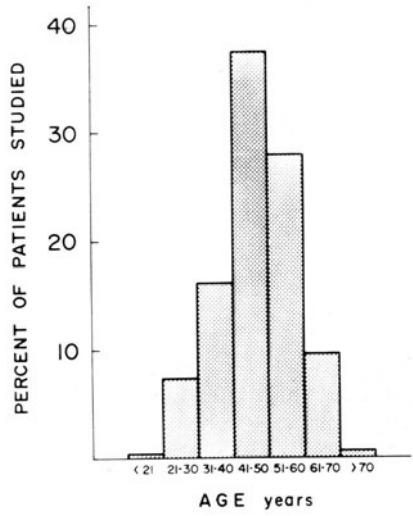

Figure 23.1 Age distribution of 1000 hypertensive patients studied in 41 drug trials during 1972–1976.

old. The neglect of the aged hypertensive was best exemplified by a long-term drug study which dropped patients from follow-up when they reached 70!

Many reports of drug studies do not give the age of individual patients. We analysed 100 such studies since 1972 involving 3063 patients. The mean age of the patients was 47.9 years; the mean age of the oldest patient in each series was 63.9. Only 16 series included any patients over 69, and, judging by the mean patient age, these must have been isolated individuals.

These 100 reports also failed to stratify results by age. Thus, even when 10 per cent of the patients studied were over 60, one learns nothing about the response of this age group, since the results are dominated by the 80 per cent or more of the study population that were middle-aged. Were the drugs less effective in patients over 60? Was the incidence of adverse effects higher? Not one of the 100 reports analysed shed any light on these questions. It may well be that no antihypertensive

drug trials ever have, with the exception of the rare study specifically directed at the elderly (MacFarlane and Kennedy, 1973; Eisalo, Heino and Munter, 1974; Lundborg and Steen, 1976).

Many paediatricians have forcefully complained that drugs are not sufficiently studied in children. Antihypertensive drug studies in the young are indeed rare, but so is hypertension. The 'therapeutic orphanage' of the old in studies on antihypertensive therapy and agents is far more puzzling and its implications are disturbing.

PREVALENCE OF HYPERTENSION IN THE ELDERLY

It is clear that hypertension is very common in old age, but estimates of its prevalence vary widely. Since hypertension is usually defined solely in terms of blood pressure, its prevalence inevitably depends on what one considers to be the upper limit of 'normal' for systolic and/or diastolic pressure (Alderman and Yano, 1976) and on how these pressures are ascertained (Carey *et al.*, 1976). Normalcy is easy to define statistically in terms of some maximum deviation from the population mean. In practice, such a definition is not used. Hypertension has been considered to begin at almost any systolic pressure between 130 and 200 or diastolic pressure between 90 and 120 mmHg. Such criteria are, of course, totally arbitrary. The Framingham study defined hypertension as systolic pressure above 160 and diastolic over 95 mmHg (Kannel and Gordon, 1974). By this definition, about 30 per cent of men between 65 and 74 entering the study were hypertensive. Others have estimated the prevalence of 'hypertension' in 70 year old men to be as high as 65 per cent (Master, 1952; Chrysant *et al.*, 1976).

Many population surveys have shown that mean systolic and diastolic pressures increase with age in both sexes, with the former rising more than the latter (Society of Actuaries, 1959; Master and Lasser, 1961; United States National Center for Health Statistics, 1977). There has been extensive and rather pointless discussion about whether these rises are 'normal'. In Western societies they are usual, but in many individuals they do not occur. In some 'non-acculturated' societies they are not seen at all (Page and Sidd, 1972).

The purely statistical definition of 'normal' has certainly contributed to the lack of interest in treating the elderly hypertensive. Unfortunately, what is common is not necessarily normal in the sense of good function (Feinstein, 1974). Disturbed function remains undesirable even if many members of a group suffer from it. A 70 year old woman with a blood pressure of 120/80 may be unusual, but she is certainly better off than her peer with a pressure of 160/90, which is closer to the mean for that age in Western society.

If abnormal blood pressure in old age is defined solely on a statistical basis, it has no inherent therapeutic implications. Instead of debating what is normal, we should focus on the association between blood pressure levels and morbidity and mortality in this age group.

RISK OF HYPERTENSION IN OLD AGE

A recent article on antihypertensive therapy in the elderly stated that '. . . systolic levels of up to 220 mmHg have been found in healthy old people' (Jackson *et al.*, 1976). Such people may be asymptomatic, they cannot possibly be considered

healthy in the sense of 'being sound in body'. Men aged 65–74 years with this degree of systolic hypertension run more than four times the risk of cardiovascular morbidity and mortality than their age peers with systolic blood pressures below 130 mmHg. This is not good health by any reasonable definition. There is nothing benign about asymptomatic hypertension in either sex at any age (Kannel, 1974).

If there is anything certain about hypertension among the elderly, it is the fact that increasing age does not diminish the value of either systolic or diastolic blood pressure levels as predictors of cardiovascular complications and death. This was shown by life insurance data some twenty years ago (Society of Actuaries, 1959) and has since been amply confirmed (Kannel *et al.*, 1970; Paul, 1971; Kannel and Gordon, 1974; Miall and Chinn, 1974). Compared with this massive epidemiologic information, the charming anecdotal accounts of elderly hypertensives who live for years contentedly and unbothered by drugs are irrelevant.

As one example from the Framingham study (Kannel and Gordon, 1974), men aged 65–74 found at biennial examinations to have systolic pressures above 160 mmHg subsequently had more than twice the all-causes mortality per year than those whose systolic pressure was below 130 mmHg (figure 23.2). The difference in

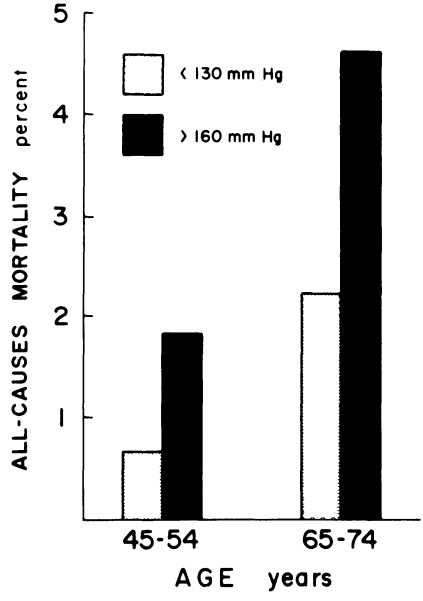

Figure 23.2 Annual mortality from all causes among untreated men with systolic blood pressures of <130 mmHg and >160 mmHg. After Kannel and Gordon (1974).

mortality was 2.4 per cent per year. Among men aged 45–54 the same comparison gave a mortality difference of only 1.2 per cent. Furthermore, 25 per cent of the older men against only 11 per cent of the younger had this degree of systolic hypertension and thus were exposed to the excess death rate associated with it.

The Framingham study and other surveys have clearly shown that the cost of

hypertension to the community in terms of associated excess deaths rises with age in both men and women. Accordingly, there is no justification for being unconcerned about high blood pressure among the elderly. We must find out if, in this age group as in the middle-aged, lowering of blood pressure by appropriate drug therapy will reduce the excess morbidity and mortality associated with hypertension.

VALUE OF ANTIHYPERTENSIVE TREATMENT OF THE ELDERLY

A recent *Lancet* editorial (1977) stated: 'In middle-aged men the risks of stroke, dissecting aneurysm, and cardiac failure, all common in elderly people, are substantially diminished by therapy so that it would be surprising if this were not at least partly true in later decades.' It would be, indeed, but it is not impossible that in the elderly the benefits of therapy are less and the risks higher than in the middle-aged. It is conceivable, for instance, that the most common mechanisms of atherothrombotic brain infarction, a complication which is effectively prevented by therapy in the middle-aged hypertensive (Cooper and West, 1977), are different in the old and less responsive to blood pressure reduction. Extrapolations of results from a different age group do not constitute a firm basis for advocating antihypertensive therapy in the aged (Proger, 1972; Alderman, 1977). Consensus among authorities yielding 'committee recommendations' (Joint National Committee, 1977) is also no substitute for controlled therapeutic studies. Which elderly hypertensives to treat, to what extent, and how, can only be answered by scientific study of the results of treatment in this age group.

A controlled, prospective, multi-centre trial of antihypertensive therapy in patients over 60 years of age with mild to moderate hypertension (EWPHE) (Amery and De Schaepdrijver, 1975) had enrolled 222 subjects, including 131 above 69 years, by early 1977, but no results will be available for several years. Meanwhile, far too little attention has been paid to the third publication of the Veterans Administration Cooperative Study Group on Antihypertensive Agents (1972), which contained an analysis of the influence of age on the effectiveness of treatment.

Of the 380 patients included in the study, 81 (21.3 per cent) were 60 years or older. Not surprisingly, the incidence of morbid events during the course of the study rose with age. In the control group, morbid events occurred in 15.2 per cent of patients under 50 but in 63.8 per cent of those over 59 years. The corresponding percentages in the treated groups were 6.9 per cent and 28.9 per cent (figure 23.3). If effectiveness of treatment is expressed as the difference between percentage incidence of events in control and treated groups divided by percentage incidence in control groups, it was 54.6 per cent in those under 50 and 54.0 per cent in the group over 59 years. Another way to express these findings is to say that treatment prevented major complications during the follow-up period in 8.3 per cent of hypertensives under 50 but in 33.9 per cent of those 60 or older. Treatment reduced the incidence of cerebrovascular accidents in those over 59 from 23.3 per cent to 7.9 per cent and of congestive heart failure from 20.9 per cent to zero. These results strongly support the value of reducing the blood pressure of hypertensives between 60 and 74 years of age. Of further interest is the finding that the 179 patients over 50, in contrast to the 201 younger hypertensives, benefited from treatment, as shown by a twofold reduction of attack rate, even if their pretreatment diastolic blood pressure had been only 90-104 mmHg.

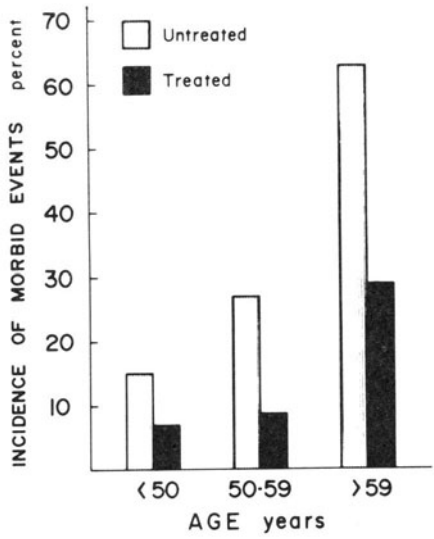

Figure 23.2 Effect of treatment on incidence of morbid events in hypertensive patients < 50 (n = 201), 50–59 (n = 98) and > 59 (n = 81) years of age. After Veterans Administration Cooperative Study on Antihypertensive Agents (1972).

Some arguments against widespread therapy of hypertension in the aged do not deserve serious consideration. These include the obnoxious question whether it is worth while or a 'wise use of resources' to postpone death in the elderly. Isolated anecdotes about an old man who suffered a stroke after he was placed on an antihypertensive drug or an old woman who 'felt worse on drugs' cannot determine treatment strategies in an age of rational therapy.

One doubt about treating the elderly hypertensive is more substantial but purely theoretical. It may be summarised as 'reduction of blood pressure in the elderly will dangerously decrease organ perfusion'. As usual, the organs of concern are brain, heart and kidneys. This argument is entirely reminiscent of the objections that were raised against all antihypertensive therapy a quarter of a century ago (Freis, 1972). It appears to be based on the assumption that perfusion pressure is the only determinant of flow through a vascular bed. While it has been thoroughly refuted in those hypertensive age groups that have had the benefit of controlled studies, it persists in the elderly, because of a postulated lesser ability of their vasculature to autoregulate blood flow.

On the average, newly discovered elderly hypertensives have probably had elevated blood pressures for longer periods than middle-aged subjects, though information on this point is obviously sparse. For this reason and because of the general progression of atherosclerotic vascular disease with age, it seems likely that elderly hypertensives generally have more structural and partially irreversible arterial disease than younger patients (Dustan, 1974). There is no evidence, however, that old hypertensive patients are unable to maintain the necessary perfusion of vital organs when their blood pressure is gradually reduced towards normal levels. In the cerebral circulation of hypertensives, autoregulation is frequently disturbed, but

this is true of all age groups (Strandgaard, 1976). Readaptation of autoregulation towards normal occurs with effective treatment in most cases and at all ages. Even in severe untreated hypertensives, mild symptoms of brain hypoperfusion did not occur until mean arterial pressure was lowered by 55 per cent to 65 ± 10 mmHg (Strandgaard, 1976). In many patients lowering of blood pressure ultimately decreases cerebral vascular resistance and increases blood flow (Meyer *et al.*, 1968). Elderly hypertensives are also generally able to maintain adequate perfusion of heart and kidneys when their blood pressure is cautiously decreased by appropriate drugs and may even improve it (Dustan, 1974; Koch-Weser, 1974*a*).

There can be no doubt that excessively vigorous and rapid reduction of blood pressure in the elderly can have unfortunate results (Jackson *et al.*, 1976). This is, of course, true of all hypertensives. Inadvertent excessive reduction of blood pressure in the elderly may be more common because of diminished effectiveness of homeostatic mechanisms, inappropriate choice of drug dosages, medication errors, and drug interactions due to polypharmacy for multiple diseases (Davison, 1972; Hall, 1973; Koch-Weser, 1975). None of these factors justify neglecting the elderly hypertensive until or even after serious complications of hypertension develop, but they certainly require special attention and care. In our experience and that of others (Amery and De Schaepdrijver, 1975; Seligman *et al.*, 1977) significant reduction with drugs of the blood pressure of most elderly hypertensives can be achieved without major side effects.

SYSTOLIC HYPERTENSION IN THE ELDERLY

One aspect of hypertension in the elderly which has been insufficiently considered and may somewhat limit our therapeutic effectiveness in this age group is its haemodynamic pattern. Since systolic blood pressure increases more with age than diastolic, the fraction of hypertensives whose blood pressure elevation is primarily, or purely, systolic is much higher among elderly patients than in the middle-aged (Society of Actuaries, 1959; Master and Lasser, 1961; United States National Center for Health Statistics, 1977).

Almost all untreated, chronic, primary hypertensives show a greater absolute elevation of systolic than of diastolic arterial pressure (SAP>DAP+40). This widened pulse pressure is partly due to the lower distensibility of the large arterial vessels at higher pressures. Furthermore, even in normotensive individuals, the arterial pressure-volume curve is displaced downward with age and its slope (arterial capacitance) decreases (Hallock and Benson, 1937; Ho, Lin and Galysh, 1972). This process is accelerated in hypertensives (figure 23.4).

A useful index of arterial rigidity is the ratio of pulse pressure to stroke volume (PP/SV). In hypertensive patients this index correlates significantly with age (Tarazi, Magrini and Dustan, 1975). Disproportionate or inappropriate systolic hypertension (DSH) has been defined as SAP>2x(DAP−15) (Koch-Weser, 1973*a*). A subgroup of DSH is isolated systolic hypertension (ISH), defined as SAP>150 and DAP<90 mmHg. The frequency of DSH increases progressively with age (Koch-Weser, 1973*a*, 1976*b*; Seligman *et al.*, 1977). ISH due to decreased arterial distensibility is very rarely seen below 45, but is quite common above 64 years of age (figure 23.5).

The fact that hypertension in the elderly is usually predominantly systolic, and

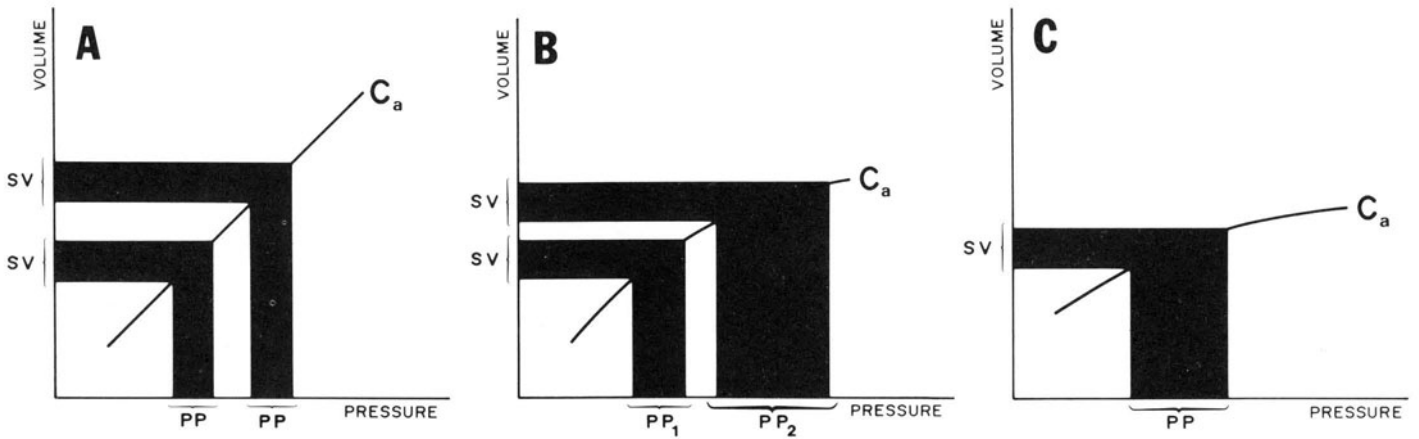

Figure 23.4 Influence of arterial capacitance (C_a) on relation between a constant stoke volume (SV) and pulse pressure (PP). (A) High arterial capacitance that remains linear over a wide range of pressures. Characteristic of young normotensives. Pulse pressure is normal. (B) Arterial capacitance curve is displaced downward and slope (dV/dP) decreases with increasing pressure. Characteristic of advancing age. Pulse pressure is slightly increased when diastolic arterial pressure is normal (PP_1), and is greatly increased when diastolic pressure is elevated (PP_2). (C) Severe decrease in arterial capacitance. Pulse pressure greatly increased even when diastolic pressure is normal (isolated systolic hypertension, common in the elderly).

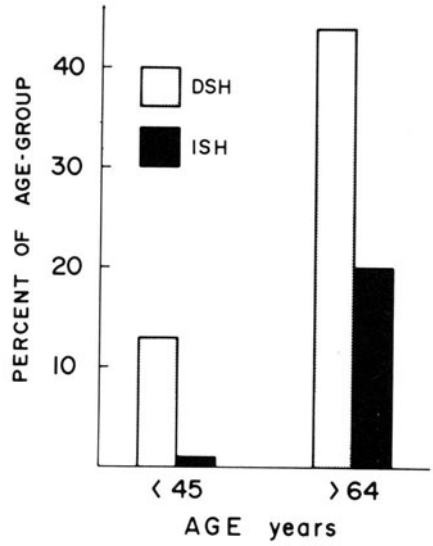

Figure 23.5 Percentage of hypertensive patients with disproportionate (DSH) and isolated (ISH) systolic hypertension. One hundred patients in each age group randomly selected from a hypertension clinic population.

often exclusively so, does not make it any more innocuous (Gubner, 1962; Koch-Weser, 1973*b*; Kannel, 1974). Elevated systolic pressure has been demonstrated to be an important and independent risk factor for cardiac and vascular complications of hypertension. Compared with diastolic pressure, systolic pressure shows the same or a stronger association with the occurrence of thrombotic strokes (Kannel *et al.*, 1970, 1976), coronary heart disease (Kannel, Gordon and Schwartz, 1971), left ventricular hypertrophy (Ramirez and Pont, 1965; Kannel, Gordon and Offutt, 1969; Kannel *et al.*, 1972), and congestive heart failure (Kannel *et al.*, 1972). Even isolated systolic hypertension is associated with a significantly increased risk of coronary heart disease, cerebrovascular accidents and renal failure (Society of Actuaries, 1959; Goss, Rosa and O'Brien, 1969; Colandrea *et al.*, 1970).

It has been suggested that systolic hypertension is only an index of the degree of atherosclerotic change in the large arteries and has no pathogenetic potential, but there is no evidence for this view (Koch-Weser, 1973*a*). Whatever the mechanisms by which elevated blood pressure damages large and small arteries, there is no apparent reason why they should apply more to diastolic than to systolic hypertension. As for the development of left ventricular hypertrophy and congestive heart failure, one would expect systolic blood pressure, the primary determinant of left ventricular afterload, to be a more important causal factor than diastolic pressure. Similarly, one might expect the occurrence of intracerebral and subarachnoid haemorrhage and of dissecting aortic aneurysm to correlate best with the peak pressure during each cardiac cycle.

The demonstrated beneficial effects of pharmacological reduction of arterial pressure on morbidity and mortality in hypertension are generally couched in terms of diastolic pressure. However, they can also be taken to reflect the value of

systolic pressure reduction. In actual fact, they almost certainly reflect the decrease of arterial pressure throughout the cardiac cycle. Thus, to be maximally effective, pharmacotherapy of hypertension must aim at both diastolic and systolic normotension. The former can usually be achieved in patients of all ages. Unfortunately, the latter is difficult to reach or even to approach closely in patients with disproportionate and, particularly, with isolated systolic hypertension.

Antihypertensive drug therapy almost always reduces systolic more than diastolic pressure. This results from the same factor responsible for the greater pretreatment elevation of systolic compared with diastolic pressure, the inverse proportionality of mean arterial pressure and arterial capacitance. However, when systolic hypertension is grossly disproportionate or isolated, systolic blood pressure often remains markedly elevated when diastolic has been reduced to 80 mmHg. In our series of 100 patients with DSH, treatment lowered DAP below 90 mmHg in 85 per cent but SAP below 150 mmHg in only 38 per cent. An SAP of less than 150 mmHg was achieved in only 16 per cent of patients with ISH at the time DAP had been reduced to 80 mmHg (Koch-Weser, 1976*b*). Others have confirmed that therapy for ISH succeeds less often than in other forms of hypertension (Seligman *et al.*, 1977).

Antihypertensive drugs are quite capable of generating subnormal DAP in patients with DSH. However, this therapeutic approach could be hazardous and is not justified at this time. We possess no information concerning the relative risks and benefits of normalising SAP in patients with DSH due to decreased arterial capacitance. The risks of reducing DAP below normal may well include decreased perfusion of the brain, the kidneys and, particularly, the heart. In the absence of careful and controlled studies, we must be satisfied with reducing the DAP of patients with DSH to normal and accept the fact that at that time such patients will still have systolic hypertension and be subject to the associated risks.

Drug therapy for the grossly disproportionate systolic hypertension so common in the elderly cannot be completely successful unless it restores the reduced arterial capacitance to normal. Drugs with this potential are at present an unlikely prospect. Thus, the frequency of DSH and ISH among elderly hypertensives inevitably limits our therapeutic success in this age group.

ANTIHYPERTENSIVE DRUGS IN THE ELDERLY

I am not aware of any controlled trials in elderly hypertensives comparing the efficacy and safety of different antihypertensive drugs or drug combinations. Recommendations abound (Harris, 1970; Davison, 1972; Chrysant *et al.*, 1976; Fishback, 1976), but they are not based on objective clinical data. Theoretically, it would seem wise not to treat the elderly with potent sympathoplegic drugs, such as guanethidine or bethanidine, because they are likely to decrease cardiac output and to cause postural hypotension and may, therefore, lead to cerebral hypoperfusion. The potential of reserpine to cause mental depression and the central nervous system side effects of methyldopa, such as lassitude, drowsiness and decrease of mental acuity, are said to be more prominent in the elderly (Lindeman *et al.*, 1963; Davison, 1972; Chrysant *et al.*, 1976; O'Malley, Judge and Crooks, 1976). However, this is not clearly established and, in appropriate dosages, both these drugs have been used successfully in elderly hypertensives.

We have found that the progression from a diuretic, to a diuretic plus a beta-adrenergic receptor antagonist, to the addition of an antihypertensive vasodilator is as effective and well-tolerated in the elderly as in younger hypertensives (Zacest, Gilmore and Koch-Weser, 1972; Koch-Weser, 1973*a*, 1974*a*, 1976*a*). All drugs are started in low dosage, the doses increased gradually and the maximum daily dosage limited to 100 mg of hydrochlorothiazide (or the equivalent for similar diuretics), 160 mg of propranolol (or the equivalent of other beta-blockers) and 200 mg of hydralazine.

Much has been written about the increased sensitivity of elderly hypertensives to antihypertensive drugs. Although this has not been convincingly documented, such enhanced response to any given dosage could have both pharmacokinetic and pharmacodynamic reasons.

The subject of pharmacokinetics in the elderly has been recently reviewed in detail (Gorrod, 1974; Triggs and Nation, 1975; Crooks, O'Malley and Stevenson, 1976; O'Malley *et al.*, 1976; Richey and Bender, 1977). In line with the well-documented decreases in old age of cardiac output (Brandfonbreuer, Landowne and Shock, 1955; Bender, 1965), renal blood flow (Bender, 1965), glomerular filtration rate (Hansen, Kampmann and Laursen, 1970; Papper, 1973; Crooks *et al.*, 1976), renal tubular function (Friedman *et al.*, 1972; Papper, 1973; Crooks *et al.*, 1976) and some hepatic metabolic functions (Crooks *et al.*, 1976), it appears that the half-life of many drugs in the body is increased and their clearance decreased in the elderly (O'Malley *et al.*, 1971; Triggs and Nation, 1975; Farah *et al.*, 1977). Since completeness of absorption is probably little affected by age (Triggs and Nation, 1975; Triggs *et al.*, 1975; Crooks *et al.*, 1976), this slower removal will result in higher concentrations of the drug in the body. However, one cannot generalise that in old age a dose of any drug will produce a higher concentration of the drug at its site of action. The situation is complex, since in the case of some drugs the elderly also differ from the young in the degree of drug binding to serum albumin (Triggs and Nation, 1975; Crooks *et al.*, 1976; Koch-Weser and Sellers, 1976) and perhaps to other inactive sites and in the apparent volume of distribution (Triggs and Nation, 1975; Crooks *et al.*, 1976). For drugs that are inactivated by hepatic biotransformation, the effect of age on the dose–concentration relationship is probably most prominent if the drug has a high intrinsic hepatic clearance, since hepatic blood flow appears to decrease with age (Triggs and Nation, 1975). However, the mechanism of biotransformation also seems to be important (O'Malley *et al.*, 1971; Farah *et al.*, 1977).

At this stage of our knowledge, we can be sure of the effects of ageing on the pharmacokinetics of a given drug only by actually determining them. Few such studies have been carried out on antihypertensive agents. Metoprolol has been found to have about the same mean plasma half-life in elderly patients as in young healthy volunteers, but there was more interindividual variation in the former (Lundborg and Steen, 1976). For 8 h after an oral dose of 40 mg, mean plasma propranolol levels were significantly higher in elderly individuals than in young subjects, there being a fourfold difference in the peak levels (figure 23.6). In contrast, we found only a slight and not significant increase in the serum concentration/dosage ratio of hydralazine in 14 hypertensives above 60, compared with 28 hypertensives below 50 years of age. This was true both of slow and of fast acetylators. Both propranolol and hydralazine undergo extensive first-pass metabolism, but the

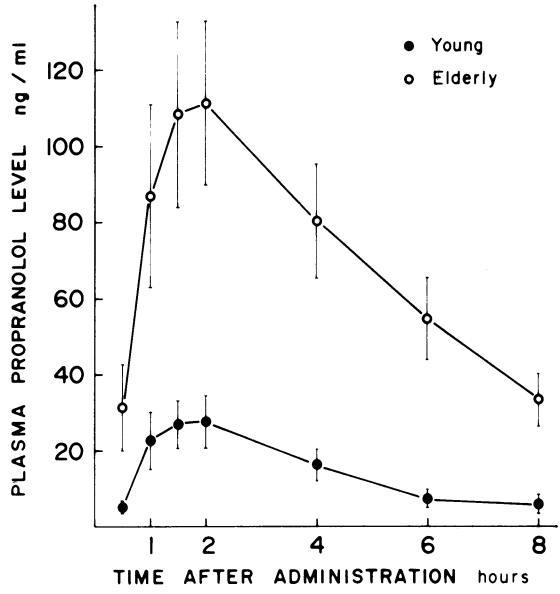

Figure 23.6 Mean plasma propranolol levels in 9 young (27 ± 2, mean ± s.e.m. years) and 9 elderly (77 ± 2, mean ± s.e.m. years) subjects after 40 mg orally. After Castleden *et al.* (1975).

former is primarily hydroxylated (Johnsson and Regårdh, 1976) and the latter acetylated (Koch-Weser, 1976*a*). It has been suggested that the dose of propranolol needed to achieve a given intensity of beta-blockade or of antihypertensive action will be lower in the elderly than in the young (Castleden, Kaye and Parsons, 1975), but this disregards the fact that hydroxylation does not abolish the action of propranolol (Zacest and Koch-Weser, 1972). There appears to be no general need to reduce the dosage of hydralazine in aged hypertensives.

It remains entirely unclear whether the old are more sensitive to a given concentration of antihypertensive drugs at the sites where they exert their effects or side effects. A decreased ability of the elderly to maintain homeostasis has been claimed in support of this possibility (Davison, 1972), but that concept, although reasonable, is too vague to carry much weight. Epidemiological studies have shown no influence of age on the frequency of adverse reactions to spironolactone (Greenblatt and Koch-Weser, 1973*a*), frusemide (Greenblatt *et al.*, 1977), reserpine (Pfeifer, Greenblatt and Koch-Weser, 1976) and practolol (Pfeifer, Greenblatt and Koch-Weser, 1977). The rate of adverse reactions to propranolol in 97 patients over 60 years of age was more than double that of 90 patients under 50, but only 12 per cent of those patients received the drug for hypertension (Greenblatt and Koch-Weser, 1973*b*). An increased pharmacodynamic sensitivity of elderly hypertensives to some or all effects of some or all antihypertensive drugs has not been established.

Perhaps we should not be too concerned about possible peculiarities of the pharmacokinetic fate and the pharmacodynamic effects of antihypertensive drugs in the elderly. These factors show marked individual differences among patients of any age group. For this reason it has been repeatedly emphasised that the selection

and dosage of antihypertensive drugs must be individualised (Koch-Weser, 1973*a*, 1974*b*). Such individualisation is easily accomplished in patients of all ages by titrating antihypertensive drug dosage against blood pressure response and side effects. What seems essential in the elderly hypertensive is to carry out this titration gradually and with particular care.

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24
Postural hypotension in the elderly

F. I. Caird (Department of Geriatric Medicine, University of Glasgow, Glasgow, UK)

Postural or orthostatic hypotension is a very common phenomenon in geriatric clinical practice. If severe, it is very disabling, since at best it leads to a self-perpetuating loss of confidence, and at worst to the patient taking to bed and staying there. It is a common cause of falls, particularly on the way from bed to toilet at night or on rising in the morning. In any elderly patient with a complaint of dizziness or falls, the blood pressure must be taken both lying and standing. If orthostatic hypotension seems likely from the history, it is wise to take the blood pressure with the patient sitting before standing, as this may avoid the embarrassment of having to pick the patient up from the floor (Caird and Judge, 1974). In some patients the pressure falls progressively on walking, and if the history suggests this possibility, then it should be taken both immediately after standing and after walking 5–10 m. If these elementary clinical observations are made, 'vertebrobasilar insufficiency' will be very rarely diagnosed in the elderly. Indeed, the heretical speculation that this diagnosis has no real existence in old age is more than tempting.

Orthostatic hypotension should only be accepted as a cause of symptoms if the systolic pressure falls on standing to less than 100 or at most 110 mmHg. The most satisfactory terminology is probably to use the term 'orthostatic' (or 'postural') blood pressure drop to describe a fall on standing of 20 mmHg or more, whatever the final value, and 'orthostatic hypotension' if the standing pressure is below 100–110 mmHg, and then to qualify the latter with 'symptomatic' if there are symptoms, as is by no means always the case.

The frequency of a fall in pressure on standing has been described in several studies of randomly selected old people (Caird, Andrews and Kennedy, 1973), old people in an institution (Rodstein and Zeman, 1957) and patients in a geriatric unit (Johnson *et al.*, 1965). In the first investigation the fall on standing was 20 mmHg or more in 24 per cent, 30 mmHg or more in 9 per cent and 40 mmHg or more in 5 per cent. The frequency of pressure drops of various degrees did not differ between the sexes, but increased with age. These figures do not refer to orthostatic hypotension as defined, and indeed symptoms were present in 1 per cent or less.

The most constant figure in all three studies was that for a fall in systolic pressure of 40 mmHg or more, which was found in 4–5 per cent.

Factors associated with a drop in systolic pressure were examined by comparing those whose pressure fell by 20 mmHg or more with a matched group of subjects whose pressure did not fall. None of the following were significantly associated with a fall in pressure : clinical or ECG evidence of heart disease, diffuse brain disease (whether vascular or 'senile' in type), absent ankle jerks, varicose veins (Rodstein and Zeman, 1957), hyponatraemia or urinary infection (Fine, 1969), anaemia or a wide variety of drugs capable of producing a fall in blood pressure (hypotensives, diuretics, benzodiazepines, phenothiazines, tricyclic antidepressants, L-dopa, antihistamines, barbiturate and other hypnotics). When the comparison was repeated for the smaller number with a systolic drop of 30 mmHg or more, the findings were essentially the same, but it was possible to show that there was a significant association, not with any one of the factors mentioned taken singly, but with combinations of two or more factors. It was concluded that orthostatic blood pressure drops in relatively healthy old people are probably determined by interaction between an autonomic disorder (Gross, 1970; Johnson *et al.*, 1965) and one or more other factors in addition. The nature of the autonomic disorder probably varies, and seems likely to be as often in the afferent as in the central or efferent parts of the autonomic reflex arc (Johnson, 1976).

In geriatric clinical practice there is no doubt that drugs are by far the commonest cause of symptomatic orthostatic hypotension. The list of causal drugs is long (Hodkinson, 1976; Caird, 1977), and there are a few specific studies of the frequency of this side effect in elderly patients treated with any one drug. In the case of L-dopa, it has been shown that the pattern of change in blood pressure is much the same in the elderly (Broe and Caird, 1973) as in the middle-aged (Calne *et al.*, 1970): standing systolic pressures tend to fall by about 20 mmHg after some weeks, but then rise towards pre treatment levels after 3 months or more. There is no convincing evidence for a special sensitivity of elderly patients to L-dopa in this respect, although the doses used in the two studies differed considerably.

Although in perhaps the majority of cases of drug-induced orthostatic hypotension in the elderly it is reasonably convincing to incriminate one drug, clinical experience suggests in many that combinations of drugs or interactions between drugs and other factors may be responsible. These other factors include, in particular, volume depletion from sodium or water shortage, and the circulatory disturbance associated with the onset of infections, whether or not there is a frank rigor.

In a small number of cases in the elderly orthostatic hypotension is clearly neurogenic in origin (Johnson, 1976). The commonest mechanism is probably a peripheral neuropathy, but in some there is degeneration of the first-order sympathetic neurones in the intermediolateral column of the spinal cord (Johnson *et al.*, 1966), usually as part of the multi-system degeneration producing the Shy-Drager syndrome.

The management of orthostatic hypotension in the elderly begins with its recognition, and continues with a resolute determination not to prescribe phenothiazines—especially prochlorperazine (Stemetil)—for dizziness. A diagnosis of the cause of the hypotension is usually fairly easy, as it is to be found in the list of drugs being taken. The causal drug(s) should be discontinued and disappearance of

the hypotension documented. If a febrile illness or volume depletion is contributing, then the remedies for these will result in improvement. If none of these seems likely, then detailed neurological examination will usually allow a credible diagnosis. This last residual group is often difficult to treat, but simple measures such as elevating the head of the bed at night, elastic stockings and teaching the patient to get out of bed in stages should be tried first. Fludrocortisone in doses of 0.1-0.3 mg/day should be employed next, but it is usually necessary to produce oedema before the blood pressure is adequately controlled. The combination of tyramine and a monoamine oxidase inhibitor (Lewis *et al.*, 1972; Nanda, Johnson and Keogh, 1975) requires obsessional accuracy in timing of drug doses, greater than most elderly patients are likely to be capable of, but can be effective.

In conclusion, orthostatic hypotension is a clinically highly significant condition in the elderly, the diagnosis of which requires only simple bedside procedures. It would repay detailed physiological study of the mechanisms by which its various causes operate. In the majority of cases treatment is easy, cheap and effective—a line drawn through the prescription sheet.

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25
Drugs and confusional states

R. D. T. Cape (Parkwood Hospital, London, Ontario, Canada)

INTRODUCTION

A confusional state is a happening which may be transient or may become permanent, in which an individual is forgetful and disorientated in time, space and person. It may be associated with behavioural disturbance varying from apathy or obtundity to delirium or mania. Such states are encountered frequently in elderly patients due to a broad spectrum of clinical causes. They are episodes of acute malfunction of the brain. The effect of drugs in either causing or treating them will, therefore, hinge on their action on this target organ.

THE AGEING BRAIN

Evolutionary note

During three million years of evolution, man's stature increased by about one-third, but the size of the brain trebled. Robert Bigelow (1969) has suggested that the major stimulus for the latter was inter-group wars. Early man existed in small communities in each of which there would be relative peace. Between neighbouring groups, however, conflict was likely to be stern and fierce, as each competed for the most desirable terrain in which to maintain themselves. In these conflicts, Bigelow believes, brain power was the key to success. Superior communication and strategy would be associated with this. As a consequence, the brain slowly but steadily increased in size, reaching its present state about 35 000 years ago with Cro-Magnon man.

During the three million years taken to treble its size, man's influence on the environment was slight. Only in the past three hundred years has the full impact of human brain power been felt by the world's ecology. If its adaptability and resourcefulness has produced this familiar pattern of history, its deterioration will produce equally important consequences. The mature man can control his environment and fend for food and shelter because of his keen mind; the old person with a failing brain becomes as helpless as the young infant, as aimless as the rudderless ship and as vulnerable as the weaponless soldier.

Structural changes

With its fifteen to twenty thousand million nerve cells, each with thousands of dendritic processes, the brain is the most complex and efficient computer that has evolved. It combines sensitive receptors with a versatile motor system, the two linked by complex connections in different parts of the brain. The autonomic system controls visceral function, while memory and thought, which are so vital to us all, appear to be associated with different areas of the cortex and the limbic system. As we age, major changes occur in our brains.

The four major pathological changes, seen on microscopical examination of cerebral substance, are senile plaques, neurofibrillary tangles, granulovacuolar degeneration and pigment deposition. The first three are seen characteristically in sufferers from dementia of the Alzheimer type, now regarded as being the same as senile dementia. Tomlinson, Blessed and Roth (1968) and more recently Ball (1976) have demonstrated that these changes occur not only in patients suffering from dementing illness, but also in old people who do not suffer from that condition. Figure 25.1 illustrates findings in a group of 28 non-demented elderly subjects studied at autopsy by Tomlinson and his colleagues. In all of them there was significant pathology as shown.

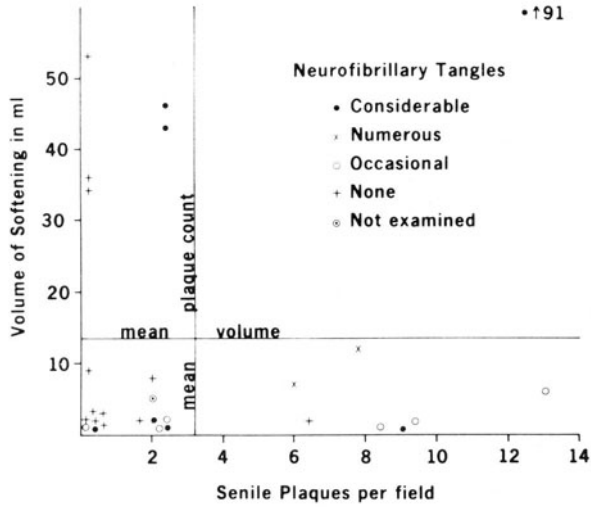

Figure 25.1 Details of pathological findings in 28 brains from non-demented elderly subjects. Softening was taken as a measure of arteriosclerotic disease. After Cape (1978). Reproduced by permission of Harper and Row.

Siakotos and Armstrong (1975) have studied the pigment which accumulates in increasing quantities in neuronal and glial cells with increasing age. They suggest that it represents inert fatty material of no further value to the cell, probably derived from lysosomes. Thus, from a pathological standpoint, there is unequivocal evidence that age alters the neurones.

Cell loss

Hanley (1974) examined the evidence for a slow, but steady fall-out of neurones with age. A detailed and searching review led him to suggest that attempts to apply the results of animal studies to the human brain were open to question. More recently, Ball (1977) has demonstrated by an elaborate quantitative technique that there is loss of neuronal cells from the hippocampal gyrus in older people (see figure 25.2). We can, therefore, add cell loss to the pathological changes described earlier.

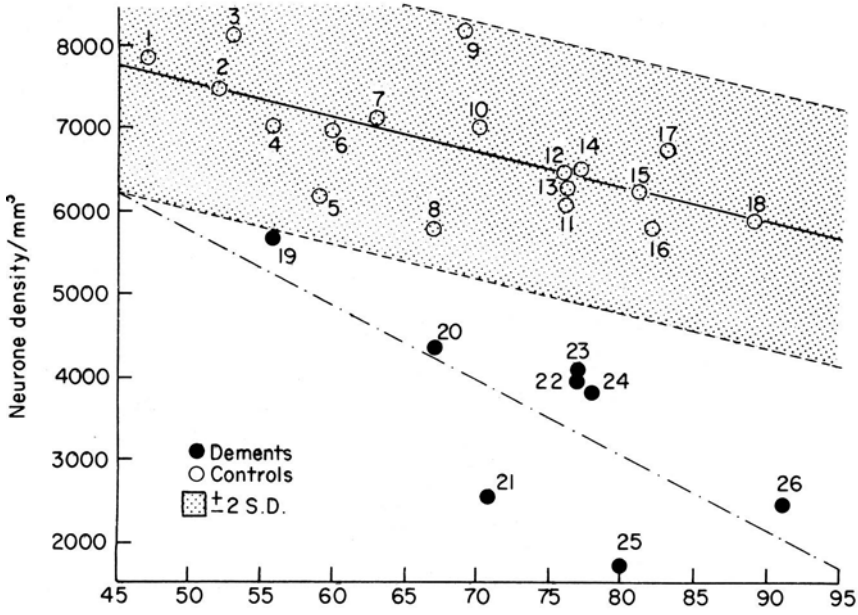

Figure 25.2 Density of neurones in hippocampal cortex at different ages. After Ball (1977). Reproduced by permission of *Acta Neuropathologica.*

Other changes

There are equally striking changes in the gross chemistry of the brain between young and old individuals. Water content falls from 92 per cent at birth to 76 per cent at age 90, while total lipids increase from 3.5 per cent at birth to 10.5 per cent at age 30, thereafter declining to 7.5 per cent in old age. Of the brain's dry weight at maturity, 140 g is protein and this is reduced to 100 g by the ninth decade (Ordy, 1975). Associated with the histological and chemical changes are alterations in the electrical patterns which the functioning brain exhibits on electroencephalography. Beck, Dustman and Schenkenberg (1975) used a visually evoked response technique to demonstrate the slowing and diminishing of the electrical reaction of the old, compared with the young or mature.

CLINICAL RELEVANCE OF THE AGEING BRAIN

The target organ, therefore, is considerably altered in the elderly person. Cerebral function involves sensory input and its translation into intellectual, motor and neuro-regulating activity. The brain achieves its optimum potential between the ages of 16 and 20 (Bromley, 1974), after which, as shown, there is a slow decline in its capabilities, which speeds up beyond the age of 70. I have used a concept of global cerebral function to imply the widespread nature of the brain's many activities (figure 25.3). A broad band indicates the wide variation in functional activity from person to person. The straight black line across the diagram represents the level of function necessary for an individual to be fully capable of an independent existence. There is a deterioration of cerebral function in the geriatric age which parallels its rapid development during the paediatric era.

If this is true, one might postulate that the loss of agility and increasing clumsiness of the motor system in the elderly would lead to increasing accidents and falls—and so it does.

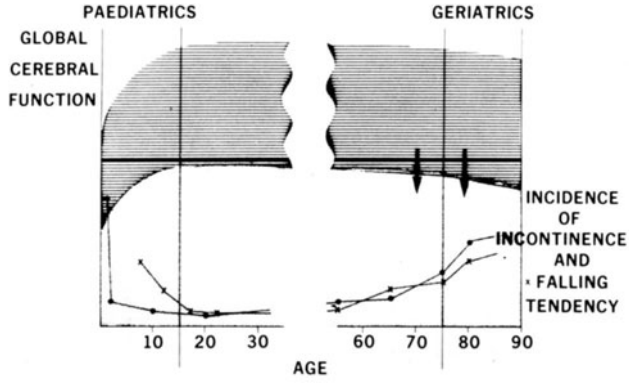

Figure 25.3 Diagram indicating the rise and fall of global cerebral function. After Cape (1978). Reproduced by permission of Harper and Row.

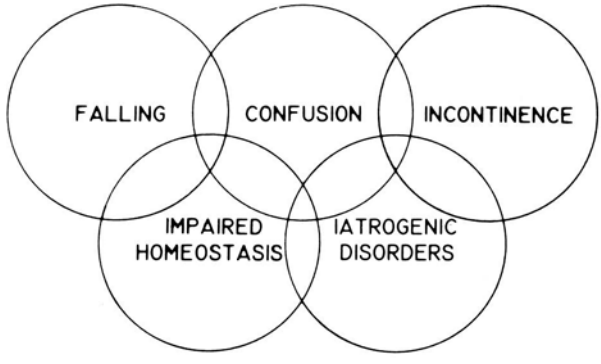

Figure 25.4 The essence of geriatric medicine. After Cape (1978). Reproduced by permission of Harper and Row.

It is obvious that failing receptors–visual, auditory and cognitive– will lead to misunderstanding and confusion will result–and so it does.

One may hypothesise that the more complex of the nervous system regulating mechanisms may be most susceptible to the deteriorating efficiency of the ageing brain and expect micturition control to break down–and so it does.

Finally, our reaction to sudden stress, physical, mental or emotional, activated by the brain's hypothalamic control of homeostasis may collapse–and so it does.

The common medical problems which we encounter in old age are confusion, falling, incontinence and homeostatic breakdown. These are not diagnoses, but represent aspects of brain failure produced by a wide variety of conditions, acting on a partly damaged organ. The reaction of the medical profession to this situation has been predictable. 'We can not do anything about progressive cerebral deterioration, but we can treat the heart failure, infections, metabolic upsets, cancer, delirium and the rest.' By so doing, they often introduce iatrogenic illness! (figure 25.4). These five clinical problems constitute the O-complex which, in my view, is the essence of geriatric medicine (Cape, 1976, 1978).

DRUGS CAUSING CONFUSIONAL STATES

To return to my subject, however, do these changes in the brain affect its reaction to drugs? It is likely that changes in the target organ will affect the sensitivity of that organ to medications of all kinds. To decide whether this means that confusional states are caused by drugs, we must examine available evidence. Flint (1959) reported on 242 cases admitted to his geriatric unit. Only 3 cases (1.75 per cent) were attributed to drugs. Fish and Williamson (1964) described 93 cases of delirium in which 6 cases were attributed to barbiturates, including one acute poisoning. Pflugfelder (1977) has recently reviewed cases seen at the Geriatric Polyclinic in London, Ontario, at which elderly patients are seen by a psychiatrist, internist and social worker. Of 226 records studied, 69 (26 per cent) were receiving psychotropic drugs. In 19 it was recommended that these be discontinued and in 7 they were regarded as the cause of the symptoms. These latter were behavioural in 42 per cent and dementing in a further 28 per cent.

In Australia, Learoyd (1972) recorded the effect of psychotropic drugs on a series of elderly patients admitted to the regional psychogeriatric service at North Ryde, New South Wales. There were 236 patients over the age of 65 admitted during a period of 2 years, of whom 37 or 16 per cent had developed disturbed behaviour, which abated on suspension of the psychotropic drugs which they were taking before entering hospital. All of these patients were subsequently discharged from the unit on greatly reduced medication.

The cases were divided into three groups (table 25.1). Learoyd pointed out that moodiness, anxiety, sleeplessness and irritability have been recognised for centuries as common concomitants of failing physical and mental prowess. When these become troublesome, physicians are prone to use psychotropic drugs to try to improve the situation. When unsuccessful, or when the condition worsens, the dose is increased or a new drug introduced. The average number of psychotropic drugs being consumed by Learoyd's series was 2.7 per patient.

The group with the most drugs were those exhibiting disinhibition reactions, which were manifested as restlessness, agitation, paranoia and aggression. Not only

did the disinhibition reaction group have the greatest number of drugs, but also in no fewer than 6 of the 14 cases, the individuals received two phenothiazine preparations. Learoyd points out that there was a considerable number of cases in which the association between therapy and confusion was less clear-cut, but in which drug effects were probably a significant contributory factor in the circumstances necessitating the patient's admission to hospital. From this experience, he claimed that at least 20 per cent of psycho-geriatric admissions are precipitated by the adverse effects of psycho-active drugs.

Table 25.1 Psychotropic drugs and the elderly patient*

	Drug Intoxication	
7 cases	Mean age 73 years (65–87)	10 drugs, 2.3/patient
Example: Male, aged 75		
Symptoms: Confusion, disorientation	Drugs: Haloperidol 18 mg Thioridazine 150 mg	
	Excess Medication with Secondary Complications	
16 cases	Mean age 71 years (65–79)	19 drugs, 2.6/patient
Example: Female, aged 70		
Symptoms: Depressed, negativistic Confused, several falls Syncope, fractured radius	Drugs: Pentobarbitone 100 mg Amitriptyline 125 mg Thioridazine 100 mg	
	Disinhibition Reactions	
14 cases	Mean age 76 years (65–93)	16 drugs, 3.0/patient
Example: Female aged 78		
Symptoms: Confused, restless Agitated, disorientated	Drugs: Diazepam 15 mg Nortriptyline 50 mg Amylobarbitone 200 mg	

*Data abstracted from Learoyd (1972), a study of 236 cases with adverse reactions occurring in 37 (16 per cent).

Sedatives and anti-convulsants are two other groups of drugs which act directly on the brain. Barbiturates are notorious for causing delirium from acute overdosage or states resembling dementia in chronic administration (Krakowski and Langlais, 1974; Davison 1965). Diphenylhydantoin (DPH), a commonly used anticonvulsant, can also cause disturbance of mental balance.

Case report: Mrs E. W.–(aged 75)

This old lady suffered from blackouts and falls which were diagnosed as epileptiform. She was treated with DPH by her family physician. He sent her to see a neurologist and she collapsed in his office in one of her 'turns'. Found to have asystole, she was rushed to hospital and admitted to the coronary care unit. In a dramatic week she had several cardiac arrests, two or three episodes of ventricular fibrillation and a pacemaker inserted and later removed. Four weeks later, I was asked to see her, at which time she was unable to speak or respond to questions, lying quietly, but completely unresponsive. My first impression was that this old lady had sustained severe, irreversible, cerebral damage during her hectic week. The resident, in the meantime, had taken a serum DPH level which proved to be 50 ng/ml. The drug was discontinued and, when the level fell below an acceptable therapeutic one, she recovered and later left hospital with a normal mental status.

Anti-Parkinsonian drugs are 'most notorious', according to Dunn and Arie (1972), at causing mental confusion. Other drugs which do not act directly on the central nervous system may cause confusional states. In elderly patients these are often associated with dehydration, sometimes as a result of diuretics. Antidiabetic drugs (including insulin, by causing chronic hypoglycemia), steroids in some cases and neuroleptics (Krakowski and Langlais, 1974) have also been reported to be responsible for such upsets.

These examples of drugs which may precipitate confusional states give some indication of the importance of therapy as an aetiological factor.

OVERPRESCRIBING?

This point is emphasised by modern prescribing practice. In a study of 731 persons living in continuing care institutions in London, Ontario, almost 20 per cent were receiving 6 or more medications daily (figure 25.5; Cape *et al.*, in press). This is not unusual in North America. The Boston Collaborative Drug Surveillance Program reported that 644 drug orders were written in their first 10 days for 78 patients, an average of 8 per patient (Borda *et al.*, 1967).

This tendency is not confined to hospitals. In a large study involving 15 000 subjects living at home in four areas of Canada, more than 50 per cent had consumed at least one drug in the previous two days (Chaiton *et al.*, 1976). Fewer were prescribed than were not. These data came from a World Health Organization Report in which the four Canadian sites ranked high among the 12 areas surveyed for total prescribed and non-prescribed medications (Matthews and Feather, 1976). The areas included the USA, Argentina, UK, Finland, Poland and Yugoslavia. There can be little doubt that the pharmaceutical industry has thrived and developed over the past twenty years.

A recent report on the United States' one million nursing home patients indicated that each takes an average of 4.2 drugs a day (Moss, 1977). Fifty-five per cent of these individuals are, reputedly, mentally impaired. There is little doubt that many psychotropic drugs are used as pharmaceutical restraints in such institutions, and no one can tell the extent of the mental confusion and behavioural disturbance that may result from this. Chaiton *et al.* (1976) examined the pattern and extent of the medical use of drugs in a rural and in a suburban Ontario family

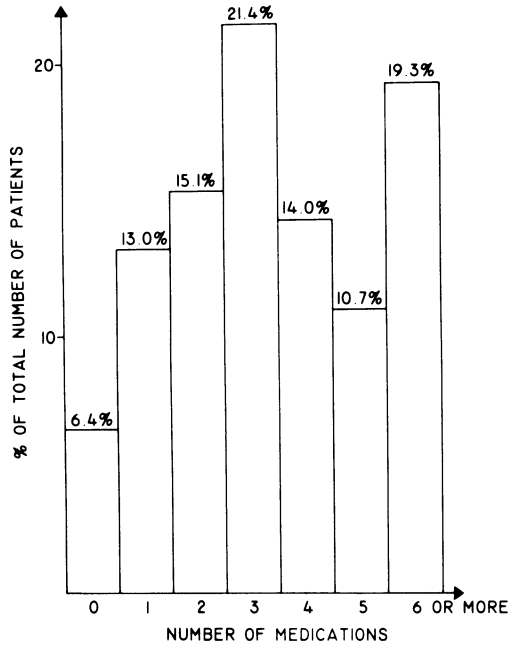

Figure 25.5 The number of drugs being taken on a regular basis by 731 residents in continuing care institutions of London, Ontario, in August 1976. After Cape *et al.* (1977). Reproduced by permission of the *Canadian Medical Journal.*

practice. Sixty per cent of respondents in both surveys were using at least one medication. While vitamins and tonics were the most commonly used drugs, from 8.8 to 10.5 per cent of respondents were taking sedatives or tranquillisers. This means that 6 per cent of the total respondents were having these drugs. One interesting finding was that, in a group of patients being managed by nurse-practitioners, the quantity of tranquillizers and sedatives was reduced over a period of a year, in contrast to the experience of a group followed by physicians in which the taking of these medications did not alter.

TREATMENT OF CONFUSIONAL STATES

The treatment of confusional states will depend on their cause and the first step is to determine this. Assessment of the situation involves a systematic approach. It is important to establish as precisely as possible when and how the confusion developed and whether there are other symptoms such as pain, cough or dysuria which may be of aetiological significance. Previous medical and family history should be obtained, and it is wise to ask for all bottles of medicines which are being or may have been taken.

Physical examination is often difficult to achieve and may take more than one visit to the patient's bedside. The subject may pace aimlessly up and down, be unwilling to sit down, listen or talk, and be quite unable to concentrate on one's questions. Attempts to examine the patient may be resented and have to be carried

out without cooperation or in the face of active belligerent hostility. In such situations patience is mandatory. One can make informed guesses at the state of hydration, observe respiration, check the pulse, look for peripheral oedema, alteration in colour or evidence of injury, and feel for temperature with little physical interference with the patient. At a suitable moment, more direct intervention may stimulate a vigorous hostile counter which will offer evidence of motor power. With the help of a nurse, relative or colleague, it may be possible to undertake a quick auscultation of heart and lungs and a brief palpation of the abdomen. These manoeuvres should be made with the express objective of looking for pneumonia, obvious arrhythmia, full bladder or evidence of an acute abdomen. Be content with a little progress at this stage, endeavour to introduce one or two basic treatments such as extra fluid and antibiotics, if indicated, and plan to see the patient again in two or three hours. All drugs should, ideally, be temporarily withdrawn and sedatives avoided to allow a satisfactory baseline to be established, uncluttered by a variety of competing drug effects. There are few drugs which can not be stopped in this way, but care would be necessary with insulin or steroids, sudden discontinuation of which might be dangerous.

One clinical procedure which should never be omitted is a rectal examination. There are a number of reasons for this. The confused person in unlikely to maintain normal bowel habits, may not eat or drink enough and become constipated. A tendency to dehydration will result in drying of the stool, which will add to the problem and may lead to impaction. The resulting discomfort or pain will aggravate the confusion by adding restlessness to it. Whenever a patient wanders during the night hours, one should suspect a degree of colonic stasis.

Investigations

During this initial phase, it is important to obtain a sample of blood for immediate testing. Initial investigations should include a chest X-ray, full blood count, including ESR and differential white count, electrolytes, urea or BUN, creatinine, glucose, liver enzymes, calcium, phosphate, uric acid, ECG and urine specimen, the last-named preferably taken by suprapubic aspiration or catheter. Estimations of any relevant drug serum levels, such as digoxin, DPH or barbiturate should not be forgotten.

Drug treatment

Drug treatment consists of therapy for the cause of the confusion, on the one hand, and to control the behavioural aspects of the situation, on the other. Specific treatment will be aimed at curing or alleviating any acute physical condition responsible for the confusion. Appropriate antibiotics for infections, adequate corrections of metabolic disorders, digitalis and diuretic in heart failure, fluids in dehydration, bowel clearance in faecal impaction, withdrawal of drugs in suspected iatrogenic states and normal clinical management of vascular accidents should all be ordered as quickly as possible to offer the patient the best chance of a return to normal.

Management of the behavioural aspects are more difficult. Drug treatment should be as simple and limited as possible. The need to discontinue most or all drugs before introducing new ones has already been stressed. It may be necessary to immo-

bilise the patient temporarily to achieve rehydration and this may require an antipsychotic drug. This should be ordered only after reassurance and persuasion have failed. Chlorpromazine or thioridazine in a dose of 50–100 mg, or haloperidol 0.5–1.5 mg, are the most effective antipsychotics, which are best given in a single evening dose by mouth. It may, however, be necessary to give an intramuscular dose of the first, which has a considerable hypnotic side effect. Sleep for 24–48 h will, in a few cases, assist in a break-back to normal sense. The golden rule is that drug treatment should be constantly monitored, with careful titration of the antipsychotic treatment. Patients who have chronic dementing illness will, sometimes, require additional phenothiazine during the day.

For most, the evening dose will obviate the need for sedatives but these may be required in some cases. Barbiturates should never be used, but chloral, nitrazepam or oxazepam are effective. Exton-Smith (1967) and Keston and Brocklehurst (1974) advocate meprobamate, which in their studies proved to produce the most relaxed sleep.

CONCLUSION

To sum up, confusional states are serious clinical episodes which carry a considerable long-term disability risk. They occur commonly in old people. Because of deterioration in cerebral function, the elderly have a predisposition to develop them, precipitated by a variety of physical factors including injudicious drug treatment.

> Better to hunt in fields for health unbought
> Than fee the doctor for a nauseous draught
> The wise, for cure on exercise depend
> God never made his work for man to mend.
>
> Dryden

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26
Drug dosage in the elderly— Theory and practice

F. Sjöqvist, G. Alván, U. Bergman and G. Boethius (Department of Clinical Pharmacology at Karolinska Institutet, Huddinge University Hospital, Huddinge, Sweden)

INTRODUCTION

Many physiological functions deteriorate with age (Kohn, 1963) and concomitant changes in drug kinetics can be expected (Ritschel, 1976). The most obvious example is the parallel decline in the renal clearance of creatinine and digoxin in the aged (Iisalo, 1977). Thus, one would expect to find in the aged a reduction in the dosage of drugs that are excreted unchanged. Unique possibilities to study how drugs are prescribed in a population exist in the county of Jämtland, Sweden (Bergman, Sjöqvist and Söderhielm, 1976; Boethius and Wiman, 1977). Through this data bank it is possible to derive figures on prescribed daily doses in different age groups (Boethius and Sjöqvist, 1978), and this paper reviews some results obtained.

MATERIAL

Since 1970 about 17 000 of the population in the county of Jämtland (figure 26.1) have been monitored with regard to out-patient prescriptions presented at pharmacies (Boethius and Wiman, 1977). The prescriptions are continuously compiled in drug lists, which contain the patient's identity number (denoting age and sex), the year and week the drug was purchased, the prescribing doctor, the dose and the total amount of drug dispensed. The indication for the drug is not available. Drugs obtained over the counter without a prescription are not recorded.

When a drug prescription is refilled, the dose on the original prescription form is written on the bottle and again recorded. At that time the physician may have instructed the patient to change the dose. Refills occurred to the extent of some 60 per cent with chronic medications such as digoxin. For beta-receptor blocking agents and antidepressants the proportion of refills was approximately 30 per cent.

Figure 26.1 A map of Sweden to show the position of the counties of Jämtland and Härjedalen (in black). The district of Funäsdalen is indicated on the large map. The dotted line divides the counties of Härjedalen (south) and Jämtland (north). The two closest hospitals are in Sveg (140 km) and Östersund (220 km).

The relationship between prescribed daily dose and age was investigated using linear regression analysis. Differences in doses between age groups were tested using Student's *t* test. For all drugs, the age intervals 15-59, 60-69, 70-79 and 80 years or more were compared. We have studied (a) drugs which are metabolised at greatly varying rates in different individuals, i.e. the antidepressants amitriptyline and nortriptyline and the beta-receptor blockers alprenolol and propranolol; and (b) drugs which are excreted unchanged in the urine, i.e. digoxin and certain chemotherapeutic agents (table 26.1). In Sweden these drugs are available only on prescription.

Table 26.1 Available strengths of studied drug products in 1975

Drug	Tablet strengths (mg)
Amitriptyline	10, 25, 50
Nortriptyline	10, 25
Propranolol	10, 40, 80, 160
Alprenolol	50, 100, 200*
Digoxin†	0.0625, 0.13, 0.25
Nitrofurantoin	5, 20, 50, 100
Sulphamethizole + sulphamethoxipyridazine	200 + 50, 400 + 100
Tetracycline, oxytetracycline	250

*Sustained release tablet.
†Predominantly Lanacrist, Draco.

An independent study of the utilisation of digoxin was performed in 1973 (Bergman *et al.*, 1976) in the district of Funäsdalen. All patients more than 60 years of age who had been treated for at least one week with digoxin (the only cardiac glycoside used) were asked to participate. The total sample consisted of 75 patients (corresponding to 3 per cent of the population) and all except one (who died in hospital in a condition reminiscent of digitalis intoxication) were able to participate. Their mean age was 75.2 years (range 60-92). They were asked to come fasting to the health centre of Funäsdalen for routine clinical examination, ECG and blood-sampling but no information was given about the planned digoxin analysis (for details, see Bergman *et al.*, 1976).

RESULTS

Prescribed doses of drugs which are metabolised

Amitriptyline was the most commonly prescribed tricyclic antidepressant in the county. The daily dose ordered varied from 10 to 250 mg, with 75 per cent of the prescriptions falling between 30 and 75 mg. The mean daily dose was 58 ± 36 mg, declining with age from 70 mg in the 15-59 year old age group to 45 mg in the 70 and above age group (figure 26.2). For nortriptyline the range of prescribed daily doses in 1975 was 10-150 mg, but 81 per cent of the doses fell between 30 and 75 mg. The mean daily dose, 48 ± 25 mg, varied little and inconsistently with age.

Regarding beta-receptor blocking drugs, two thirds of the prescriptions in 1975 were for propranolol. The daily dose prescribed varied between 10 and 960 mg.

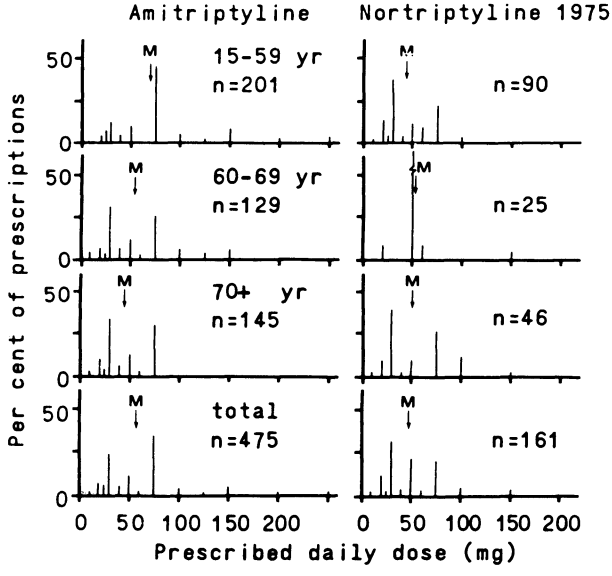

Figure 26.2 Variability in prescribed daily doses of amitriptyline and nortriptyline in different age groups in 1975 (computed from Boethius and Sjöqvist, 1978).

The mean dose decreased from 160 mg in the 15-59 age group to 70 mg among the oldest, the total mean daily dose being 147 mg (table 26.2). The dosage of alprenolol varied from 100 to 800 mg per day, more than half (53 per cent) of the prescriptions being for 400 mg. The mean dose decreased with age from 462 mg to 393 mg.

Table 26.2 Percentage distribution of prescribed daily doses of propranolol in different age groups in 1975

	Years of age				
Daily dose (mg)	15–59 $n = 624$	60–69 500	70–79 354	80+ 62	Total 1540
10–20	2	2	3	5	2
30–40	15	11	23	32	16
60–120	33	40	40	53	39
160–320	45	45	34	8	41
360–960	5	2	–	2	2
Mean daily dose (mg)	160	157	122	70	147

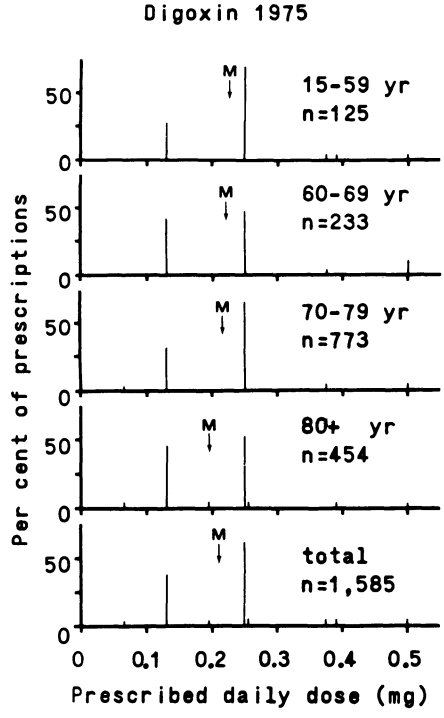

Figure 26.3 Variability in prescribed daily doses of digoxin in 1975. Percentage distribution of prescriptions within age groups and totally. M = Mean daily dose. (Computed from Boethius and Sjöqvist, 1978.)

Prescribed doses of drugs which are excreted unchanged by the kidney

Of the prescriptions for *digoxin* in 1975, 96 per cent were for doses between 0.13 and 0.25 mg (figure 26.3). There was a slight decrease in dose with age from 0.23 to 0.20 mg ($P < 0.001$).

The daily dose of *nitrofurantoin* prescribed for children in 1974 was markedly lower than for adults (table 26.3). In older age there was a slight reduction of the prescribed daily dose ($P < 0.001$).

Table 26.3 Percentage distribution of prescribed daily doses of nitrofurantoin in different age groups in 1974

	Years of age						
Daily dose (mg)	1–5 $n = 28$	6–14 36	15–59 255	60–69 79	70–79 96	80+ 41	Total 535
10–40	79	19	–	–	–	–	–
50–80	21	56	2	–	9	2	8
100–150	–	25	43	52	51	78	45
200	–	–	55	48	40	20	42
Mean daily dose (mg)	37	71	169	165	157	153	151

The most common of the sulphonamide preparations prescribed for adults in the county was a combination of the short-acting *sulphamethizole* (0.4 g) and the long-acting *sulphamethoxypyridazine* (0.1 g). The mean daily dose was 3.9 tablets in the 15–59 and 60–69 year olds, 3.8 in the 70–79 year olds and 3.6 tablets in the oldest (above 80 years).

Prescriptions of *tetracycline* and *oxytetracycline* were rare in children under 15 years of age. In 1974 a 'standard' dose of 1 g daily was prescribed in all adult age groups.

Plasma concentrations of digoxin in a sample of elderly out-patients in Funäsdalen

The prescribed daily doses of digoxin in the 74 patients were either 0.13, 0.25 or 0.37 mg, the average prescribed daily dose being 0.25 mg. There was a wide range of plasma concentrations at each dose level. The mean plasma concentration of digoxin for the group as a whole was 0.85 ± 0.52 (mean ± s.d.) ng/ml. Eleven patients had no measurable digoxin in their plasma. Two of the 74 patients had plasma digoxin levels above 2 ng/ml, one of whom showed signs of toxicity. A follow-up study was performed in 14 patients with digoxin levels below 0.5 ng/ml. In 8 of these the mean level rose significantly after they were informed about the importance of taking digoxin regularly; in the remainder the dose of digoxin had to be increased.

The distribution of digoxin concentrations has been compared in two patient categories in the same age group in figure 26.4. The 300 'first-time' hospital analyses, representing mainly in-patients, showed that in 36 per cent (109/300) the plasma level was below or equal to 1.0 ng/ml, as compared with 68 per cent (50/74) of the out-patients. On the other hand, in 22 per cent (66/300) of the former it was above 2.0 ng/ml, compared to 2.7 per cent (2/74) in the material from

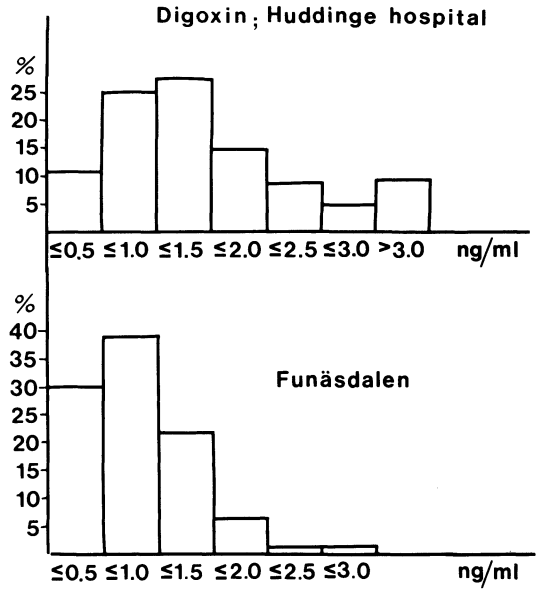

Figure 26.4 Distribution in percentage of plasma digoxin values in patients over 60. Upper part: 300 'first-time' analyses were performed, mainly in hospitalised patients, at various times after admission. Below are shown the 74 patients in the district of Funäsdalen, most of whom were out-patients. (From Bergman *et al.*, 1976.)

Funäsdalen. The actual size of the daily dose in mg was known for 271 of the 300 'first-time' analyses, who were prescribed a mean daily dose of 0.23 mg., as compared with 0.25 mg in the out-patients.

DISCUSSION

The ability to metabolise drugs such as antidepressants and beta-blockers varies considerably between individuals (Sjöqvist, Borgå and Orme, 1976; Alván, 1978). This variation is far more important than the age-dependent impairment of drug metabolism which has been demonstrated only for a few drugs (Crooks, O'Malley and Stevenson, 1976). The decrease in propranolol dosage in the elderly probably reflects the usage of high doses in young and middle-aged hypertensives. On the other hand, the mean plasma levels of propranolol after the administration of 40 mg are four times higher in elderly than in young patients (Castleden, Kaye and Parsons, 1975).

The tendency towards the use of lower dosages of antidepressants in the elderly agrees with the finding of higher plasma concentrations of such drugs in this age group compared with younger individuals (Braithwaite *et al.*, 1979; Collste and Bergman, 1976).

The inter-individual variability in the dosage of antidepressants and beta-blockers is consistent with the many-fold differences between patients in the metabolism of those drugs.

Beeley and Brooks (1976) reported that physicians paid little attention to kidney function when prescribing drugs which either were contra-indicated or had to be given in lower doses in patients with kidney failure. As an example, cotrimoxazole (trimethoprim-sulphamethoxazole) and digoxin were not infrequently prescribed in full dosage, even in the presence of severe renal failure. For drugs which are excreted unchanged a reduction of dose with age should be expected because kidney function declines with age.

Inulin clearance in 80 year olds is approximately half that in 40 year olds (Davies and Shock, 1950). It has been shown that the clearance of digoxin is related to that of inulin (Steiness, 1974) and creatinine (Iisalo, 1977). Accordingly, aged patients have reduced renal clearance (Ewy *et al.*, 1969; Iisalo and Ruikka, 1974). Taking these findings (and the extrarenal elimination of digoxin) into account, a reduction of digoxin dose of the order of 50 per cent in patients older than 80 years would be expected. A decrease of digoxin dose with age was demonstrated in our study but the reduction did not correspond to the pharmacokinetic prediction (table 26.4). The dose in the younger age group in our material (0.23 mg; cf. figure 26.3) may be too low. Therefore the irrational feature of the prescribing pattern is the small difference in dose between the extreme age groups rather than the absolute dose level used in the elderly.

Table 26.4 Calculated doses for different renal capacities: For digoxin calculated according to Koup *et al.* (1975); for tetracycline calculated according to Detti (1976); for nitrofurantoin calculated assuming renal elimination to be the quantitatively important route

Clearance of creatinine (ml/min)	Dose of digoxin (mg)	Dose of tetracycline (g)	Dose of nitrofurantoin (mg)
100	0.25	1.0	200
80	0.23	0.82	160
60	0.17	0.65	120
40	0.14	0.47	80

The clinical significance, if any, of this discrepancy between pharmacokinetic facts and prescribing habits was not evaluated. The independently performed field study in the district of Funäsdalen showed that plasma levels of digoxin were significantly lower in out-patients above 60 years of age than in hospitalised patients of the same age group and at the same dose level. Non-compliance definitely contributed to this.

In the elderly no reduction of tetracycline and oxytetracycline dosage occurred and only a slight reduction in nitrofurantoin dosage was seen (cf. table 26.4). Of patients aged 80 years or more, 76 per cent were prescribed the standard dose of two tablets t.i.d. of a combined sulphonamide product. By contrast, the two latter drugs were prescribed in lower doses to children, possibly owing to explicit recommendations by the manufacturers on this point.

CONCLUSION

This survey points to a possible discrepancy between drug-prescribing habits of physicians and established pharmacokinetic knowledge. There are several explanations, one being insufficient drug information at the general pharmacological level

as compared to information about specific products. Even the well-informed doctor will find it difficult in certain situations to prescribe in a rational way, one example being lack of suitable tablet strengths. The many dosage forms and strengths available for penicillin, a remarkably non-toxic drug, is explained mainly by the many paediatric preparations. Consideration of the introduction of *geriatric dosage forms* for drugs having age-dependent renal excretion is overdue. This may be one way to prevent concentration-dependent side effects in the aged.

ACKNOWLEDGEMENTS

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27
Compliance problems

O. L. Wade (Department of Therapeutics and Clinical Pharmacology, University of Birmingham, UK)

INTRODUCTION

The pharmaceutical industry may produce drugs to the highest specifications and doctors may prescribe competently and carefully, but patients will not benefit fully, if at all, from medication unless they take the drugs as and when they should. It is widely assumed that patients take drugs as they are prescribed, yet whenever this assumption has been examined objectively, the results have been most disquieting.

Most studies of compliance or, perhaps better, non-compliance, have been conducted from hospitals or clinics. Patients have been cross-questioned about the way they have taken the drugs prescribed for them or have been asked to fill in questionnaires. Sometimes the tablets remaining in their possession have constituted an inappropriately large residue indicating, at any rate in part, their defection from instructions, and occasionally urine or blood samples have been analysed to provide evidence of consumption or otherwise.

One of the first studies that aroused concern demonstrated that patients with tuberculosis often failed to take their medication (Fox, 1962). Bonnar, Goldberg and Smith (1969) showed a poor compliance in taking iron tablets by women attending an antenatal clinic; Gibberd *et al.* (1970) found epileptic patients did not take phenytoin as prescribed and Parkes, Brown and Monck (1962) showed, perhaps not unexpectedly, that many schizophrenic patients were not adhering to the intended medication one year after discharge from hospital. Parkin *et al.* (1976) followed 130 patients leaving hospital in Dundee and showed that 66 of them were not complying with instructions, 46 of them because they had not comprehended the instructions. More recently MacDonald, MacDonald and Phoenix (1977), in a study of 165 elderly patients leaving hospital in Nottingham, showed that 15 minutes of personal instruction to the patient by a ward pharmacist improved compliance substantially.

Studies of compliance in general practice in Britain are surprisingly few in number. Porter (1969) looked at the compliance rate of four groups of patients, receiving antidepressant drugs, short-term antibiotics, treatment for long-term chronic illness and prophylactic iron during pregnancy. Compliance was far better than in

previous studies, but one-third of patients receiving short-term antibiotic therapy did not comply fully with instructions. Gatley (1968), in a much smaller survey of 86 patients, showed that the percentage of tablets ordered to be taken that were not taken increased as the number of times in the day for which they were prescribed increased.

BIRMINGHAM STUDIES

I wish to report briefly on two studies that have been carried out in Birmingham. The first was a study of compliance in a practice of 9000 patients with five practitioners (Drury, Wade and Woolf, 1976). In this survey, 521 patients who had had medicines prescribed for them at a surgery consultation were followed up. The details of the drugs prescribed and of any instructions given to the patient were recorded by an observer at the time of the consultation. After an appropriate interval—usually three weeks if a month's supply of drugs was prescribed but sooner if the prescription was for a shorter time—284 of the patients were visited and 237 were sent a questionnaire, which 28 did not return. (One of the purposes of the survey was to assess the value of such questionnaires.)

Table 27.1 gives details of the sex and age of the 521 patients. Table 27.2 shows that, in this practice, there was an 86 per cent compliance rate among the 493 patients for whom data were available. Only 14 per cent of the patients did not take the right doses at the right times. Differences in the compliance rate were not re-

Table 27.1 Patients receiving prescriptions

Female	355
Male	166
Total	521
Age under 20	109
21–60	301
61–70	57
70+	54

Table 27.2 Compliance rate

Complied	No.	%
Dose and time	424	86
Dose only	17	3.4
Time only	19	3.9
Neither dose nor time	33	6.7
Total	493	
Questionnaires not returned	28	

Table 27.3 Doctor and non-compliance rate

Doctor	Scripts written	Non-compliers	%
A	137	25	18
B	100	9	9
C	87	17	20
D	83	12	15
E	86	6	7
Total	493	69	14

Table 27.4 Compliance

Prescription	No.	% non-compliance
First	266	20
Repeat (consultation)	133	8.2
Repeat (no consultation)	94	4.2
Total	493	14

Table 27.5 Number of drugs prescribed by group in total sample and non-compliant sample

System or drug group prescribed	Total no. of patients	% (a)	Non- compliant patients	% (b)
Infections	159	20.0	37	28.0
Nervous system	180	22.7	32	24.0
Rheumatoid disease	80	10.0	19	14.2
Cardiovascular	106	13.4	10	7.5
Respiratory	60	7.6	6	4.5
Alimentary	58	6.1	5	3.7
Nutrition and blood	27	3.3	5	3.7
Ear, nose and throat	13	1.7	4	3.0
Genital system	32	4.0	4	3.0
Eye	18	1.7	3	2.2
Skin	29	2.5	3	2.2
Metabolism	21	2.6	3	2.0
Allergic reactions	16	2.0	2	1.5
Malignant disease	3	0.4	0	0

Values are expressed as (a) percentage of total number of patients (802) or (b) percentage of total number of non-compliant patients (133).

lated to age, sex or social class of the patients but were related to which of the five doctors wrote the prescription, Drs B and E having the lowest rate of non-compliance (table 27.3). Compliance was greater amongst patients receiving a second or subsequent prescription compared with those receiving a first prescription (table 27.4). Compliance was lower for antibiotics, antirheumatic drugs and drugs acting on the nervous system than for other drugs (table 27.5).

We concluded from this study that it is possible for good compliance to be achieved, but further studies are needed to determine firstly whether it is easier for a family doctor to achieve high compliance among his patients than for a hospital- or clinic-based doctor and secondly whether it is as difficult in hospital as in general practice. Furthermore success in achieving a high compliance seems to depend on the personality of the doctor or on his technique in explaining to the patient what medication he is having and how he is to take it.

Table 27.6 Survey of patients leaving hospital with tablets: questions

(1) What are they for?
(2) What time of day will you take them?
(3) Are there any side effects?
(4) Were you given warnings, etc.?
(5) What will you do when you finish these?
(6) Have you any other tablets at home and do you intend to take them?
(7) Have you any questions?

The second study was a survey of patients being discharged from hospital with, as is usual, a supply of medicines to cover the next four or five days. As patients left the hospital, they were interviewed and asked a series of questions shown in table 27.6 about the medicines they had been given. This survey has not been fully analysed yet but it showed:

(1) Communications to the patients were poor.

(2) Patients had a strange passive apathy about their medication, probably because they were perplexed and mystified about it.

(3) Many of them expressed the intention of taking the medicines given them as they left hospital and at the same time starting again to take the medicines that had been prescribed by their general practitioner prior to admission and which might be awaiting them when they got home.

CONCLUSIONS

My conclusions from both our own work and reading of other studies suggest that there are at least six factors which may play a part in reducing compliance (table 27.7).

I believe that compliance may be increased if attention is given to the rules set out in table 27.8, but far more research is needed to see which of these rules are the most important and which are the best ways of implementing them.

Table 27.7 Factors that decrease compliance

(1) Many drugs.
(2) Complicated regimen.
(3) Few symptoms.
(4) Non-comprehension.
(5) Age or disability (visual, mental, etc.).
(6) No help or relatives in home.

Table 27.8 Aids to improving compliance

(1) Few drugs.
(2) Simple regimen.
(3) Explanation.
(4) Written instructions.
(5) Good labels.
(6) Special packaging.

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Conclusions: Perspectives in geriatric clinical pharmacology

J. Crooks and J. Feely (Department of Pharmacology and Therapeutics, University of Dundee, Ninewells Hospital, Dundee, UK)

The main objectives of this Symposium were, firstly, to identify those areas of geriatric clinical pharmacology where our ignorance is so marked that research effort with appropriate techniques would be rewarding, and secondly, to evaluate the contribution of recent advances in geriatric pharmacology, both in improving patient care and as a stimulus to further research.

Research in geriatric clinical pharmacology has a number of aspects. At a laboratory level it deals with the effect of ageing on basic pharmacology and with the effect of certain drugs on the ageing process. At a clinical level, where particular problems of quantitative and qualitative assessment require solution, it deals with the effect of ageing on drug handling and response. The contribution of each of the four sessions of this symposium towards achieving the above objectives is described below.

THE AGEING PROCESS

As far as the ageing process is concerned, there is no unifying explanation which is applicable to cells and organ systems as well as to whole organisms. Many of the studies relate only to the fibroblast model, and it is clear that these cellular studies must be complemented by additional observations on both specialised cells and whole organisms. An example of the danger of extrapolating from cellular studies is that of hydrocortisone, which may slow down the ageing process of the isolated fibroblast but is not likely to modify the ageing process in man. There is a need for a comprehensive description of the sample population studied, whether cellular or animal, and of the many diverse environmental parameters operating in each study. Future research should concentrate on studying control mechanisms with the recognition that the ageing process begins from birth. Much of the information to date in gerontology has been derived from animal models, and it is widely recognised that further work is required in developing model systems which are particularly appropriate to the study of the human ageing process. Furthermore, because of the

many problems in maintaining aged animal colonies, including expense and expertise required, there is a need for centralisation of facilities, which could then be used by interested researchers on a shared cost basis. This would also allow for standardisation of strains, environment etc. Additionally, a central coordinating body may attract resources and initiate research. There is little information to date on the effect of drugs on the ageing process. Now that the baseline data on cellular turnover are being established, it will be of interest to see the variation in doubling capacity which occurs with age and the possible influence of drugs on this, particularly of those affecting protein synthesis.

PHARMACOKINETICS IN THE ELDERLY

Almost all the work to date in this field is based on single-dose studies. There is an obvious need for data on steady-state and chronic-dosage pharmacokinetics. Although a good deal of work has been done on the absorption of drugs, we cannot yet predict the effect of ageing on any particular drug. It is particularly important now to look at the effect of age on poorly absorbed drugs. The findings in relation to distribution and metabolism suggest the need to study individual drugs. With distribution in particular, the situation is complex, differential binding within compartments influencing the apparent volume of distribution and, overall, there is no consistent age-related effect. While it is clear that the metabolism of many drugs is impaired in the elderly, particularly so in the case of drugs metabolised by oxidative processes, the studies to date have almost exclusively been based on the disappearance rate of unchanged drug. There is therefore an urgent need for data on precise patterns of metabolism in the elderly as well as on the minor pathways of metabolism.

Of the pharmacokinetic processes studied, the most consistent pattern of change in the elderly occurs in the renal excretion of drugs. The renal elimination of several drugs is impaired in the elderly, owing to reduction of renal function and, although dose adjustment based on nomograms produces plasma levels within the 'therapeutic range', it is uncertain whether 'therapeutic ranges' may vary with age.

DRUG SENSITIVITY IN THE ELDERLY

Major problems exist in the assessment of drug sensitivity, as there is a shortage of reliable methods of determining end-organ response. Furthermore, in the elderly, impaired homeostatic mechanisms, for example thermoregulation, glucose homeostasis, coordination of motor function and postural hypotension, complicate the investigation of drug effect. Thus, assessment of the influence of commonly used drugs on homeostatic mechanisms in elderly subjects is currently needed. The increased susceptibility of the elderly to mental confusion also complicates the investigation of drug effect and points to the need for increased research activity in the field of human neuropharmacology in this age group. Disease processes, so common in the elderly, are also important in modifying drug response.

New techniques in clinical pharmacology allow the isolation and measurement of the distribution, density and *in vitro* activity of receptors for a variety of drugs. It seems possible that the number of receptors and their responsiveness may vary with increasing age. Recent developments in biochemical pharmacology, demon-

strating a depletion of certain neurotransmitters in the elderly and in certain disease states, may lead to a rational use of substitution therapy, for example cholinergic drugs in certain confusional states and monoaminergic drugs in Parkinsonism and possibly Alzheimer's disease. If one is to distinguish the contribution of various factors to altered drug response, pharmacodynamic studies must inevitably be complemented by pharmacokinetic studies. Again, chronic dosage must be undertaken and the possible role of tolerance examined.

CLINICAL ASPECTS OF DRUG USE IN THE ELDERLY

It is important here to distinguish two major levels of enquiry—gerontology (study of the ageing process) and geriatric medicine (medical care of the elderly)—although there is frequently an interaction between the two. We must recognise our inability to separate chronological from biological ageing and the difficulty in delineating disease processes from ageing. The diversity of the population under study, varying from the prematurely aged to the very old 'biologically elite', and from healthy elderly individuals at home to institutionalised elderly patients suggests that we may have to examine appropriate subgroups.

There is a paucity of information, in the elderly, concerning the efficacy and toxicity of commonly used drugs, and it is irrational that the design of clinical trials, particularly of new drugs, does not include assessment in the age group where the drugs are likely to be used widely. Although adverse drug reactions occurring in the elderly frequently have a pharmacokinetic basis, a recognition of the contribution of impaired homeostasis to adverse reactions should make us re-evaluate the true 'therapeutic ratio' for the elderly. In the use of 'at risk' drugs such as antihypertensives, diuretics, digoxin, psychotropic and antitremor drugs, etc., in an 'at risk' group like the elderly, we must assess the efficacy of these agents in terms of realistic therapeutic objectives, as well as possible toxicity. In a population with diminished life expectancy, in whom the quality of life may be more important than the quantity, the value of long-term antihypertensive, hypoglycaemic, etc., therapy remains to be established, even when the agents are therapeutically effective. The practice of prescribing could be improved if the indication for drug usage and rationale of drug selection and dosage were recorded. Drug non-compliance may arise from poor communication and non-comprehension and is likely to be improved by simple techniques of counselling, packaging, etc.

There are many examples of profitable interaction between basic and applied research, particularly in the field of medicine. The perspectives in geriatric clinical pharmacology which have been discussed in this symposium point to the need for more interaction and for collaboration between the disciplines of gerontology and pharmacology, on the one hand, and geriatric medicine, on the other.

This International Symposium was the first of its kind to attempt to assemble current knowledge in the field and it is hoped that the developments envisaged will lead to a better understanding of the ageing process as related to drug action and ultimately to a more rational and consequently more effective use of drugs in the elderly.

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Numerals in heavy type refer to tables and figures