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A primary aim of *Understanding Ageing* is to dispel the view that ageing is a major unsolved problem in biology. The adult organism is maintained in a functional state by at least ten major mechanisms, which together comprise a substantial proportion of all biological processes. It can be shown that these maintenance mechanisms ultimately fail because the evolved physiological and anatomical design of higher animals is incompatible with continual survival. Studies with different mammalian species strongly indicate that cellular maintenance mechanisms are more effective in long-lived animals than in those with a short lifespan. The investment of metabolic resources into rapid growth and reproduction diminishes the resources available for maintenance, whereas this is much more effective in slowly-breeding animals. The eventual breakdown of maintenance leads to many age-related diseases, and the study of these in humans is documented by a huge biomedical literature, which is not generally regarded as being within the province of gerontology. The reality is that this information provides much insight into the changes in cells and tissues that accompany ageing. To understand in more detail the origin of all these diseases demands future research into the failure of maintenance at the cellular and molecular level. This in turn will make it easier to devise preventative measures.

This book is thought provoking because it outlines a new approach to a fundamental biological process. It will appeal to all students and researchers who are interested in ageing, whether they are working in the clinical or basic research sphere.

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Preface

It is very commonly believed that the causes of ageing are unknown. For an inaugural professorial lecture, P. B. Medawar (1952) chose the topic 'An unsolved problem in biology', and this wide-ranging discussion of ageing has been influential and frequently cited. Since that time much has been learned about ageing, but most in and outside the field of gerontology would believe that the mechanism or mechanisms involved remain elusive.

My own interests in ageing began in the mid-1960s, and in the following two decades I had the same viewpoint, because it seemed that progress in research worldwide was extremely slow, so the unsolved problem remained. More recently, I have become more optimistic and have come to believe that the biological basis of ageing is now well understood. This is in part due to a consideration of the biological reasons for ageing, from an evolutionary standpoint. Also, the evolved physiological and anatomical design of mammals is well understood. The changes that occur during human ageing are documented by an enormous range of studies on age-related pathologies. A great deal is known about the many homeostatic, repair or maintenance mechanisms, which preserve the adult in a functional state for a given length of time and allow it to propagate itself. All this comprises a substantial part of biology. I believe that to understand ageing one need only look at and appreciate this vast body of existing knowledge. Those who believe ageing is a mystery cannot see the wood for the trees around them. The trees are described in considerable detail, but by concentrating on these details, many miss what the collection of trees actually comprises. I stress that the understanding to which I refer is at the broad biological level, not at the level of fine detail, which will come from future cellular, molecular and genetic studies. One cannot overemphasise the importance of such studies, because they are essential if we are ever to understand the origins of the age-related diseases. In countries with good health care where expectation of life is high, the treatment of the diseases of the aged consumes a greater and greater proportion of the total budget. Successful research in cellular and molecular aspects of ageing will inevitably improve this situation.

One reason for confusion about the causes of ageing is the continual polarisation between so-called programme theories of ageing and those that are

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usually described as 'wear and tear', stochastic or error theories. These have commonly been regarded as opposing viewpoints, but I no longer believe this to be true. The lifespan of the organism is determined by its genes, the products of those genes and the interaction with the environment. The genes are responsible for all those features of organisms that have been studied with success, and that provide the basis for our understanding of ageing. In this wide context, one can include development, regulation and programme, as well as wear and tear, or molecular defects. In any realistic approach, the distinction between programmed and stochastic events continually breaks down.

There is also the contentious question of single or multiple causes of ageing. Many who have proposed specific theories tend to believe their theory is the one that *explains* all of ageing. I take a different viewpoint: I believe many existing theories have some validity, and that a more global interpretation that encompasses specific theories is the most appropriate. This implies that there are multiple causes of ageing, but also multiple interactions between components of cells, or between different types of cells. In such a situation, a single molecular defect may have a wide range of effects. This interpretation is not new, and previous publications that come to similar conclusions (Olson 1987; Holliday 1988a, 1992) serve as summaries or abstracts of this book.

I am not attempting to review the field of gerontology, that is, the whole study of ageing. Many such reviews exist, most recently that of Finch (1990), which lists over 3500 references. There are, in addition, innumerable volumes that provide reviews and discussions of particular topics. Indeed, the field is extremely well endowed with review material. Instead, this book presents a particular point of view and argument. It draws on information that is relevant, and ignores a great many studies of ageing. Many of these studies are interesting and important; they may, for example, document the change of a particular physiological or biochemical parameter with age. Nevertheless many such observations are at present not interpretable. In my opinion, they comprise part of the level of fine detail, and their significance will be understood only in the future. In developing the major theme, I draw only on material that I believe is relevant to *Understanding Ageing*.

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Author's note

As I indicated in the Preface, this book is not a review of ageing. It will also become apparent to the reader that the level of documentation and citation of previous publications is quite uneven. Sections of the book that deal with general or biomedical topics, such as the pathological changes that often accompany human ageing, are almost absent of references. Much of this information is available in standard medical texts or monographs. In other parts of the book I cite wherever possible previous reviews or collections of publications that cover a particular topic. There are innumerable reviews of different aspects of ageing, including three editions of the *Handbook of the Biology of Aging* (Van Nostrand Reinhold, 1977, 1985; Academic Press, 1990) and the CRC series on ageing, which comprises at least 12 volumes on diverse topics in gerontology. The sections that are most thoroughly documented with references are those that have over the years been the focus of my own research and interests: those related to cellular ageing, the accuracy of information transfer between macromolecules and the evolution of ageing. Some of this work has been previously reviewed (Holliday 1984c, 1986b). I am well aware of the more limited discussion of equally important topics, such as the accumulation of abnormal proteins in various tissues, or neuroendocrine interactions. To keep the text as readable as possible, I have assigned specific technical or theoretical points to a series of appended Notes, supported with further references and, in some cases, with illustrations. Finally, I wish to apologise in advance to any authors whose work I may discuss without an appropriate citation, and also for any errors in citations.

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