In this series of special themed editions of the *Journal of Gerontology Biological Sciences and Medical Sciences*, reviews and commentaries have been solicited that focus on the basic biology, animal models, translational research, physiology, epidemiology, and public health aspects of aging. This emphasizes the multidisciplinary and translational nature of modern aging research. Aging is stochastic, complicated, and complex; therefore, answers and solutions to the problems of old age will almost certainly require multidisciplinary teams that focus on translating research into outcomes that are ultimately beneficial for humans. In this edition, our theme is “Drugs and Drug Metabolism.”

Why should biogerontologists be interested in drugs and drug metabolism? These topics would seem, superficially at least, to be very medical and quite distant from the cellular and physiological focus of most aging biologists. In fact, there are many reasons. First, old age is associated with marked changes in the response to medications, which are a consequence of age-related changes in both the pharmacokinetics and the pharmacodynamics of drugs. These pharmacological changes are caused by the same biological mechanisms as other aging changes, including altered gene expression, oxidative injury, and mitochondrial dysfunction (1). Thus, age-related changes in drug metabolism should be considered a typical phenotypic characteristic of the aging process. Generally, older age is associated with increased blood concentrations of drugs and altered metabolism, reduced effectiveness, and increased risk of adverse reactions for many medications (2). Impaired response to pharmacotherapeutic interventions is a critical yet underemphasized aspect of older age. If medical therapies for disease were effective in old age, then it would not matter that old age is the main risk factor for disease because diseases would still be able to be treated and cured. Impaired responsiveness to therapeutic interventions has such important implications for older people that we believe it should be included in any definition of aging.

Furthermore, by studying the effects of old age on drug disposition, we can gain insights into the aging process itself. For example, age-related changes in the hepatic microcirculation were discovered as a direct consequence of research into the effects of age on hepatic drug metabolism (3, 4). It should also be recognized that drug metabolism is only one aspect of the body’s response to any potentially toxic and disease-causing xenobiotic. Therefore, age-related changes in drug metabolism and elimination have much broader implications for disease susceptibility. For example, age-related changes in hepatic cytochrome P450 enzymes not only increase drug concentrations but also increase an older person’s susceptibility to pesticide neurotoxins thought to contribute to the risk of developing Parkinson’s disease (5).

There is no doubt that a major aim of many scientists involved in aging biology research is to develop pharmacological therapies that delay aging, diseases and disabilities that accompany older age, and, ultimately, improve function. Recent research into the biology of aging has led to an increased understanding of the cellular mechanisms and pathways involved in generating the beneficial effects of caloric and protein restriction on aging, such as the target of...
rapamycin, insulin/insulin-like growth factor-1, and sirtuins (6–8). Application of the principles of drug discovery to these novel aging targets has led to major advances in therapies to delay aging. Regardless of controversy, resveratrol and rapamycin have provided proof of principle that aging is plastic and a valid target for drug discovery (9, 10). Now, every scientist involved in biogerontological research could be considered to be undertaking early phase drug discovery that will potentially benefit all humans, not just those with a particular disease.

Notwithstanding the biological significance, the use of drugs in older people is one of the most important issues for the practice of medicine this century. However, it is also a minefield, often without a map. Old age is the main risk factor for disease, and accordingly, most medications are used in older people, and it is usually conceded that over one half of medications in the Western world are used by this group of patients. On one hand, it is well established that there are marked aging changes in drug disposition and harm from medications is much more common in older people. On the other hand, there is only limited evidence to support the efficacy and safety of many medications in older people, especially frail older people taking multiple medications (2). Much clinical geriatric research is needed to provide the evidence base for the future quality use of medicines in older people.

In this issue, Le Couteur and colleagues (11) point out that recent dramatic advances in drug discovery technology have not been rewarded by any increase in the rate of discovery of new drugs and drug targets for specific diseases. However, research into the biology of aging is generating many potential targets for drug development that may delay all age-related diseases and be used long term by the entire population—clearly “blockbusters” for the pharmaceutical industry. Aging biology is a promising arena for new drug targets—the current focus is on pathways that mediate the effects of caloric restriction (11). Rodents are the usual model for establishing the proof of principle for a novel drug target or drug for most diseases, and as Lebel and colleagues (12) have shown, this is also the case for aging. There are 68 genetic mouse models with either premature aging or extended life span as well as dietary manipulation with caloric restriction and high-fat diets—these all provide useful models for testing new drugs. They emphasize that there are many phytochemicals, antioxidants, and other drugs that have been shown to be effective in delaying aging in rodents. Unfortunately, as Smoliga and colleagues (13) note in their review on resveratrol, there is often a very long journey in translating promising drug targets in experimental animal models to successful human medications that improve outcomes. After the initial excitement associated with the discovery of a new target or drug, subsequent translation into human pharmacotherapy generates new and frustrating issues around intellectual property, non-availability of commercially sensitive clinical trial data, and industry’s interest only in those chemicals that can be protected by patent. Apparently, mundane (but essential) issues such as pharmacokinetics, toxicology, regulatory requirements, and commercial interpretation of market opportunities determine go/no-go decisions in subsequent drug development.

The first three reviews in this series focus on the development of therapies to delay aging and age-related diseases. Such therapies are likely to be used by people in mid-life before the onset of age-related pathologies and perhaps extended into later years. Of course, today most medication is utilized by older people for treatment of individual diseases. Lindley (14) concludes that it is a failure of modern medical research that clinical trials have rarely recruited those older frail participants with comorbidities who are most likely to be prescribed medication in real life. Lindley has been a strong proponent for the removal of age as an exclusion criterion in clinical trials and for the recruitment of frail older people (or at least the measurement of frailty in participants) in clinical research. One of the key considerations in achieving optimal outcomes with medicines in older people is the effect of aging on drug metabolism. Mclachlan and Pont (15) describe how biological aging processes influence hepatic drug metabolism and provide evidence that the age-related changes in the liver decrease the clearance of any unbound drug and also influences variability in response to medicines in older people. In the absence of good quality evidence on prescribing in older people, the principles of pharmacokinetics can be utilized to individualize and hopefully optimize new and existing pharmacotherapies. However, too often we must rely on postmarketing data to determine whether medications are effective or indeed causing harm in older people. Hilmer and colleagues (16) report that pharmacoepidemiology can be used to assess medication outcomes in real-life older people and the challenges therein. Few clinical trials are appropriately designed to establish medication safety, and regulatory guidelines have yet to come to terms with the needs of older people. Therefore, it has been left to the pharmacoepidemiologists to provide us with evidence about risk, and less frequently efficacy, of medications in older people.

It is certainly an exciting time to be a scientist working in the field of geriatric pharmacology but perhaps not such a good time to be an older person needing pharmacotherapies. There is an overwhelming and unmet demand, driven by demographic change, for effective and safe medications that delay aging and/or treat diseases in older people. As the reviews in this special issue indicate, the demand will only be met by a coalition including pharmaceutical industry, government regulators, biogerontologists, clinical pharmacologists, and of course older people themselves.

References


