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As in preceding years, the lay-out of this review is essentially systematic – with articles across various organ systems of the body. On closer perusal, however, other cross-cutting themes emerge.

One of these themes is the physiology of ageing. For human physiologists this is a particularly important area given the ageing population. India, for instance, will have over 300 million people above the age of 60 by 2050, and this is a conservative estimate. In the article 'Cardiac Pacemaker activity and Aging' Peters *et al.* delve deeper into the tissue, cellular and molecular mechanisms that explain the reduction in maximal heart rate that occurs with ageing. Students of human physiology will be aware of the simple calculation of maximal heart rate as 220-age in years. This is clearly simplistic and variable but emphasizes the scale of change in pacemaker activity of the sinoatrial node over the course of a lifetime. This is important because maximal heart rate is a major determinant of aerobic capacity; when this is reduced in the elderly, it limits functional independence as well. The authors review the extensive literature on the ionic basis of pacemaker potentials in the heart and in the process highlight the potential for the development of drugs that can increase the maximal heart rate, aerobic capacity and functional capacity of the elderly. De Silva and Faraci focus on the phenotypes and mechanisms that underlie microvascular ageing in their article 'Contributions of aging to cerebral small vessel disease'. This is clearly an important area of medical physiology since small vessel disease can affect regional cerebral blood flow, impair the transport of oxygen to sites where it is needed and can result in lacunae, infarcts, and brain atrophy. Small vessel disease can also impair the integrity of the blood–brain barrier which protects the brain from a host of insults – infective and noninfective. The clinical manifestation of small vessel disease can range from mild cognitive impairment to severe dementia, as well as loss of gait and balance, among others. The authors extensively review the haemodynamic changes in cerebral blood flow with ageing, endothelium-dependent mechanisms that regulate blood flow, age-related changes in vascular structure and ageing and sex-dependent effects. In their article on 'Aging and lung disease', Cho and Stout-Delgado start off with a comprehensive review of the structural and physiological changes that occur in the ageing lung. Three broad areas that are covered are the changes that are seen in conducting airways, respiratory airways and in immune function. Having discussed the physiology of ageing in the lungs, the authors then go on to review how these changes impact disease in the elderly, specifically chronic obstructive pulmonary disease, interstitial lung disease, lung infections and acute respiratory distress syndrome. Two areas which I would have liked to know more about are the effect of smoking cessation and physical activity/exercise on the age-related changes in the lungs. This is important since these behavioural modifications have largely been studied in relation to cardiovascular disease but are likely to have more extensive benefits. Sensory perception with ageing is an important area of concern for clinicians given the fact that many elderly have sensory neural deficits often associated with comorbidities. The article on 'Neuronal mechanisms that drive organismal aging through the loss of perception' by Gendron and colleagues opened for me a completely new area of understanding. The authors provide compelling evidence from studies on *C. elegans* and *Drosophila* that sensory perception (food and social) not only influences decision-making behaviours but also directly impacts the ageing process. Experimental evidence in mammals is limited but growing.

Life on earth is subjected to dramatic diurnal environmental influences, of which the day–night cycle is the most obvious. There are of course many other cyclical influences and organisms, including humans, have evolved to adapt to these environmental oscillations. In humans, circadian oscillations are entrained to a 24-hour cycle and include a large range of biochemical and metabolic parameters. Research following the second world war demonstrated these circadian rhythms at a whole-body level. The suprachiasmatic nucleus of the hypothalamus was identified as a major circadian clock. In more recent years, the focus has shifted to circadian clocks within cells. In the article 'Circadian regulation of cardiac physiology: rhythms that keep the heart beating', Zhang *et al.* review the circadian clocks in cardiac myocytes in relation to its electrophysiological processes, contractility, and metabolism at a cellular and molecular level. While much has been learned in recent years, there is still a lot to understand in terms of how cellular circadian clocks in cardiac myocytes impact function in health and disease and how they interact with the neurohumoral system – a major driver of cardiac function. In a related article 'Why lungs keep time: Circadian rhythms and lung immunity' Nosal *et al.* review our current understanding of circadian rhythms in the lungs. These rhythms are related to three major parameters – airway resistance, the ventilatory response to hypercapnia and the response to allergens. Asthmatics often report a worsening of their symptoms at night – a living example of the role of circadian rhythms in the lungs. However, despite major advances in the molecular understanding of circadian rhythms in the lungs, the implications for physiology as for instance, ageing, and for disease and its treatment remains to be understood. The kidney has the second highest number of genes that follow a circadian pattern of expression after the liver. Zhang and Pollock comprehensively discuss the 'Diurnal regulation of renal electrolyte excretion: The role of paracrine factors'. Circadian variation in urine volume and electrolyte output have been known for nearly 70 years, but it is only in recent years that the mechanisms involved, and the role of paracrine factors have been elucidated. The kidney is also critical for the long-term control of blood pressure and this has been demonstrated in various ways including the classic experiments of Goldblatt. Circadian kidney function is important because it is associated with nocturnal hypertension (associated with critical events such as myocardial infarction and stroke) and diabetic nephropathy and chronic kidney disease. While the article is largely cellular in its approach, the authors effectively provide the links to whole body human physiology and clinical medicine in their discussion which many will find particularly appealing.

The special topic in this edition focuses on the physiology of bone. The first of three articles focus on the origin, structure, and function of marrow adipocytes. For many years, these cells were seen as ‘passive fillers’ of the marrow when bone or haematopoietic cells were absent. Thus, marrow adipocyte cells increased with ageing and while associations were seen between marrow adipocytes and various diseases such as osteoporosis and cancer, it was clear that these associations did not imply causality. In their article, de Paula and Rosen summarize recent data on the lineage of marrow adipocytes and its paracrine and endocrine function but recognize that our understanding of these cells is still in its early stages. The next two articles in this section address the functions of two cells: the osteocyte and the osteoclast. Robling and Bonewald focus their article on newer functions of the osteocyte. These include its ability to mimic both osteoclasts and osteoblasts during remodelling of the bone matrix, its function as a mechanosensor and its regulation of distant organs such as the kidney and muscle. Bone remodelling involves resorption of bone by osteoclasts and the laying of new matrix by osteoblasts. In their article, Sims and Martin discuss the process of bone modelling in detail and address the issue of how osteoclasts provide signals to osteoblasts to initiate new bone formation. I found this special topic very timely not only because bone health is an important issue in a demographically shifting population but also because this has been a relatively neglected part of physiology.

Several other topics that gripped me included the physiology of the carotid body involved in the chemical regulation of respiration, the genetics of chronic obstructive pulmonary disease – a condition of particular concern to clinicians given the extent of ambient and indoor air pollution and of smoking, and the biology of the acid tumour microenvironment as a driver of cancer and as a site of potential therapeutic interventions.

The study of physiology has inevitably and understandably become more cellular and molecular. As a human physiologist in a medical college, I was happy that the articles to a large extent located the biology within an integrated human physiology or clinical setting. I found the present edition particularly absorbing and informative in its depth and breadth. I look forward to each new edition of the Annual Reviews of Physiology, and the present edition reminds me why.

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