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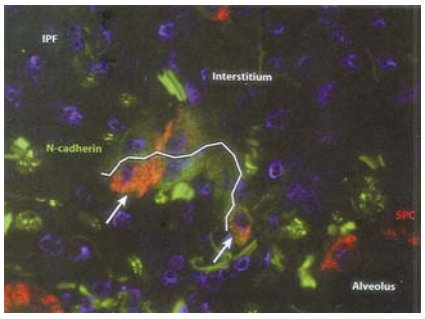
The first chapter of this volume is devoted, as has been the case for some time now, to an autobiographical account of the times and work of a prominent physiologist. This year, the chapter entitled 'A long affair with renal tubules' outlines the life and work of the noted renal physiologist, Gerhard Giebisch, and continues this long-standing tradition of the *Annual Review* which has, in the past, included great, path-breaking scientists, including several Nobel laureates. This chapter is one which I never skip and never fail to encourage my students to read. The present chapter, not only documents the difficult choices that researchers need to make, but is also a remarkable example of the evolution and application of newer research methods during the course of a single lifetime. Gliebisch first started his work using the classic 'clearance' methods to study renal function in his native Austria. His migration to USA also resulted in a shift to other techniques; single nephron micropuncture studies, the patch-clamp method and finally, molecular techniques, in a gradual progression of mechanistic studies firmly grounded in whole-body integrative physiology. His own concluding remarks provide food for quiet refection on the tussle between issues of science versus issues of self. Advocating the need for continued work on single nephrons, he states 'it remains an eminently useful, essential and incisive tool … it should not be neglected. No doubt work on single nephrons is time-consuming, yields fewer publications, and hence is less popular at a time when funding for such projects is uncertain and the pressure to produce an adequate (large) number of papers with high impact factors becomes critical for career survival.' If anything, the life of Gliebisch is a strong reminder that staying the course in science, despite the difficulties, pays rich dividends.

There has been a considerable focus, of late, on studies that address the mechanisms of obesity and obesity-related disease. This is important given the rapid rise in the prevalence of obesity and its clinical sequelae, across the globe and increasingly in developing countries. The bulk of the obesity literature that deals with mechanistic issues focuses on individual-level factors that govern energy expenditure and energy intake. More recently, however, researchers have begun evaluating contributory factors at family, community and environmental levels. It is in this context that the article entitled 'Endocrine disruptors: from endocrine to metabolic disruption' by Cristina Casals-Casas and Beatrice Desvergne is particularly interesting. Much of the work in this area earlier focused on reproductive and developmental issues. As the title suggests, the current chapter goes further. There is now a body of evidence that indicates a link between environmental pollutants, adipogenesis and insulin resistance. The authors discuss these linkages extensively and despite the obvious relevance, given the increasing exposure to environmental pollutants from plastics, industrial pollutants and pesticides, there are many challenges to research in this area. This includes the evaluation of exposures in populations and individuals, the practical and ethical issues of interventions, and the difficulties in ascertaining an effect size, independent of the more proximal determinants of obesity, among others.

Among the many problems that mankind has had to increasingly contend with as part of an acculturation process from traditional lifestyles, is that of hypertension or high blood pressure. Over a hundred years ago, at a meeting in St. Petersberg, Tigersted and Bergman presented evidence for a renally derived factor that could raise blood pressure. This factor was subsequently determined to be renin. Further work elucidated the renin–angiotensin system and led to the development of angiotensin-converting enyzme inhibitors as part of the clinical armamentarium against hypertension. The chapter entitled 'Renin release: sites, mechanisms, and control' takes us back to more basic science issues, which have intrigued physiologists for many years. For instance, the nature of the renin-releasing cell has had to undergo rethought with the determination that renin is produced not only in the kidney but also in a range of cells, including mast cells, macrophages, and cells of the adrenal cortex, ovary and testis, among others. The dynamic induction of renin-producing cells in states of salt depletion is of great functional interest. Also discussed is the process of renin release. Earlier ascribed to classic exocytosis, there are, however, several atypical aspects of renin release that suggest, in the authors' own words, that the 'release mode of renin is mysterious in several aspects' and may resemble more the pathways of lysosomal secretion than those of typical endocrine secretion. The chapter 'Mechanisms underlying rapid aldosterone effects in the kidney' by Thomas and Harvey fits in naturally with the chapter on renin, given that angiotensin, and elevated plasma K^+ concentrations are two prominent but distinct physiological stimuli for aldosterone release. The chapter describes the process by which aldosterone induces the rapid nongenomic activation of cascades that express the mineralocorticoid receptor in various tissues, including the renal tubules, its primary site of action.

Traditional teaching of the role of gut microbiota to students of human physiology has often been confined to the process of gut fermentation in the large intestine and the importance of fermentation products in maintaining a healthy epithelial lining. Gut flora, do, of course, play additional roles in immunity, regulation of the development of the gut, prevention of the growth of harmful pathogenic bacteria and in the provision of several micronutrients. More recently, work has focused on the potential role of the gut microbiota on regulating digestive processes and in the genesis of



Immunostaining of an idiopathic pulmonary fibrosis (IPF) lung biopsy for prosurfactant protein C (SPC) (red) and N-cadherin (green). The photograph illustrates the presence of both an epithelial (SPC) and a mesenchymal (N-cadherin) marker in cells within the interstitium. The collection of cells is separated by a thin interface (white line) that likely indicates their origin in prior alveolar collapse. The residual SPC staining (arrows) along with N-cadherin expression indicate epithelial–mesenchymal transition.

overweight/obesity. This is part of the focus of the chapter 'Ecological physiology of diet and digestive systems' by Karasov *et al*. The authors provide an overview of the evidence that suggests that diet and the characteristics of the microbiome appear to be correlated. For example, using the strategy of comparative physiology, it has been determined that bacterial diversity in the gut is lowest in carnivores, intermediate in omnivores and highest in herbivores. In most animals with well-developed microbiotas, diet changes are accompanied by changes in microbiome composition, diversity and function. Human obesity appears to be associated with lower phylum-level diversity in the microbiome.

Environmental impacts on respiratory function are dealt with in two separate chapters. Cigarette smoking is responsible for lung cancer and chronic obstructive pulmonary disease (COPD), among other problems. There are, however, no tools currently that predict the risk of developing these diseases at an individual level. The chapter 'Interaction of cigarette exposure and airway epithelial cell gene expression' by Brody and Steiling reviews data that measure global gene expression in epithelial cells in the airways to address this issue. The chapter 'The lung: the natural boundary between nature and nurture' by Seibold and Schwartz discusses the recent advances in knowledge and technology on the role of genetics, the environment and gene–environment interactions in the genesis of common lung diseases such as asthma, COPD and lung fibrosis.

The 'special topic' in the current volume focuses on thrombosis. 'The link between vascular features and thrombosis' by Charles and Naomi Esmon discusses the anticoagulant properties of the vascular endothelium, particularly in the microcirculation, which is characterized by a high ratio of endothelial cells to blood. The impact of inflammation and stasis on anticoagulation pathways in the endothelium is reviewed. Venous thromboembolic disease is a major cause of morbidity and mortality across the globe. In the other two chapters devoted to the discussion of thrombosis, Manly *et al*. discuss the 'Role of tissue factor in venous thrombosis', while Bovill and van der Vliet focus on the role of the venous valves in the genesis of a thrombus in the chapter entitled 'Venous valvular stasis – associated hypoxia and thrombosis: what is the link?' In both chapters, the authors discuss the molecular pathways involved in venous thrombosis and outline potential therapeutic targets that could lead to the prevention and treatment of venous thromboembolism.

This volume, like its predecessors, continues to have a wide appeal. The chapters cover a large part of the broad canvas of physiology. The approaches in the chapters are varied – some are more clinical and human, others more cellular in their content with comparisons across species. However, all provide readable material that would address the needs of a range of physiologists. For the student of physiology, the book is indispensable. For more focused researchers, the *Annual Review* provides a rapid overview of the advances in physiology across multiple systems. For me, the *Annual Review* has always been something to look forward to – this issue does not disappoint.

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The topics covered in this volume can be broadly categorized into five areas: inflammatory responses, humoral or B cell responses, T cell biology, immune regulation and autoimmunity.

This volume starts off with an insightful observation by Max D. Cooper about the status of biomedical research these days: 'One of the most remarkable things about a career in biomedical research is that one can start almost anywhere and end up in the most unforeseen places, being constantly amazed by what you are learning along the way.' Cooper talks about his training as a doctor and his bewildering entry into immunology research. He recalls a talk by Linus Pauling on the structure of the antibody molecule, which is revealing of Pauling and times in those days: 'If I couldn't find out how monovalent Abs work, I figured God wouldn't either'. Cooper's use of diverse animals (chickens, frogs, rabbits, lampreys, etc.) to answer immunological questions is impressive. He has made several contributions, and the three main ones are: First, the identification of the bursa of fabricius as the site for B cell development and antibody production in chickens. Subsequently, efforts to find the bursa equivalent in mammals led to the identification of the mammalian hematopoietic tissue as sites where B cells are generated. Second, the demonstration that lymphocytes belong to at least two distinct categories: B cells (humoral response) and T cells (cellular response). These studies have implications for patients with immunodeficiencies. For example, patients suffering from Bruton's X-linked agammaglobulinemia are deficient in B cell differentiation and immunoglobulins, whereas those suffering from DiGeorge's syndrome have a deficient cellular immune response, but Ig amounts are not affected. Third, identification of mammalian equivalents of the adaptive immune system, i.e. B cell receptors (BCRs), T cell receptors (TCRs) and major histocompatibility complex-encoded molecules (MHC). Also several diverse leucine-rich repeat (LRR) sequences were identified in jawless vertebrates. Unlike the more evolved jawed vertebrates, jawless vertebrates use variable lymphocyte receptors (VLRs) comprising LRR sequences. In these cases, the VLR gene flanks hundreds of LRR coding sequences and VLRs are assembled by a gene-conversion process mediated by activation-induced cytidine deaminase (AID). Most interestingly, VLRA and VLRB are on distinct populations representing the counterparts of T and B cells.

Among the topics discussed is the inflammatory response, which results in redness, heat, swelling, pain and pus, and is well known to be involved in the immune response. However, it is a double-edged sword: defects in this pathway result in increased susceptibility to infections, whereas too much of a response leads to tissue/organ damage in the host. Microbial components, e.g. lipopolysaccharides are well known to activate this response; however, the role of endogenous activators of this pathway, e.g. urate crystals, dead cells, cholesterol crystals, etc. is emerging. In particular,