THE KIDNEY

Physiology and Pathophysiology

Second Edition

Volume 2

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To the memory of
John P. Peters and Robert F. Pitts
for their distinguished roles as
educators and investigators.

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Preface to the First Edition

Before the Second World War, an understanding of kidney function in broad outline had gradually emerged. The filtration–reabsorption theory formulated by Cushny and based on earlier proposals by Ludwig was placed on firm footing by the pioneering micropuncture studies of Richards, Wearn, Walker, and their associates. Marshall and his school, resurrecting the earlier views of Heidenhain, demonstrated the participation of tubular secretion in urine formation. It became clear that three processes, glomerular filtration, tubular reabsorption, and tubular secretion mediated the urinary excretion of water and electrolytes.

Two great methodologic advances facilitated the translation of this conceptual framework into quantitative terms. Smith, Rehberg, and their associates successfully elaborated and then applied noninvasive techniques to the measurement of renal hemodynamics in both animals and human subjects. As a consequence, it became possible to assess quantitatively glomerular filtration rate, renal blood flow, and tubular secretion under normal and abnormal circumstances. At the same time, Peters and Van Slyke developed and consolidated a precise methodology for measurement of the composition of body fluids and urine.

The initial studies emanating from these conceptual and methodological developments were utilized principally for a static portrayal of the chemical composition of body fluids and urine. The function of the kidney as a regulatory organ governing the maintenance of the volume and composition of body fluids was only dimly perceived. The mechanisms responsible for the adjustments of renal function under the impact of physiologic disturbances or frank disease states were almost wholly unknown. In part, this focus on chemical anatomy was the inevitable expression of technical limitations: Analytic methods were painfully cumbersome and time-consuming, and usually required substantial amounts of material; furthermore, many critical constituents simply could not be measured. In part, this narrow preoccupation with static steady state measurements reflected the relatively primitive conceptual system: The kidney was conceived in the main as a black box, so that input in the form of glomerular filtration and output as urine flow constituted the principal analytic framework.

It was the application to biologic systems of the methods and principles of the generalizing sciences, physics and chemistry, after World War II, that transformed renal physiology from a crude empirical enterprise into a formidable discipline of explanatory power and technical sophistication. Powerful analytic methods—typified early by the flame photometer and later by sensitive micromethods involving isotopes, microchemistry, immunoassay, microelectrodes, electron microscopy, optics, nuclear magnetic resonance, and the like—paved the way for truly novel advances. At first, the newer analytic armamentarium was utilized by Albright, Peters, Pitts, and many others in balance and clearance studies to investigate the adaptations in renal function under the impact of physiologic and pathologic derangements. Then, the reintroduction of micropuncture and the development of microperfusion of isolated tubules permitted an assessment of segmental function which Richards and his associates, a decade earlier, had just begun. At the same time, the introduction by Ussing and his associates of an isolated two-membrane epithelial system, the frog skin, provided an enormously fruitful model for the exploration of the transport properties of the renal tubule. Later still, the study of membrane vesicles *in vitro*, coupled with micromethods of exquisite sensitivity, permitted the formulation of principles of cellular and epithelial function. As a result, the investigation of renal physiology could progress from the analysis of the whole organ to the level of the nephron and finally to the basic domains of epithelial and cellular function. The fundamental mechanisms underlying changes in overall renal function were now available for study and began to provide a conceptual framework for powerful theories of renal regulation.