I. INTRODUCTION

The goal of this chapter is to chart procedures for identifying endothelial transport pathways and mechanisms for water and solutes. An excellent description of the discovery of the microcirculation, of the identification of the capillaries as the main sites of interchange of fluid and solutes, and of the development of the concept of capillary permeability has been written by E. M. Landis. In the first half of this century, it was recognized that capillaries in most organs of the body allowed relatively free exchange of water and small solutes (crystalloids), but restricted the escape of plasma proteins and other macromolecules (colloids). In 1896, Ernest Starling explained the retention of vascular volume as the result of a balance of the osmotic pressure of plasma colloids and the hydrostatic pressure of capillary blood. Imbalance of hydrostatic and colloid osmotic forces results in fluid movement into or out of the bloodstream. This process is called ultrafiltration. The fluid moved (ultrafiltrate) contains water and small solutes in equilibrium with plasma, but only traces of plasma proteins. The direction and rate of fluid movement are proportional to sign and magnitude of the difference between hydrostatic and effective osmotic forces (positive = outward). Exchange of water and solutes smaller than plasma proteins was attributed to passive diffusion. Differences in capillary permeability from organ to organ were recognized: the capillaries of the brain were known to be nearly impermeable to ions and small molecules, while the sinusoids of the liver and spleen were known to be permeable to plasma proteins. It was also recognized that capillaries in most organs allowed small ("trace") amounts of plasma proteins to escape into the interstitial fluid, and that the lost protein was returned to the bloodstream by the lymphatics.

Knowledge of endothelial structure before 1950 was limited by the resolution of light microscopy: in capillaries of most organs, a layer of thin cells on a basement membrane; in brain capillaries, thicker cells; in liver and spleen sinusoids, large openings between cells, with an incomplete basement membrane. Compar-
isions of capillary permeability with that of epithelial membranes drew attention to the possible role of intercellular junctions as pathways for substances which could not penetrate the cells themselves. Chambers and Zweifach\(^5\) suggested that the junctions were filled with a gellike "intercellular cement" which acted as a molecular sieve.

II. THE "PORE" THEORY OF CAPILLARY PERMEABILITY

It was from this background that a simple, passive, geometrically defined model of capillary transport was developed by Pappenheimer and his collaborators.\(^{26,33,34,43,47}\) Their model was based on experimental measurements of capillary ultrafiltration and diffusion, and analysis by then-current physicochemical theories of fluid movement and molecular diffusion. The physiological evidence on which the original pore model was based may be summarized as follows:

1. The osmotic effects of lipid-insoluble solutes are graded with respect to the size of the transported particles (molecules or ions). Small solutes which penetrate capillary walls exert a transient osmotic influence on fluid movement which increases in magnitude and duration as molecular size increases, approaching full osmotic pressure and lasting effect for serum albumin and larger molecules.

2. Transcapillary diffusion rates of such lipid-insoluble molecules are similarly graded with respect to molecular size. The time constants of decay of osmotic effect and transcapillary diffusion rate are the same.

3. Small lipid-soluble molecules have smaller shorter-lasting osmotic effects, and diffuse faster than lipid-insoluble molecules of similar size.\(^{41,42}\)

Because of the close parallelism of transient osmotic effects and diffusion rates for lipid-insoluble solutes, Pappenheimer and his colleagues concluded that the pathways used for ultrafiltration and diffusion were the same. Because these effects were dependent on molecular size, they concluded that these pathways acted as a molecular sieve, offering progressively increasing resistance to permeation of larger molecules, reaching a cutoff at the size of serum albumin. They identified this pathway with the endothelial cell junctions. They attributed the faster diffusion of small lipid-soluble molecules and their weaker osmotic effects to the ability of these substances to penetrate the endothelial cell lipid membranes, as well as through the junctions.

Pappenheimer et al.\(^{34}\) modeled the junctional pathways as uniform cylindrical pores through the intercellular cement of the junctional regions, or as long slits between the cells. Applying hydrodynamic theory (Poiseuille's law for circular pores or its equivalent for parallel-walled slits) and diffusion theory (Fick's law) to their measurements of fluid and solute transport rates in isolated, blood-perfused hindlimbs of cats, they were able to calculate an effective pore diameter or slit width for the capillary membrane, and to estimate the total cross-sectional