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Editorial Focus

ESSAYS ON APS CLASSIC PAPERS

Microvascular permeability, ultrafiltration, and restricted diffusion

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This essay looks at the historical significance of two APS classic papers that are freely available online:

Pappenheimer JR and Soto-Rivera A. Effective osmotic pressure of the plasma proteins and other quantities associated with the capillary circulation in the hindlimbs of cats and dogs. *Am J Physiol* 152: 471–491, 1948 (http://ajplegacy.physiology.org/cgi/reprint/152/3/471).

Pappenheimer JR, Renkin EM, and Borrero LM. Filtration, diffusion and molecular sieving through peripheral capillary membranes: a contribution to the pore theory of capillary permeability. *Am J Physiol* 167: 13–46, 1951 (http://ajplegacy.physiology.org/cgi/reprint/167/1/13).

FOR ANYONE WANTING TO LEARN about microvascular permeability, ultrafiltration, and the restricted diffusion of solutes through intercellular spaces and membrane channels, two papers by John Pappenheimer (Fig. 1) and his colleagues that were written over 50 years ago (5, 6) are of more than historical interest. While their importance derives from the ideas they introduced, they are both models of scientific writing and contain comments and observations that continue to stimulate thinking.

It is best to read the papers in the order in which they were published, for the second paper starts as a sequel to the first. The first paper (6) is concerned with Starling's hypothesis. Before 1948 this was widely accepted to account for blood-tissue fluid balance but was supported by few direct observations in mammalian vascular beds. The missing evidence is provided by Pappenheimer and Soto-Rivera. It builds on the argument that the mean capillary pressure is related to the arterial and venous pressures through the ratio of precapillary to postcapillary resistances. The authors show that the pre- and postcapillary resistances can be estimated in isolated perfused hindlimbs. In these preparations, net fluid movements between the blood and tissues are directly proportional to the difference between mean capillary pressure and the osmotic pressure of the plasma proteins. There is great attention to experimental detail, and after the principal results are described, other subsidiary observations are reported. One cannot read the paper and not feel confident about its conclusions.

The 1951 paper (5) is even more comprehensive. It is the first successful attempt to relate physiological measurements of permeability to the structure of microvascular walls. It is also the first comprehensive theoretical analysis of diffusion and convection of solutes through channels of molecular dimensions. Using a simple model of permeability pathways as uniform cylindrical pores penetrating an otherwise impermeable membrane, the authors proceed to calculate the fractional area of microvascular wall occupied by the pores. Two estimates are made. The first is based on comparisons between filtration coefficients in capillary walls and those of collodion membranes. The second is derived from estimates of permeability of hindlimb capillaries to a series of hydrophilic solutes of differing molecular size. Both approaches indicate that the pores need occupy only 0.2–0.02% of the area of the capillary walls. This was the first quantitative evidence supporting the hypothesis (1) that permeability to hydrophilic solutes is restricted to the intercellular regions.

Even more impressive at the time were the estimates of pore radii in capillary walls. Two approaches were used, and they both yielded values for pore radii in the range of 3–4 nm, i.e., consistent with capillary walls retaining serum albumin and larger plasma proteins.

The measurements of permeability revealed that the fractional area available for exchange decreased as the size of the diffusing molecule increased. This led to the theory of restricted diffusion, an enormous achievement, which is devel-

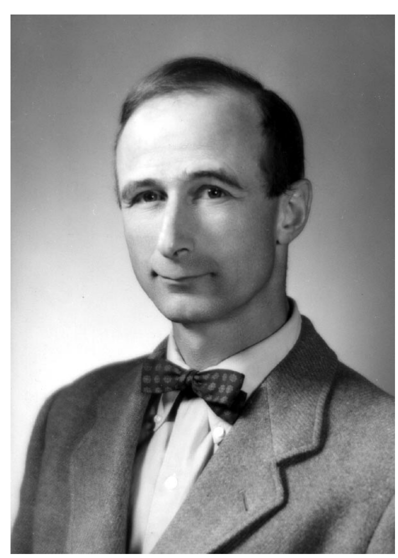

Fig. 1. John R. Pappenheimer.

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oped in the next section of the paper (5). There are later sections on the diffusion and convection of larger molecules and a discussion that points out the importance of lipoid solubility for oxygen (showing that its exchange cannot be confined to intercellular regions) and a note pointing out errors in estimating vascular permeabilities to Na^+ and Cl^- from plasma disappearance curves.

It is remarkable how much is achieved here, and while this was widely recognized, the paper (5) soon became the center of controversy. In 1951, the year it was published, Staverman (12) argued that solutes exert their full osmotic pressures (i.e., those predicted by van't Hoff's law) only across membranes to which they are impermeable. If solutes penetrate a membrane, they exert a fraction of their full osmotic pressure, that fraction being the reflection coefficient. Pappenheimer et al. (5) had used van't Hoff's law to calculate transcapillary concentration differences across capillary walls from transient osmotic pressures as solutes equilibrated between the perfusate and tissues. If reflection coefficients to permeating solutes were considerably less than unity, concentration gradients had been underestimated and the permeabilities to small molecules overestimated. This criticism did not affect the conclusion that porous area occupied only a tiny fraction of capillary walls, but it did compromise one of the calculations of pore radius. Discussion of this point continued for over 25 years (4, 7, 9). During this period the role of nonequilibrium thermodynamics in biological transport processes was clarified, and at the same time, the lasting importance of Pappenheimer's contribution was established (2).

After half a century, the legacy of these two papers (5, 6) is enormous. Quite apart from stimulating both experimental work and thinking on fluid exchange in different tissues (3), the separation of vascular resistance into precapillary and postcapillary components in the first paper (6) soon influenced studies on the regulation of the peripheral circulation. The current picture of vascular resistance consisting of many components, each of which may be independently regulated, dates from this paper.

The second paper (5) has had an even greater influence. The theory of restricted diffusion received support from measurements on artificial membranes, first by Renkin (8), who as Pappenheimer's graduate student had made many of the measurements that led to its conception, and later by investigators working on membranes that have structurally identifiable pores (2). The pore hypothesis itself has been developed (2) and is widely used today not only by physiologists and physicians as a very convenient way of describing microvascular permeability, glomerular filtration, etc. (10), but also by engineers to describe properties of artificial membranes. Pore theory is also used to develop new strategies for managing patients undergoing renal and peritoneal dialysis (11). Its lasting value is not that it is correct in the sense that biological membranes are indeed made of impermeable material penetrated by cylindrical pores but rather that it offers a functional understanding of passive transport processes in terms of a structure that can be immediately understood.

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