PATHOBIOLOGY OF THE ENDOTHELIAL CELL

Edited by

HYMIE L. NOSSEL

HENRY J. VOGEL

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New York, New York

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Preface

A harbinger of endothelial pathobiology can be seen in Lister's 1865 paper on the role of vessel wall injury in promoting blood clotting. Despite this early interest in the vessel wall, studies of hemostasis and thrombosis tended to focus on the fluid phase and on platelets which were described by Bizzozero just 100 years ago. Only rather recently have components of the vessel wall begun to attract the attention they seem to deserve in the context of hemostasis and thrombosis as well as of such areas as atherosclerosis and pulmonary function. Now, research on the endothelium and on the remarkable and versatile endothelial cell is increasing dramatically.

A symposium on the "Pathobiology of the Endothelial Cell" was held at Arden House, on the Harriman Campus of Columbia University, from June 5 through June 7, 1981. The meeting was the sixth of the P & S Biomedical Sciences Symposia. The proceedings are contained in this volume. Dr. Donald F. Tapley, Dean of the College of Physicians and Surgeons (P & S), which sponsors the symposia, welcomed the participants.

We are grateful to George E. Palade for his delivery of the Opening Address. The contributions of the session chairmen, Dr. Judah Folkman, Dr. John C. Hoak, Dr. Salvador Moncada, Dr. Ralph L. Nachman, Dr. David Shepro, and Dr. Gerard M. Turino, are acknowledged with much appreciation. A session was also chaired by one of us (H. L. N.).

Several colleagues from P & S, Dr. Vincent P. Butler, Jr., Dr. Robert E. Canfield, Dr. Shu Chien, Dr. DeWitt S. Goodman, and Dr. Turino, kindly agreed to serve as honorary hosts.

Many thanks go to Dr. Ruth H. Vogel for her contributions to the organization of the symposium and the preparation of this volume.

Hymie L. Nossel
Henry J. Vogel

Opening Address

Differentiated Microdomains in the Vascular Endothelium

George E. Palade, Maia Simionescu and Nicolae Simionescu

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The vascular endothelium is a simple, squamous epithelium differentiated for rapid exchanges between the blood plasma and the interstitial fluid. Its permeability to water and small, hydrophilic solutes is 2 to 3 orders of magnitude higher than that of any other epithelium in a mammalian body, and its high permeability to large molecules is unique—the only possible exception being the mesothelium of the peritoneal and pleural cavities.

The structural basis of these unusual properties consists of (a) extreme attenuation to less than 300 nm in the highly functional parts of the endothelial cells, (b) simplified intercellular junctions, and (c) special, differentiated structural features such as plasmalemmal vesicles present in high volume density in all endothelia, transendothelial channels (that occur only in low volume density) in the endothelial cells of the microvasculature, and diaphragmed (or apertured) fenestrae restricted in their distribution to the capillary endothelium of glands and visceral mucosae.

STRUCTURAL SUBSTRATE OF CAPILLARY PERMEABILITY

In characterizing vascular permeability, it has been assumed that the determining parameter is simply the size of the permeant mole-

cule, expressed as effective molecular radius (1). Evidence implicating the net charge on the molecules as an effective parameter has been limited (2) and largely disregarded. Physiological data on capillary permeability are currently explained in terms of two postulated pore systems, or water-filled channels cutting all the way across the endothelium. Small pores ($r \simeq 6$ nm, surface density $\simeq 15$ μm^2 or much less in some estimates) would account for the high permeability for small- and medium-size molecules, and large pores ($r \simeq 25$ nm; surface density $\simeq 0.05$ μm^2) could explain the unusual permeability of the endothelium for macromolecules (3,4).

In spite of a substantial amount of work carried out in many laboratories over the last 20 years, there is still no agreement concerning the structural equivalents of the two pore systems, primarily their possible relations with the large population of plasmalemmal vesicles involved in transcytosis or diacytosis from the blood to the tissue front of the endothelium. Our findings indicate that these vesicles, which have an average inner diameter of ~27 nm, function in the transport of water and small and large hydrophilic molecules, their contribution being particularly important in macromolecular transport. In this respect, they could be considered as an equivalent of the large pore system; they are different, however, from the original concept in the sense that they represent discontinuous transport devices rather than continuous channels. In addition, plasmalemmal vesicles generate transendothelial channels at low surface density (5). These channels could function as small pores when provided with stomatal diaphragms or structures that limit the movement of molecules of radius larger than ~10 nm or as large pores when such limiting structures are absent. An alternative location for small pores (of slit rather than cylindrical conformation) along intercellular junctions has been postulated by other investigators (6,7,14), but our results indicate that the junctions are not detectably permeable to molecules of radius >2 nm in the endothelium of the blood capillaries (the situation is different in the venular endothelium).

In capillaries provided with a fenestrated endothelium, plasmalemmal vesicles and transendothelial channels function as described above, whereas the fenestrae could act as either small or large pores according to the limits imposed by the texture of their fenestral diaphragms. For a more extensive review of the current status of structural–functional correlations in the vascular endothelium, the reader could consult references (8) and (9). It should be clear that more work is needed for achieving general agreement in this field of research.

SURFACE CHEMISTRY OF THE VASCULAR ENDOTHELIUM—DIFFERENTIATED MICRODOMAINS

In the meantime and prompted by results obtained on renal glomerular capillaries (10,11), we decided to survey the surface chemistry of the vascular endothelium in a capillary bed in which structural differentiations connected with blood–tissue exchanges, e.g., plasmalemmal vesicles, transendothelial channels, and fenestrae, occur at a high surface density. Such capillary beds are found in the pancreas and the intestinal mucosa. In these capillaries, the size and charge diffusion barrier must be located in the endothelium proper, in contradistinction with glomerular capillaries in which both barriers are in the glomerular basement membrane.[1]

Two different protocols were used. In the first, a cationic probe (cationized ferritin, pI = 88.4, r = 5.5 nm) was injected directly into the systemic circulation of mice, and specimens (pancreas and intestine) were fixed *in situ* at intervals ranging from 30 sec to 24 hr after injection. In the second protocol, the vasculature of the pancreas and intestine was perfused in sequence with a tissue culture medium (to remove the blood), with the tracer in the same medium, with the medium alone (to remove excess tracer), and finally with a buffered[2] mixture of glutaraldehyde (3%)–formaldehyde (5%), to fix *in situ* the cationic probes still attached to the endothelium. Over short intervals, the results obtained in the two types of experiments were similar, but the probes could be visualized more clearly in perfused specimens rather than in intact animal experiments, since in the former the background given by fixed plasma proteins was absent. In both cases, the first structures to bind the cationic probe were the fenestral diaphragms. They were the only structures decorated at time 0 to 30 sec. They were also the last to lose the cationic probe decoration after ~20 hr in intact animal experiments (perfusion experiments were not carried out for longer periods than 60 min). The plasmalemma proper became decorated almost as rapidly, though less heavily than the fenestral diaphragms (Figs. 1 and 2), but it lost the label by ~4–7 hr in intact animals. Hence, it can be concluded that the surface density of anionic sites as well as their affinity for the cationic probe are higher on the fenestral diaphragms than on the plasmalemma proper. In con-

[1] The fenestrae of the glomerular endothelium are large (~100 nm) and have no diaphragms. At their level, the blood plasma is in direct contact with the glomerular basement membrane.

[2] 0.1 *M* HCl–Na cacodylate or HCl–Na arsenate buffer, pH 7.2–7.4.

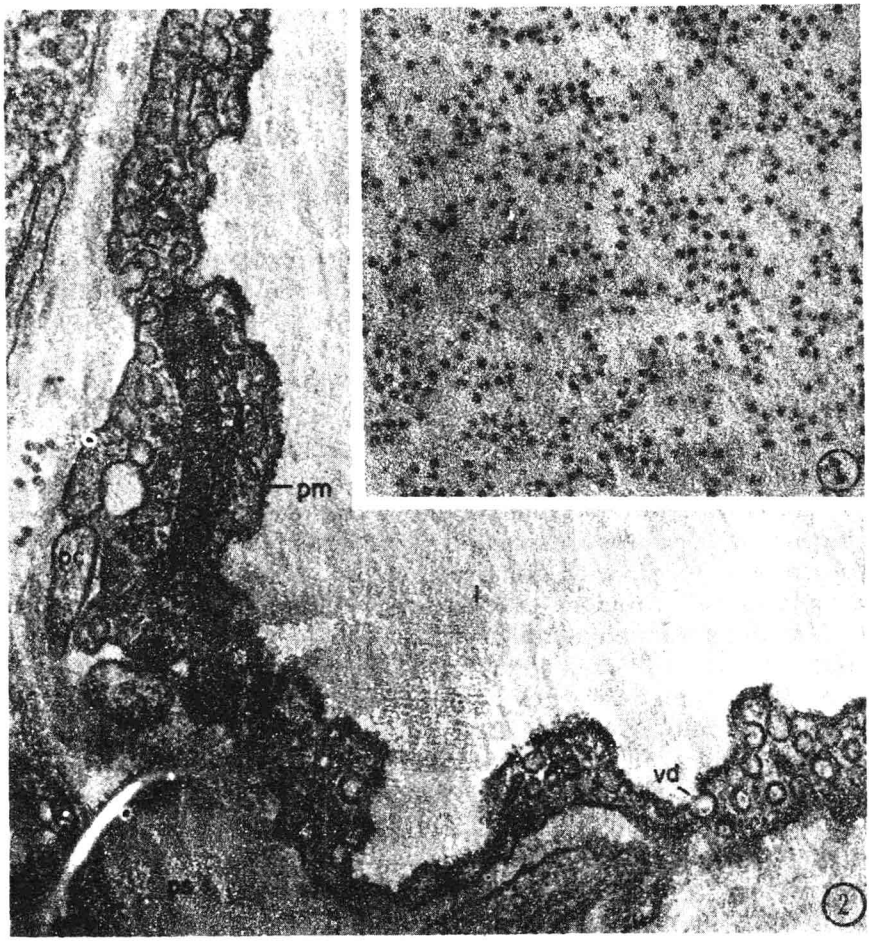

Fig. 1. Cationic ferritin molecules in the tracer solution: the molecules, in their majority, appear randomly and individually dispersed. ×140,000.

Fig. 2. Mouse pancreatic capillary, 30 sec after *in situ* perfusion with CF. The ligand decorates almost continuously the plasmalemma proper (pm); it appears in characteristically high concentration on fenestral diaphragms (f), but it does not decorate the membrane or diaphragms (vd) of plasmalemma vesicles. (e) endothelium; (l) lumen; (bm) basement membrane; (pc) pericyte; (ps) pericapillary space. ×48,000.

tradistinction to these structural elements, plasmalemmal vesicles, transendothelial channels, and (when present) their stomatal diaphragms remained unlabeled throughout the duration of the experiments (Figs. 3 and 4). In addition to plasmalemmal vesicles, the endothelial cells examined have a small population of coated vesicles. The latter bound the cationic probe shortly after the beginning (Fig. 3) of the experiments and retained it longer than the plasmalemma proper. For further details concerning the experimental protocol and the description of the results (especially after late intervals in intact animals), the reader should consult reference (13).

The findings presented so far indicate clearly that the endothelial

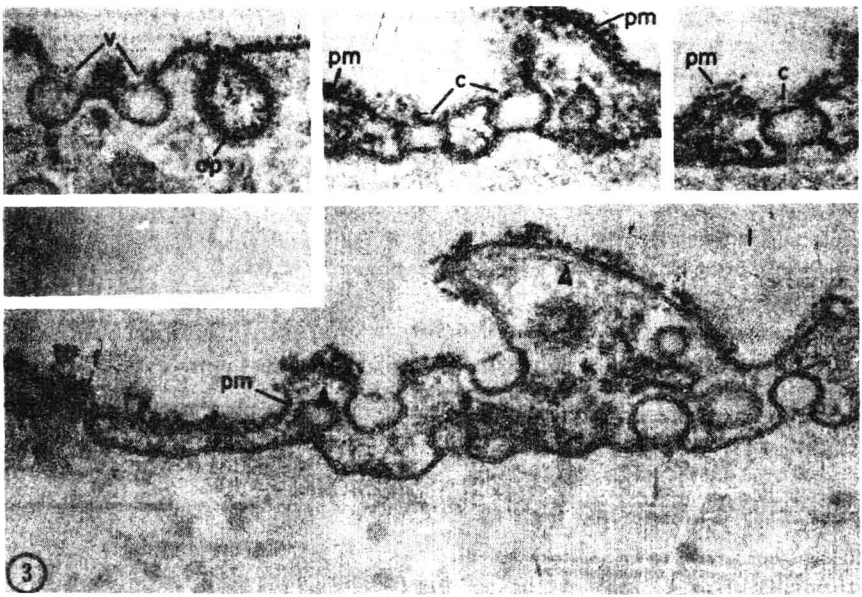

Fig. 3. Mouse pancreatic capillary 1 min after *in situ* perfusion with CF. The ligand is densely bound to an (f) and, to a lesser extent and with some discontinuities, to the pm. It is absent from the membranes of plasmalemma vesicles and their associated diaphragms (v). A grazing section through a labeled coated vesicle or pit appears at cv. Note the accumulation of fibrillar material beneath the regions of the plasmalemma to which CF is bound (arrowheads). × 65,000. *Right inset:* this micrograph illustrates the striking difference between the intense labeling by CF of a coated pit (cp) (in this case, in its course of internalization) and the absence of CF decoration from the membranes and the diaphragms of two adjacent plasmalemma vesicles (v). × 85,000. *Left insets:* details of CF decoration in a mouse pancreatic capillary 1 min after a CF injection *in vivo*. The membranes and diaphragms of transendothelial channels (c) are not labeled by CF whereas the pm is labeled. ×85,000.

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