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LETTER TO THE EDITOR

BASIC CONTRIBUTIONS TO LYMPHOLOGY

In my Letter to *Lymphology* (1), there was an error in the text. Starting on line 17 the text should properly read "lymph arises initially from mesenchyme in the form of separate plasma-filled spaces wherein red blood cells become suspended; *and that the primitive blood vascular system arises by coalescence of such plasma filled spaces when the definitive heart becomes established to propel the flow of plasma containing suspended red blood cells.*"

In the invertebrates, the mesenchyme does not produce red blood cells and there is no sharp division between the blood vascular and lymphatic systems. In those species where mesenchymal cells or derivatives give rise to free extracellular pigments, such as chlorocrurins or hemocyanins to facilitate oxygen transport, a lymphatic system or "hemolymph" system develops, with usually anterior and posterior lymph hearts propelling lymph forward. What is most important is that Sabin (2), Kampmeier (3), and others (4) recognized that mesenchyme, not endothelium, is the entity from which vessels, support for the vasculature, as well as its liquid plasma and suspended cellular elements, are derived throughout embryogenesis and phylogenesis.

It is cogent to see the elegant studies of Castenholz (5) on the initial lymphatics of the Wistar rat tongue in the same issue of *Lymphology*. He emphasized that fibrillar organization of the extracellular matrix (ECM), another derivative of local mesenchyme in each portion of the body, is what enables the peripheral lymphatics both to transmit and prefilter lymph. I was especially pleased to see that he mentioned the differences in organization of the ECM in different vascular beds, such as the liver and kidneys, and that he referred to Azzali's studies on migration of mononuclear cells through the ECM into lacteals.

On the same day I received my "reprints" from *Lymphology*, I received a copy of *Nature*, which featured an article by Secor and Diamond (6) on alimentation in Burmese pythons. Essentially, they showed a 600% increase in intestinal villus length and a 220% increase in gut mucosal mass after feeding, along with a 50-80% increase in stomach, lung, heart, pancreas, liver, and kidney mass. These findings were associated with up to a 44-fold increase in oxygen consumption, largely owing to the specific dynamic action of ingested proteins. The more or less comparable figures for humans and rats are gut mucosa + 58%, spleen + 35%, remaining body organs <10% after with alimentation 48 hours starvation (4,7). Thus, postprandial hypertrophy and hyperplasia and subsequent involutional changes between meals in the mesenchymal elements in gut mucosa, including the stromal cells, endothelium and lymphoid cellular elements, along with the columnar epithelial cells, is a homeostatic phenomenon that is often underestimated. In a sense, lacteals are not only the principal sources of milky lymph every time we eat, but also the primary lymph hearts whose shortening via smooth muscle contractions pumps nutritious lymph into the systemic circulation with every meal thereby sustaining homeostasis ad infinitum.

From a structural and hydrodynamic point of view, it seems noteworthy that the ECM although variable with time and with special adaptations in differing organs, forms the ground substance which supports all

living parenchymal and mesenchymal cells separated into definitive tissues (4). As shown by Sabin and Kampmeier (2,3), parts of the mesenchyme ("middle juice") dissolve to produce lymph-filled spaces which coalesce with the onset of flow to produce vessels lined by progressively flattened mesenchymal cells called endothelium. Because the ECM and ground substance between living cells consist largely of water variably bound by highly polymerized low molecular weight glycoproteins (glyco-aminoglycans), one can expect dissolution to give rise to sols in the form of liquid lymph with relatively great colloid osmotic effect compared with the globulin-rich sols which arise by clasmatosis from mononuclear mesenchymal cells (4,7). Fig. 12 in Castenholz' article (5) clearly shows precipitated ECM entering an initial lymphatic.

From a bioenergetic point of view, all living mesenchymal and parenchymal cells in vertebrates require oxygen and glucose in order to grow and function. Under aerophilic conditions, each cell normally oxidizes one molecule of glucose to produce six molecules of water and six molecules of water-soluble carbon-dioxide, plus energy transferred via variably bonded phosphate to a variety of nucleotides which supply the energy as well as some of the substrate to mold the structure, function and rate of growth of each cell. Thus, in addition to the water absorbed via the gut epithelium and that which filters from blood capillaries, the water and energy produced from the oxidation of glucose in each living cell is a factor in the production of definitive protoplasm, the secretion of definitive products, and performance of definitive functions within the ECM of each definitive organ. The heart and blood vascular systems are responsible for distributing adequate water, oxygenated blood, glucose and dissolved nutrients to the mesenchymal and parenchymal cells of each organ. However, after the egg yolk is largely absorbed from the gut entoderm of each vertebrate embryo and placental connections are severed in mammals, each host with a cartilagenous or bony backbone depends on the residual gut entoderm, the gut mesenchymal components, the lacteals, ECM and mesenchymal mononuclear cells (which evolute with feeding and involute with starvation) to nourish the rest of the body via effluent lymph which flows to become the plasma in circulating blood (see Claude Bernard, 8). Apart from the gut, it is the coordinate evolution of local mesenchymal cells into stromal elements, ECM, sessile and motile mononuclear cells and endothelium which allows each parenchymal cell not only to function and contribute its special attributes or definitive products toward maintenance of homeostasis throughout the body, but also help control coordinate cell growth in the remaining cells by donation of sequenced phosphorylated nucleotides, or induction of apoptotic lysis of cells whose DNA is recognized as foreign or genetically incompatible (4).

REFERENCES

1. Shields, JW: Letter to the Editor. Lymphology 31 (1998), 141.
2. Sabin, FR: Preliminary notes on the differentiation of angioblasts and methods by which they produce blood vessels, blood plasma, and red blood cells as seen in the living chick. Anat. Rec. 13 (1917), 199-204.
3. Kampmeier, OF: *Evolution and Comparative Morphology of the Lymphatic System.* Thomas, Springfield, 1969.
4. Shields, JW: *The Trophic Function of Lymphoid Elements.* Thomas, Springfield, 1972.
5. Castenholz, A: Functional microanatomy of initial lymphatics with special consideration of the extracellular matrix. Lymphology 31 (1998), 101-118.
6. Secor, SM, J Diamond: A vertebrate model of extreme physiologic regulation. Nature 395 (1998), 659-662.
7. Shields, JW: Intestinal lymphoid tissue during absorption. Am. J. Gastroenterol. 50 (1968), 30-36.
8. Bernard, C: Leçons sur les Phénomènes de la Vie Communs Aux Amimaux et Vegetaux. Paris, Baillière, 1878.

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