Cytoclasmosis in Central Lymph Production

J.W. Shields

Department of Medicine and Hematology, Santa Barbara Medical Foundation Clinic, Santa Barbara, California, U.S.A.

Summary

Electron microscopic observations and ancillary data are reviewed to show that lymphatic organs produce quantities of central lymph by releasing cytoplasm-depleted cells into colloidal hydrosols produced by cell fragmentation (cytoclasmosis).

Peripheral lymph usually poor in cells and proteins, is produced principally by filtration from arterovenous capillaries, but regionally contains characteristic proteins from parenchymal cells, such as enzymes, hormones, lipoproteins or antigens which induce sensitization if tissues are transplanted (1). The purpose of this review is to show with electron photomicrographs that organized lymphatic tissues not only filter peripheral lymph, but also contribute substantially to the production of cell- and protein-rich central lymph by cytoclasmosis.

The term *cytoclasmosis* (Gr. KYTOS, cell; KLASMA, fragment, and OSIS, -ation) connotes cell fragmentation, and was originally used by *Ranvier* (2) to describe how large mononuclear phagocytes (*"clasmatocytes"*) excrete that which they have ingested and digested. Because the term *macrophages* (popularized by *Metschnikoff* [3]) came into common use; and because large lymphocytes (4-13), plasmacytes (5-6, 10-11, 14, 18-19), monocytes (5-6, 10), macrophages (5-6, 10, 16), and reticular cells (5-6, 10-11, 16) have been observed to undergo fragmentation in organized lymphatic tissue (and in tissue culture [11, 17-19]) the term *cytoclasmosis* will be used here to describe the frag-

mentary process in such cell types, and the term *cytoclasmids* will be used to describe the fragments originating from such cells. Others have called such fragments hyaline bodies (5-6, 10), cytoplasmic bodies (9), burgeons (11), cytoclasmatats (11), lymphoglandular bodies (12), leptons (13), cytoplasmic portions (17), cytoplasmic processes (20), buds (21), blebs (22), cytoplasmic droplets (23) and globulines (24).

Material and Methods

Organized lymphatic tissues (thymus, avian cloacal bursae, nodes, tonsils, Peyer's patches and diffuse intestinal lymphatic tissue) and lymphoid tissues (spleen and marrow) obtained surgically from variously aged, anesthetized, healthy, untreated ducklings, rats and humans were fixed promptly in Karnofsky's glutaraldehyde-formaldehyde mixture, minced, and prepared for conventional electron microscopy in a Phillips 300 EM. Wright's stained imprints, ultra-thin 2% glutaraldehyde-fixed and 10% neutral buffered formalin sections stained with hematoxylin and eosin and other stains (May-Grunewald-Giemsa, PAS, Methyl green pyronine) were studied simultaneously. The focus was on cytoclasmosis and on cytoclasmids in the interstices, lymphatics and blood vessels. Cytoplasmic organelles served as indices of cytoclasmosis and the dispersion of cytoclasmids into lymph and blood.

Observations

As shown in Figures 1-6, cytoclasmosis is normally observed in diverse organized lymphatic (and lymphoid) tissues. Myriad cytoclasmids appear to separate from all kinds of relatively large mononuclear cells, either by budding or intracytoplasmic demarcation of separate plasmalemma. Separate cytoclasmids contain or-
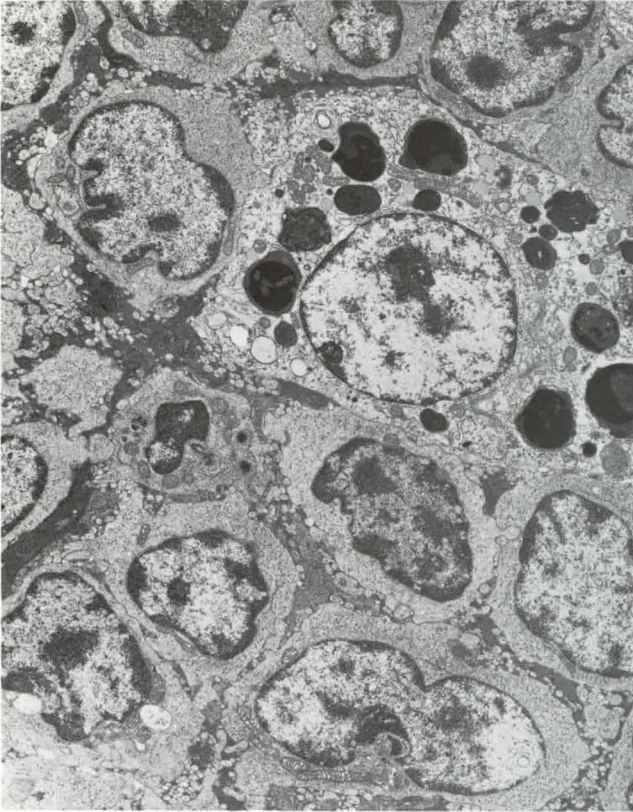
Fig. 1. Rat Peyer's patch germinal center (x 3300). Above, a macrophage containing ± 10 small cytoplasm-depleted lymphocytes in progressive stages of digestion, and showing ectoplasmic cytoclasmosis. To the left and below, ± 7 large lymphocytes showing ectoplasmic cytoclasmosis into the interstices.
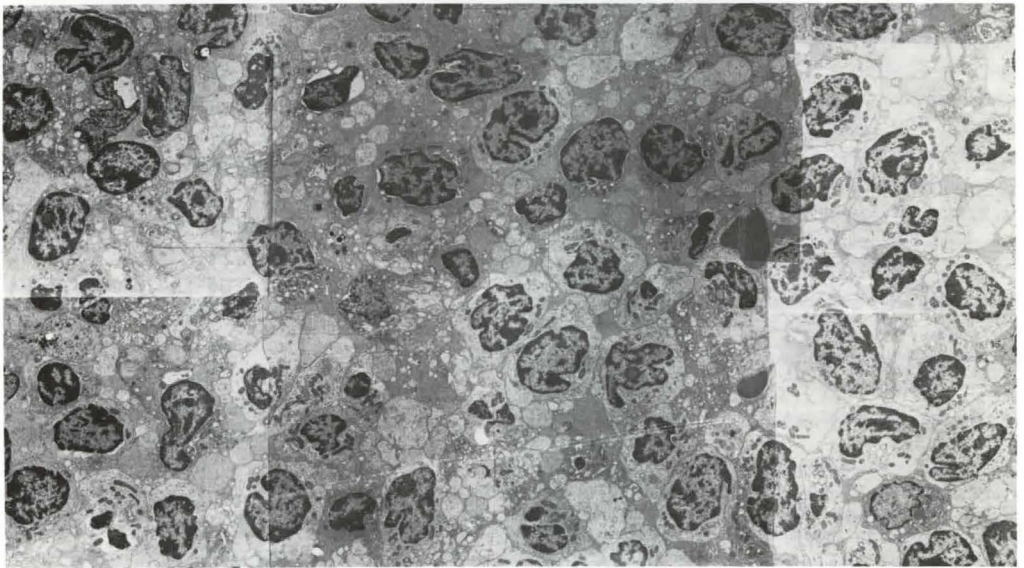

Fig. 2. Paracortical portion of a histologically normal human low cervical lymph node (x 1000). Myriad cytoclasmids apparently separating from medium-sized lymphocytes and separate in the interstices.

Fig. 3. A sinus in the same lymph node (x 4600) containing lymphocytes variably depleted of cytoplasm and cytoclasmids with differing organelle content. The cytoclasmids (left) mostly contain ribosomes and polyribosomes; while those (right) also contain mitochondria, vesicles, smooth ER (endoplasmic reticulum) profiles or lysosomal residua. Extracellular mitochondria in various stages of disintegration are scattered about. Throughout, but especially above, the cytoclasmids and their contents appear to fade imperceptibility into the background of precipitated proteins in the sinus.
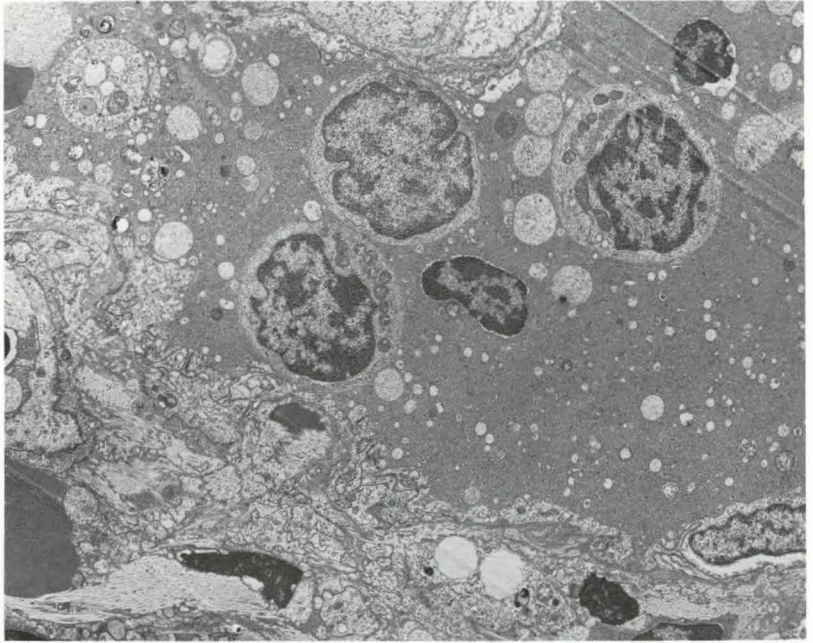

Fig. 4. Human thymus (x 4600), resected for myasthenia gravis. Below, efferent lymphatic containing cytoclasmids mostly lacking in plasmalemma, with varying stages of organelle disintegration and dissolution into a coarse background or protein precipitate. Above, a small blood vessel containing relatively few recognizable cytoclasmids in an amorphous, relatively homogeneous plasma protein precipitate.
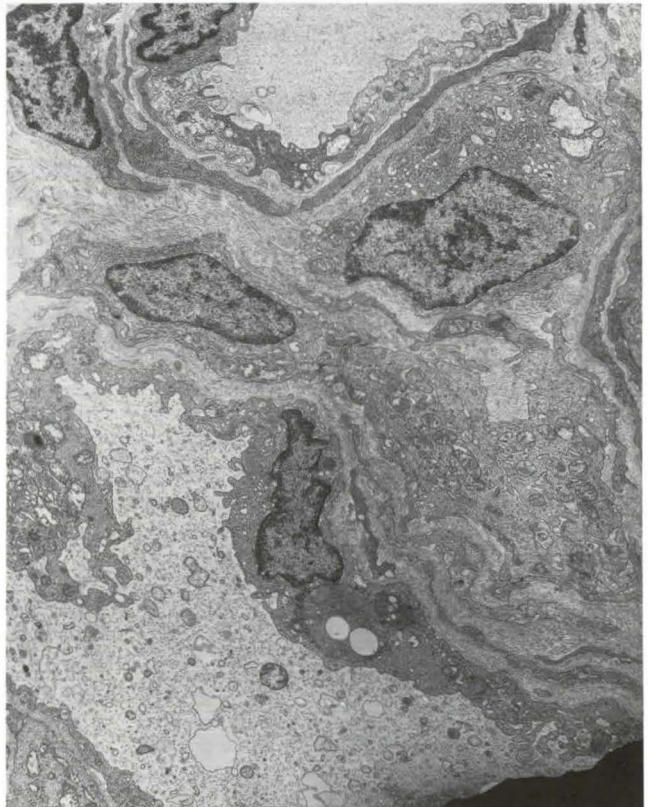
Fig. 5. Human cervical lymph node obtained during thymectomy for myasthenia gravis x 3300. Centrally, a large lymphocyte undergoing mitosis, surrounded by reticular cells, small cytoplasm-depleted lymphocytes and relatively small cytoplasmids (especially to the right). Note the disparity in size, cytoplasmic volume and organelle content between the large and small lymphocytes.

ganelles (ribosomes, smooth or rough endoplasmic reticulum, vesicles, mitochondria, lysosomes) characteristic of the ectoplasm in adjacent mononuclear cells in various stages of differentiation. Large and medium-sized lymphocytes appeared the most common sources of cytoclasmids in all the tissues studied, except bone marrow (where megakaryocytes normally produce cytoclasmids, commonly recognized as thrombocytes containing characteristic dense bodies). In all lymphatic (and lymphoid) tissues, small lymphocytes show relatively little evidence of cytoclasmosis and appear depleted of ectoplasm. Cytoclasmids are common in the interstices and lymphatics (and in arterovenous sinusoids), but few are found in peripheral blood vessels, either separate or in the act of separation from circulating cells. In lymph sinuses and efferent lymphatics, the cytoclasmids appear to degenerate with disruption of plasmalemma and dispersion of disintegrating organelles into lymph containing relatively small, cytoplasm-depleted lymphocytes.

Interpretation

One may interpret these observations to indicate that, along with small cytoplasm-depleted lymphocytes, the organized lymphatic tissues normally contribute relatively large quantities of cytoclasmids from various kinds of growing mononuclear cells into central lymph (as diagrammatically outlined in Figure 7). Because cytoclasmosis and microscopically recognizable cytoclasmids are relatively absent in peripheral blood vessels, it appears that most of the cytoclasmids (and their diverse molecular constituents) dissolve into the circulating plasma, either within central lymphatics or in the pulmonary circulation (Fig. 8).

Functional Implications

Ranvier (2) and *Sabin* (15) were among the first to recognize that macrophages ("*clasmatocytes*") excrete ingested, digested foreign matter by cytoclasmosis, so that the products can be reutilized in other cells for immunologic or
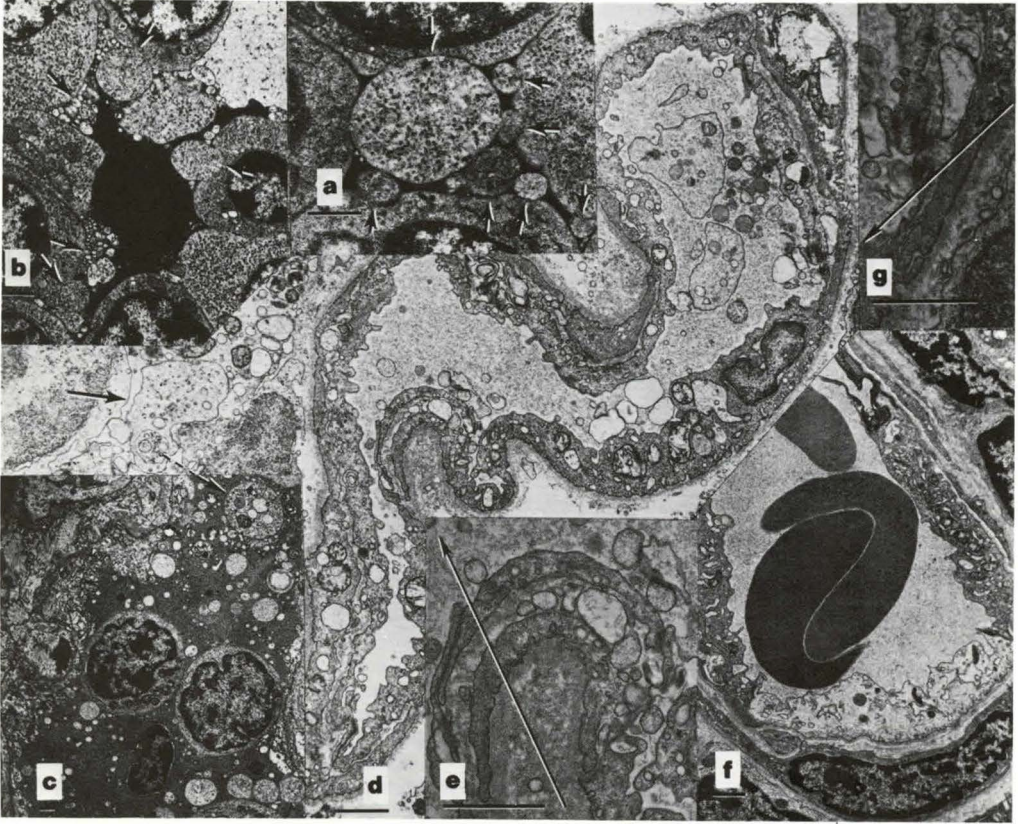
Fig. 6. Cytoclasmosis (Horizontal markers indicate one micron)
a. Duckling bursa. Arrows indicate cytoclasmosis from bursal lymphocytes.
b. Rat thymus. Arrows indicate cytoclasmosis from thymic lymphocytes.
c. Human cervical lymph node. The central lymph sinus contains cytoclasmids of varying size and organelle composition, along with small cytoplasm-poor lymphocytes.
d. Human thymus. Arrows on the left between insets b-c indicate cytoclasmosis from a large lymphocyte and similarity of organelles in cytoclasmids outside and within lymph sinuses. The thymic efferent lymphatic in the central portion of the photomicrograph contains similar cytoclasmids in various stages of disintegration.
e,g. Magnified insets to d – showing cytoclasmids apparently entering the thymic lymphatic through the amorphous (probably dissolving) reticular connective tissue between endothelial cells.
f. A small blood vessel from the same thymus, showing the relative absence of recognizable cytoclasmids in the amorphous precipitated plasma suspending three erythrocytes. (This suggests relatively complete dissolution of cytoclamids in lymphatics or the pulmonary circuit before circulation in peripheral blood.)

nutritive purposes. *Dougherty and White* (7) found that, under the influence of cortisol, lymphatic organs release relatively large quantities of normal nutritive, as well as immune globulins by cytoclasmosis and lymphocytolysis. *Leitner* (25) noted that large immature plasmacytes may release relatively large quantities of "paraproteins" similarly. Although relatively unconcerned with the fate of the

cytoclasmids, *Downey and Weidenreich* (5-6) observed that in the organized lymphatic tissues of many species, relatively large numbers of small cytoplasm-poor lymphocytes with relatively high nucleocytoplasmic ratios are differentiated by progressive nucleocytoplasmic changes, mitotic divisions and cytoclasmosis in larger and medium-sized lymphocytes (Fig. 6). Considering that cytoplasm (although charac-

Fig. 7. Central lymph production (based on Refs. 5-6, 14-16, 23, 30, 35 and the photomicrographs)

LYMPH SECRETION

LYMPHOCYTES

II

LYMPH

PLASMA

1. Derived from undifferentiated mesenchyme, stromal reticular cells give rise to stem cells (arrow) and undergo cytoclasmosis, releasing cytoplasm which dissolves (to the right).
2. Differentiated from reticular cells, stem cells "round up" with nuclear enlargement, gradual chromatin condensation, nucleolar enlargement and increasing cytoplasmic differentiation of ribosomes, endoplasmic reticulum, vesicles, mitochondria and Golgi apparatus – all of which are relatively non-specific, as DNA and RNA synthesis increase during early (pyroninophilic) stages of differentiation. Cytoclasmosis continues (to the right).
3. In the reticular connective tissue of definitive hemopoietic organs characteristic of species and stage of development, pyroninophilic stem cells develop into erythrocyte, granulocyte and megakaryocyte precursors which differentiate around veins; into monocyte and macrophage precursors which differentiate around venous or lymphatic sinusoids; into plasmacyte precursors which (after birth) differentiate around tiny (precapillary) arterioles; and into large lymphocytes which differentiate around larger (muscular or meta-) arterioles. Whereas the erythrocyte and granulocyte precursors cease cytoclasmosis with the differentiation of hemoglobin or specific granules, the thrombocyte, monocyte, macrophage, plasmacyte and lymphocyte precursors continue cytoclasmosis. Lymphocyte precursors normally being most common in all organized lymphatic and lymphoid tissues (other than avian and mammalian marrow), their subsequent differentiation is depicted below.
4. Derived from larger lymphocytes, myriad small cytoplasm-poor lymphocytes are differentiated through repeated mitoses and gradual loss of cytoplasmic organelles through cytoclasmosis (to the right), as DNA and RNA synthesis gradually subside.
5. Many small cytoplasm-poor lymphocytes and quantities of plasma produced by dissolution of cytoclasmids of all cell types, together, constitute central lymph which flows from lymph sinuses to join the blood circulation (along with filtered and, often, macrophage-processed peripheral lymph).
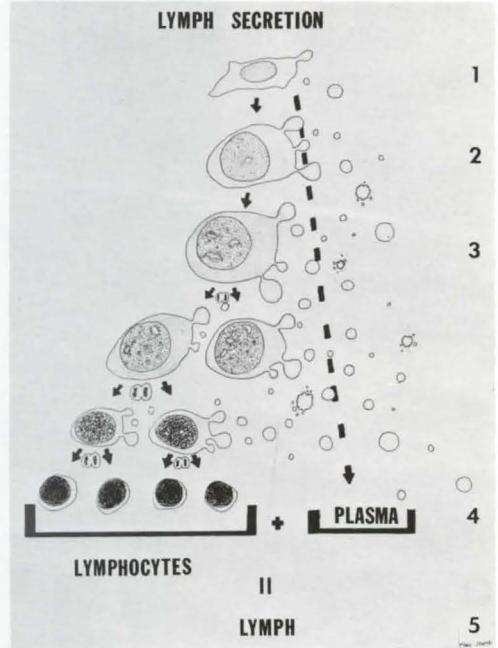
teristically different in various cell types or in the same cell type at different stages of differentiation) is a complex gel made up of water, minerals, salts, carbohydrates, amino acids, lipids and many kinds of organelle proteins, I have emphasized in addition that cytoclasmosis is not only instrumental in lymphocyte differentiation and the release of complex substances from other kinds of mononuclear cells, but also instrumental in the production of colloidal hydrosols, such as lymph and blood plasma, which *flow* to carry a spectrum of dissolved cytoclasmids and suspended cells to other lymphoreticular and extra-lymphatic tissues – where they can be *reutilized* for nutritive, as well as immunologic purposes (10, 23).

Han et al. (26) found that specific antibodies are secreted from lymphocytes and/or plasmacytes by clasmatosis. From a purely immunologic point of view, cytoclasmosis explains how different kinds of mononuclear cells commonly excrete proteins of differing immunologic specificity, and do so into sols arising by cytoplasmic dissolution, such that dissolved, relatively high molecular weight globulins can *flow* between cells or tissues at rates much faster than simple diffusion will allow (23).
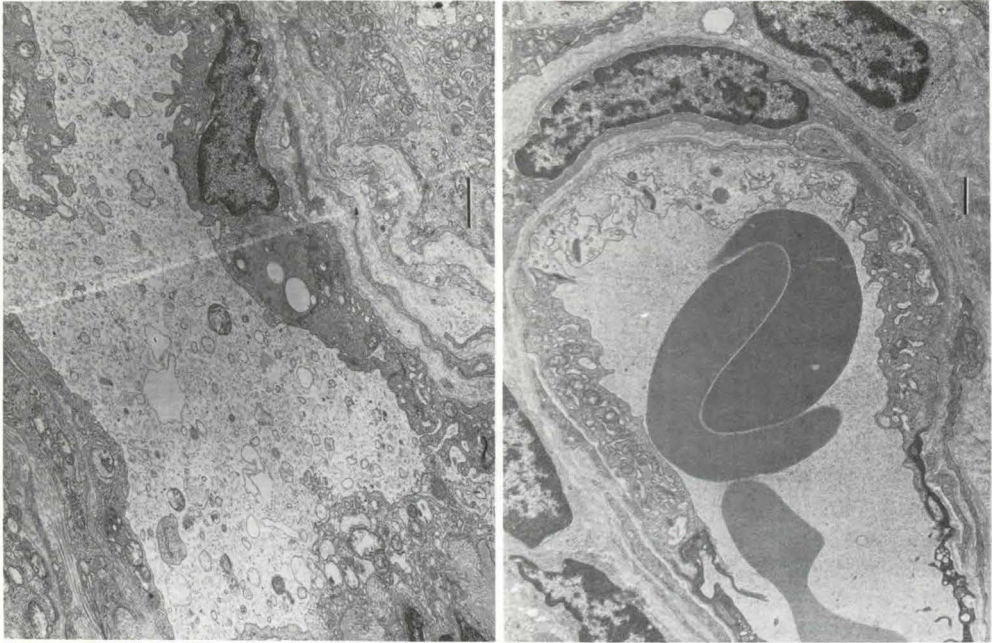
Fig. 8. Left, a capsular lymphatic in a human thymus removed for myasthenia gravis x 9000. Right, a small blood vessel from adjacent area in the same thymus x 7600. The lymphatic contains precipitated cyto-clasmids, including mitochondria, smooth and rough ER profiles and vesicles dispersed in a background of granules resembling dispersed ribosomes. All lack surrounding plasmalemma and appear in various stages of disintegration. The blood vessel contains three erythrocytes "suspended" in a relatively homogeneous background of precipitated plasma protein, possibly containing a single undissolved vesicle (below-right).

Moreover, with respect to lymphocytes, cyto-clasmosis explains why nucleocytoplasmic ratios rise while ectoplasm is shed, such that different intracytoplasmic and surface proteins may be reflected as DNA and RNA synthesis subside during successive stages of normal differentiation – perhaps as exemplified by shifts in IgM, IgG, IgA production; in changing surface antigens during mouse thymocyte development; and loss of surface markers in humans such that B-cells may become D-(doubly marked) cells, then T-cells and, finally, "null cells". (Several investigators, including *Schlesinger* (27) and *Warner* (28) have considered that different surface markers may be expressed during progressive stages in lymphocyte differentiation, while *Cone* (29) suggested that the various surface proteins produced by lymphocytes are released by shedding. In my experience, cytoplasmic shedding by fragmentation appears

to decrease with lymphocyte differentiation, while oxygen dependence increases (30). From a metabolic point of view, it seems that the rate of lymphocytic glycolysis and lactic acid production normally decreases with differentiation (31), but increases after PHA stimulation *in vitro* (32)).

With respect to quantitative aspects of cytoclasmosis, it should be mentioned that, as calculated either by mitotic indices (33) or by radiophosphate turnover (34) (the latter reflecting both DNA and RNA synthesis), the lymphoreticular tissues in healthy mammals normally grow at a rate sufficient to double (or replace) their aggregate mass (1-3% of total body weight (1)) every two days. Assuming that the aggregate lymphoreticular mass during equilibrium is normally dissipated through cytoclasmosis, the release of large numbers of small cytoplasm-depleted lymphocytes and relatively small number of mono-

cytes into circulation – one may estimate the rate of lymph production in organized lymphoreticular tissues to be 0.5-1.5% of total body weight daily. The daily disposition of the sols generated by cytoclasmosis, as well as the suspended, emperipoletic, small cytoplasm-depleted lymphocytes, are considered in detail elsewhere (23).

In lymphomyeloid organs, such as adult mammalian bone marrow, cytoclasmosis not only appears instrumental in the megakaryocytic release of thrombocytes, but also in the transport of mature myeloid elements into sinusoids. As originally demonstrated by *Isaacs* (35), the gelatinous stroma formed by reticular cells normally disintegrates and dissolves when myeloid elements become mature. In the resulting sol, thrombocytes and anucleate erythrocytes lacking the capacity to move independently are suspended, along with mature granulocytes, so that all can *flow* together into venous sinusoids lined by relatively permeable reticulo-endothelium. The situation is similar in lymphoid organs relatively lacking in lymphatics (e.g. spleen, hemal nodes) and lymphatic organs with well-developed efferent lymphatics (e.g. nodes, tonsils, thymus, avian bursa, intestinal lymphatic tissue), but varies because:

1. After birth in mammals, relatively few granulocytes, thrombocytes or erythrocytes differentiate in the reticular stroma. Consequently, relatively large numbers of lymphocytes are produced, instead of erythrocytes.

2. During lymphocytopoiesis and erythrocytopoiesis in mammals, as cellular DNA and RNA synthesis subside, lymphocytes shed or extrude ectoplasm to produce relatively soluble heterogeneous cytoclasmids as shown in Figures 1-8; whereas erythrocytes extrude nucleoplasm to become relatively insoluble homogeneous cytoclasmids filled with hemoglobin. The extruded nucleoplasm apparently disintegrates, dissolves or is phagocytized, as the anucleate hemoglobin-filled cytoclasmids are released by marrow stromal dissolution to circulate, along with anucleate thrombocytes and polymorphonuclear granulocytes. Conversely, in the stroma of lymphoid or lym-

phatic organs, the heterogeneous cytoclasmids extruded from lymphocytes disintegrate or dissolve, as small cytoplasm-depleted lymphocytes almost filled with nucleoplasm are released to circulate – either via arterovenous sinusoids in lymphoid organs or lymph sinuses in lymphatic organs. Because the contents of lymph sinuses normally pursue a relatively long course via central lymphatics before hemodilution takes place in central veins, such small cytoplasm-depleted cells and heterogeneous cytoclasmids are relatively easy to find in the sinuses or central lymphatics (Fig. 6, 8).

3. Upon systemic circulation, the insoluble homogeneous erythrocytic cytoclasmids from marrow uniformly contain hemoglobins adapted to concentrate and transiently carry molecular oxygen and/or carbon dioxide between respiring tissues, while the soluble heterogeneous lymphocytic cytoclasmids from lymphocytopoietic organs contain diverse globulins admirably adapted to concentrate and in transit carry relatively complex nutrient molecules and/or immunologic protection to the respiring tissues (23).

With respect to the plasmacytes and macrophages which develop in the reticular stroma of normal lymphatic, lymphomyeloid and lymphoid tissues, it seems established that immature plasmacytes can release relatively large quantities of circulating "monoclonal" or "polyclonal" immunoglobulins during inflammation or neoplasia, and were found to do so during neoplasia by cytoclasmosis (25). *Ranvier's clasmatocytes* (now called macrophages (3) or mononuclear phagocytes (36)), as a generic class, not only release processed antigens when stimulated appropriately; but also normally release variable quantities of lysosomal enzymes, plasminogen activators, collagenase, elastase, cell stimulating and inhibiting substances, complement components, interferons and endogenous pyrogens (36) – a panoply of proteinaceous substances mostly unheard of when *Ranvier* (2) and *Sabin* (15) published their original observations on clasmatosis.

Finally, it seems prescient that in 1844, *Donné* (24) considered lymph glands to be

sources of *globulines* (diminutive globules) which he found in lymphatics. Of course, the term, *globulins,* is used now to connote globular proteins of nutritive and immunologic importance which vary in molecular complexity, are insoluble or sparingly soluble in water, and are relatively soluble in neutral salt solutions. In parts of the body where peripheral and central lymph can be sampled more or less simultaneously, as in afferent and efferent nodal lymphatics, lymphatic catheterization (1, 37) has shown that globulin/albumin ratios, protein content and mononuclear cell counts are relatively high in central lymph. Accordingly, it may be concluded that organized lymphatic tissues, such as nodes, not only filter peripheral lymph produced by capillary filtration, but also contribute to the production of central lymph relatively rich in small cytoplasm-depleted lymphocytes and globular proteins. While such proteins dissolve, the lymphocytes become suspended in relatively neutral colloidal hydrosols generated by disintegration of heterogeneous cytoclasmids (as depicted in Figures 1-8), so that the composite may *flow* centrally under the influence of favorable hydrostatic pressure gradients.

Discussion

It can be argued that cytoclasmosis is a methodologic artifact produced by smearing, imprinting or sectioning relatively fragile mononuclear cells; compressing or decompressing them during operative or aspirational removal, killing them by dehydration and precipitating their characteristic proteins, or evaluating their contents and contours in random (not necessarily serial) microscropic sections after they are cadaveric. If so, why did the histologists quoted report such artifacts not only in tissue sections, but also during phase contrast observation of living cells? Why did *Downey* (6) and *Heidenhain* (quoted in 26) suggest that megakaryocytic and lymphoid cell fragmentation are analogous processes? Why do cells removed from circulation not appear to fragment similarly, except in unusual cases of acute leukemia (39) or after phytohemagglutinin stimulation with dedifferentiation *in vitro* (23)? Why have cells other than mega-

karyocytes and lymphoid cells not been found to fragment similarly under similar conditions? The scanning electron microscope, incidentally, shows fragmentation from splenic lymphocytes and apparently separate fragments in splenic sinusoids (8), but, unlike the transmission electron microscope, does not delineate or show subtile changes in their internal structures.

While the observation of living cells *in vivo* or in tissue culture has advantages with respect to observing movements and changing contours, the microscopic resolving power which can be applied without interfering with normal cellular behavior is relatively limited. Moreover, *in vitro* the cells, if still living, must be nurtured in artificial media where circulating blood does not continually supply (or remove) balanced concentrations of small rapid-diffusing molecules essential to their respiration and growth, while lymph carries away relatively large slow-diffusing molecules which they secrete or excrete (1).

Figures 1-6 do not show how many ectoplasmic extrusions retract vs. how many separate from given mononuclear cells in lymphatic and myeloid organs per unit of time, but they show that many cytoclasmids (or polymorphous residua) accumulate in lymphatics (or in arterovenous sinusoids (8, 23)). Of course, relatively active cytoplasmic fragmentation has been described from macrophages, plasmacytes and lymphocytes during antibody production (15, 23, 26) or after cortisol stimulation *in vivo* (7-8) and *in vitro* (19); but these illustrations are chosen to show that cytoclasmosis proceeds under normal physiologic conditions in random-sampled hemopoietic organs of diverse species and appears to be a universal method of apocrine or rhagiocrine secretion, as described by *Heidenhain* (26, 39) and *Renaut* (40), respectively. Therefore, instead of belaboring what artifactually happens to cellular water and proteins during tissue fixation, sectioning and staining; or what happens to the water and proteins in fragments commonly observed to separate from the cells *in vitro* — it seems relatively cogent to consider the movement and ultimate disposition of the fluid products produced by dissolution of cytoclasmids *in vivo* (23).

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Jack W. Shields, M.D., Dept. of Medicine and Hematology, Santa Barbara Medical Foundation Clinic, P.O. Box 1200, Santa Barbara, California, USA 93102