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Cells and Immunoglobulins in Lymph

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Summary

Studies of the free-floating lymphocytes and of the immunoglobulins in lymph collected over long periods of time from ducts draining individual tissues of the body as well as from the thoracic duct of the fetus in utero have been reviewed. The findings show that stimuli within the internal milieu act on different classes of lymphocytes to alter their migration pattern, morphology, metabolic activity, and range of immunological potentialities. As the lymphoid cells migrate between the blood, tissue fluid, and lymph, a continual process of reassortment occurs leading to the establishment of heterogeneous lymphoid cell populations in different regions of the lymphatic apparatus. It seems that the biological activities of these cells are not decided only in terms of a thymus or a bone-marrow origin.

The immunoglobulins, like other proteins in lymph, are mainly derived by filtration from the circulating plasma. Some of the immunoglobulins and specific antibodies are synthesized, however, by lymphoid cells and secreted directly into the lymph.

The development of physiological techniques for collecting lymph over long periods of time from normal, conscious animals has revealed differences in the number and morphology of lymphocytes in lymph coming from different regions of the body. Nonrandom patterns of lymphocyte migration have also been identified which lead to significant differences in the physiological activities of the various lymphoid cells collected from different sites in the lymphatic apparatus. These findings have emphasized the heterogeneity that exists among the free-floating lymphoid cell populations of the body and the continual processes of reassortment that occur as these cells migrate between the blood, tissue fluid, and the lymph.

The protein content of lymph from different areas of the body also varies due, for the most part, to differences in the permeability and hemodynamics of the blood capillary beds of the various tissues. While most of the macromolecules in lymph are derived by filtration from the circulating plasma, some of the differences occurring in the concentration of various classes of immunoglobulins and specific antibodies are due to the synthesis and secretion of these molecules by lymphoid cells and their addition, locally, to the lymph stream.

The Content of Cells and Immunoglobulins in Lymph

Cells. Lymphocytes and macrophages are present in the lymph draining from all non-lymphoid tissues of the body, but their numbers have no relation to the permeability characteristics of the blood capillaries of the region in which the lymph is formed. Large numbers of lymphocytes are present consistently in central lymph, and the majority of these form part of an extensive recirculating population of cells passing between the blood and the lymph via the blood capillaries within lymph nodes (1).

Lymphocytes are present in the lymph of fetal animals at an early stage of development. It has been possible to collect lymph from fetal lambs at 75-days gestation. Already at this time, there are significant numbers of lymphocytes in the thoracic duct lymph (2). Since these cells are present in the blood at about 40-days gestation, it seems certain that lymphocytes enter the lymph of the fetal lamb at about this time. The cell output from the thoracic duct increases exponentially after 75-days gestation and reaches a maximum in lambs 3 to 6 months post partum. Most of the increased cell output from the thoracic duct during this time increases in the number

Table 1 Content of Cells and the Cell output from the Thoracic Duct of Fetal Lambs and the Intestinal Lymph Duct of Lambs after Birth. Cell Outputs are Calculated over a 24-Hour Period from 12 to 36 Hours after Cannulation.

Age	Cells Per Ml x 10^{-6}	Cell Output x 10^{-6}
Fetal Lamb		
Days Gestation		
75	1.1	1.02
99	2.6	3.75
131	2.2	31.0
148	7.2	117.7
Postnatal		
1 week	6.9	116
1 month	18.4	270
3 months	61.7	864
6 months	35.0	560
12 months	16.8	415

of cells coming from the gut via the intestinal lymph.

In fetal lambs the cells of thoracic duct and intestinal lymph are almost all small lymphocytes. Within a week of birth, many large lymphoid cells and blast cells appear in the lymph coming from the gut; cells of this type remain a characteristic of intestinal lymph of sheep throughout life (3). Table 1 gives the content and the output of cells from the thoracic duct of fetal lambs in utero and the intestinal duct of lambs up to 12 months after birth.

Table 2 Content and Output of Cells from Various Lymphatics in Adult Sheep.

Source of Lymph	Cells Per Ml x 10^{-6}	Cells Per Hour x 10^{-6}
	Peripheral (Afferent) Lymph	
Hind Leg	0.2– 0.7	0.2 – 5.6
Foreleg	0.5– 1.0	1.5 – 5.0
Prescapular	0.6– 0.8	1.5 – 4.0
Prefemoral	0.5– 0.8	0.75– 2.4
Liver	2.0– 6.0	2.0 – 18.0
Kidney	0.1– 0.7	0.1 – 2.1
Ovary	0.2– 0.7	0.2 – 6.65
Testis	0.1– 0.7	1.0 – 9.0
Thyroid	0.2– 0.8	0.06– 0.48
	Central (Efferent) Lymph	
Popliteal Node, Efferent	3.0–10.0	3.0 – 90.0
Prescapular Node Efferent	8.0–12.0	36.0 – 96.0
Prefemoral Node, Efferent	5.0– 8.0	15.0 – 48.0
Portal Node (Liver), Efferent	8.0–12.0	8.0 –120.0

The cell content and the cell output from various lymphatics of adult sheep under normal physiological conditions are shown in Table 2 (4). Peripheral lymph (lymph that has not passed through a lymph node) is distinguished from central lymph by its lower content of cells and by the presence of macrophages. Macro-Phages are rarely found in central lymph as they appear to be removed from the lymph within the lymph node. Peripheral lymph from the liver and the intestines differs from the lymph from other nonlymphoid tissues in that there is a much greater cell traffic from these organs. In the intestines there is a very large amount of lymphoid tissue in the Peyer's patches, and cells newly formed in these structures may enter the intestinal lymph directly (5). Because of this, the peripheral lymph draining from the guts is not strictly comparable to that coming from other somatic tissues.

The cell population in central lymph (lymph that has passed through a lymph node) is normally made up of about 95% small lymphocytes and 5% large cells. The cell output from different lymph nodes in sheep is related to the size of the lymph node and varies from around 5 x 10^7 to 2 x 10^8 cells per hour. The cell output from the large prescapular lymph node is higher than the cell output from the smaller popliteal node.

Surface Ig is present on about 2% to 5% of lymphocytes in the thoracic duct and in the lumbar lymph of the fetal lamb prior to birth (6). Within 4 to 8 weeks of birth between 30% to 40% of the cells in lymph from these sources have surface Ig indicating that, outside the uterine environment, a large proportion of the circulating lymphocytes begin to synthesize immunoglobulins. Removal of the thymus reduces the number of lymphocytes in the lymph and leads to an increase in the proportion of cells with surface Ig. Fetal

lambs thymectomized at around 60 to 65-days gestation have about 15% of cells with surface Ig in their lumbar lymph just before birth (2, 6).

In the sheep the distribution of lymphocytes with surface Ig in lymph from various tissues is nonuniform.The lymphocyte population of peripheral lymph has between 59% to 10% of surface Ig bearing cells compared with 25% to 30% in central lymph (7, 8). Since the proportion of cells bearing surface Ig in central lymph increases during chronic lymph drainage, this suggests that the nonimmunoglobulin-bearing cells are more rapidly depleted from the recirculating pool than are those with surface Ig (9).

IgM is the most common immunoglobulin class on the surface of sheep lymphocytes and characterizes 80% to 90% of the Ig-bearing cells in the thoracic duct and lumbar lymph and in lymph from the hepatic, prescapular, and popliteal lymph nodes (9, 10). The lymphocyte population coming from the guts is unique in that a significant number of the Ig-bearing cells in intestinal lymph carry surface IgA (9). This immunoglobulin class is rarely identified on lymphocytes in lymph from other tissues.

Immunoglobulins. Immunoglobulins are not detectable in the blood or lymph of most fetal lambs up to 120-days gestation. In a proportion of fetuses closer to term, very low concentrations (less than 100 μg/ml) can be detected and the Ig class is usually IgM (6). Since there is no exchange of maternal plasma proteins across the ovine placenta, most of the immunoglobulins present in the lymph of newborn lambs are derived from the maternal colostrum following their absorption into the intestinal lymph during the first 48 hours after birth (11). From then on the gut epithelium becomes impermeable to extrinsic proteins. All of the Ig classes absorbed from the colostrum appear subsequently in the lymph from tissues other than the gut as they become distributed throughout the intravascular and interstitial fluid pools. In colostrum-deprived lambs, no maternal antibodies are acquired and Ig molecules first appear in lymph at around 10 to 14 days when endogenous immunoglobulin synthesis begins. IgM is the first Ig class synthesized to appear in the lymph; IgG_1 appears next in lymph at around 4 weeks after birth and IgG_2 at around 6 to 7 weeks (12).

The concentrations of the various Ig classes are normally lower in lymph than in blood plasma and reflect the relative size of the different immunoglobulin molecules and their diffusion coefficients. IgM is present in significantly lower relative concentrations in lymph than is IgG_1 or IgG_2. The IgA content of intestinal lymph is higher than in plasma and much of this antibody class is synthesized locally in the gut from where it is added to the intestinal lymph (13).

The immunoglobulin content of peripheral and central lymph is different due to the formation of lymph within the node itself, to modifications that occur in the protein content of peripheral lymph after it enters the node, and to the synthesis and secretion of immunoglobulins by cells within the lymph node. *Quin* and *Shannon* (1977 [14]) found that there was about twice the concentration of IgG_1, IgG_2 and IgM in efferent lymph from the normal popliteal node than there was in afferent lymph entering the node. While these differences in Ig concentration may be due to the formation of lymph with a relatively high protein content within the lymph node itself, or to the reabsorption of water from peripheral lymph, the normal popliteal node of the sheep has quite a high endogenous rate of IgM and IgG synthesis in the absence of any antigenic stimulus (15). These molecules would normally be added to the lymph as it passed from the node.

The Recirculation and Reassortment of Lymphocytes in the Body

Lymphocytes, both small and large, are migrating continually between the blood, the tissues, and the lymph. This migration is established early in fetal development, probably as soon as lymphocytes first enter the blood (2). In the fetal lamb only a small proportion of the lymphocytes have surface immunoglobulins and none have encountered any extrinsic antigenic stimuli. It thus seems that the capacity

of lymphoid cells to migrate between the blood tissues and the lymph is not directed by any specific Ig membrane receptor or by antigen but is an inherent physiological property of virgin lymphocytes. It has not been established whether or not the recirculation of lymphocytes in the fetus is directed through the fixed lymphoid tissues, but it probably is. Certainly in animals soon after birth, the majority of migrating lymphocytes leave the blood stream in lymph nodes; this accounts for the much higher content of cells in central lymph than in peripheral lymph. In sheep there is no particular class of blood vessel that can be identified morphologically as being responsible for the transmission of lymphocytes; it seems that, in this species, lymphocytes migrate through the blood capillaries in lymph nodes with great facility and rarely accumulate within or around the post capillary venules as they usually do in rats and mice.

However, while most of the lymphocyte traffic is directed through lymph nodes, some cells do migrate through nonlymphoid tissues. The characteristics of migrating cells in these two situations are different (7, 8). The higher concentration of lymphocytes with surface Ig in central lymph when compared with peripheral lymph attests to some selective pattern in the migration of lymphocytes through nonlymphoid and lymphoid tissues. It seems that cells bearing Ig molecules on their surface membrane are restricted in their passage through the blood capillaries in nonlymphoid tissues or that cells leaving the blood outside the lymphoid tissues in some way lose their surface Ig.

It has been found that in several species the residual lymphocytes in thymectomized animals migrate between blood and lymph with less facility than do lymphocytes from normal animals (16. 17, 2). These findings also suggest that cells with surface Ig may encounter more restrictions during their migrations than do cells lacking this membrane component.

When a functional test is applied to the cells in peripheral and in central lymph, differences in the physiological activities of these two cell populations become apparent. Lymphocytes from peripheral lymph of sheep lack graft versus host reactivity when injected into the skin of an allogeneic recipient (18), even though they are effective in stimulating allogenic lymphocytes to incorporate ^{3}H-thymidine and to proliferate in vitro. Other physiological differences are found in lymphocytes collected from different regions of the body. Lymphocytes collected from intestinal lymph, for example, have been shown to have a predilection to return to the gut in their migrations rather than to other tissues, while lymphocytes collected in lymph from nodes divorced from the gut do not (19, 20, 21). These nonrandom migration patterns, superimposed on the morphological and functional changes that are taking place among the migrating lymphocytes, continually sort the recirculating lymphocytes into subpopulations with different activities. While this reassortment of cells occurs as part of the normal physiology of the lymphatic system, once externally derived antigenic stimuli are introduced into the body, these and other processes take place much more rapidly as characteristics of the immune response.

Effects of Antigenic Stimulation on the Lymphocyte Populations and the Immunoglobulin Content of Lymph

Humoral Antibody Responses. An antigenic stimulus affects the composition of the cell population of lymph in several ways. In fetal sheep, the lymphatic apparatus is capable of responding to a variety of antigens from about 65 days after conception. Immune responses in fetuses of this age give rise to the proliferation and differentiation of lymphocytes into specific antibody-forming cells and the production of immunoglobulins (22, 23). In fetal sheep of less than 90-days gestation, only IgM antibodies are synthesized; the amount of antibody produced and the kinetics of the immune response differ from responses in mature sheep (23). The kinetics of the immune response of a single lymph node and the production of antibodies by cells in the lymph node and in the lymph have been described for a variety of antigens by *Hall* and

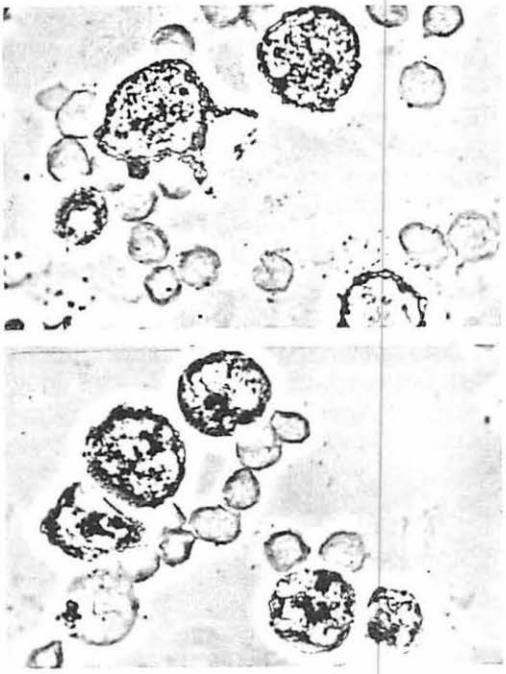

Fig. 1 Antibody-forming cells in the efferent lymph draining from a lymph node challenged with horseradish peroxidase. Samples collected 72 hours (left) and 96 hours (right) after challenge. Phase magnification: x 920.

Morris (1963 [24]), *Smith* and *Morris* (1972 [25], *Hay* et al. (1972 [26], and *English* et al. (1976 [15]. Although there are differences in some aspects of the immune response that characterize different antigens, the general features of each response are similar. Initially, the arrival of antigen in the lymph node reduces the number of cells leaving the node so much that, in the case of influenza virus antigen, the efferent lymph may be virtually free of cells for several hours after the antigenic challenge. During the first 48 hours of an immune response, the cell population in the thoracic duct lymph and in lymph coming from the challenged node is depleted of lymphocytes with a specific immune reactivity against the antigen (27, 28, 29). This is thought to be due to the selection of antigen sensitive cells out of the recirculating lymphocyte population (30).

Subsequently, specific antibody-forming cells are generated in the node and enter the lymph (Figs. 1 and 2). In primary responses to most antigens, the first antibody-forming cells appear in lymph between 60 to 70 hours after challenge; these cells reach a peak around 96 hours. These antibody-forming cells are the progeny of blast lymphoid cells which proliferate both in the node and in the lymph (Fig. 3). Once these cells enter the lymph, they pass to other lymph nodes further along the lymphatic chain where many settle down to continue the production of specific antibody. It also seems that, as well as stimulating the production of specific antibody-forming cells, an antigenic challenge induces other lymphoid cells to proliferate and to produce immunoglobulins with specificities different from the stimulating antigen. Other molecules

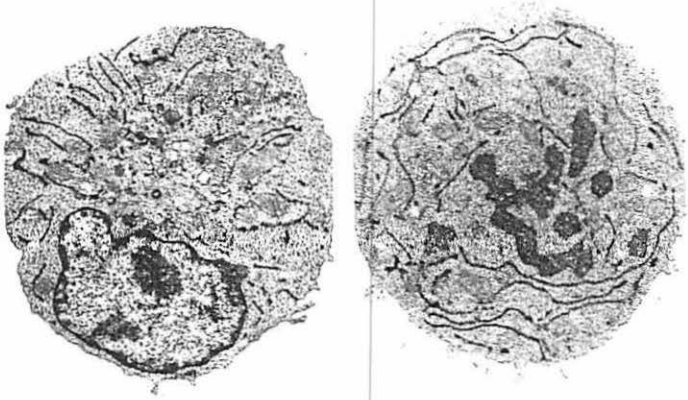

Fig. 2 Electronmicroscope pictures of antibody-forming blast cells in lymph. Cells collected 96 hours after challenge with horseradish peroxidase. Profiles of endoplasmic reticulum contain specific antibody. Antibody is present in the perinuclear space of the cell on the left. The cell on the right is in mitosis. Magnification: x 8.120

which may play a part in regulating the immune response are also produced by free-floating and fixed lymphoid cells (15, 31).

The changes that occur in the efferent lymph of the popliteal node of a sheep following primary antigenic challenge with salmonella lipopolysaccharide are shown in Fig. 3. Up to 5 x 10^8 blast lymphoid cells and 2-3 x 10^7 specific antibody-forming cells leave the node via the efferent lymph during the course of the response. In addition to these cells, many antibody-forming cells remain in the node and continue to secrete antibodies for several weeks after the cellular response in the lymph has died down. The production of specific antibody by the free-floating cells of lymph has been measured during the immune response and compared with that of cells within the lymph node (15, 32). The amount of specific antibody IgM synthesized by the free-floating cells has been found to be at least equivalent to the amount produced by cells within the node.

It also seems that the location of the antibody-forming cells within the lymphatic system affects the spectrum of immunoglobulins produced by the same population of cells. *English* et al. (1976 [15]) reported the sequence in which specific and non-specific immunoglobulins were secreted by cells in the lymph nodes and in the lymph during the primary immune response to salmonella lipopolysaccharide. The showed that IgM, IgG_1, and IgG_2 were produced by cells in the node and in the lymph and that the primary immune response continued over a period of at least 20 days. As the response progressed, more of the IgM and IgG_1 immunoglobulins in the lymph showed specificity for the antigen; no specific IgG_2 was produced until very late in the response. The same population of cells secreted relatively more IgM and relatively less IgG after they entered the lymph than when they were in the lymph node; this was due to a reduced production of IgM by cells within the node. This is a further example of the effect of the immediate environment of lymphoid cells on their physiological activities.

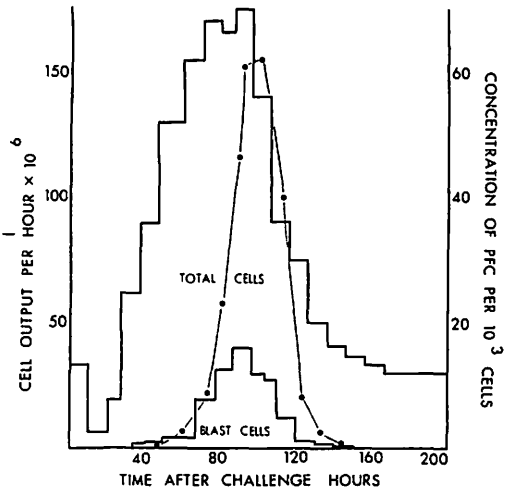

Fig. 3 Primary immune response to salmonella lipopolysaccharide in the efferent lymph from the popliteal node of a sheep.

Transplantation Reactions. In allograft and graft versus host reactions, obvious alterations occur in the cellular and protein content of the lymph draining the site in which the allogeneic tissue is placed. However, changes also occur in lymphocyte populations in other parts of the body due to widespread processes of cell reassortment that take place during this type of immune response.

The installation of a renal allograft in a sheep is followed over the first 4 to 5 days by an exponential increase in the output of lymphocytes in the peripheral lymph draining from the grafted organ. Large numbers of blast cells appear in the renal lymph so that, by the fourth day, the cell output may be as high as 4-5 x 10^8 cells per hour, a 500-fold increase over the cell traffic that enters the lymph draining from a normal kidney. In contradistinction to the blast cells generated in response to antigens such as salmonella lipopolysaccharide, very few of the blast cells in lymph draining from an allograft are synthesizing immunoglobulins (3), although these cells are very active metabolically and synthesize as well as secrete large amounts of protein. Later in the rejection process, large numbers of macrophages filled with cell detritus appear in the lymph from the graft.

From the outset, only about 10% of lymphocytes in lymph from the graft have surface Ig; this percentage changes little during the response (8). When tested for their capacity to give a graft-versus-host response in the kidney donor, the cells in the graft lymph are found to be quite anergic and give reactions similar to those seen when cells from normal afferent lymph are injected into an allogeneic recipient (30). The cell population coming from the lymph node regional to the graft contains a much higher proportion (around 30%) of Ig-positive cells. In contrast to the cells leaving the graft via the lymph, those draining from the regional lymph node give very strong graft-versus-host reactions when injected into the kidney donor.

Although transplantation reactions are generally classified as cell-mediated responses, humoral antibodies are produced during the primary rejection process. This antibody is produced at different sites and times in the lymphatic apparatus. *Pedersen* et al. (1975 [31]) examined the kinetics of appearance of immunoglobulins in the lymph draining from allografted kidney, in the lymph coming from the lymph node regional to the graft, and in lymph from nodes remote from the transplant. The first detectable antibody appeared in the efferent lymph from the regional lymph node about 110 to 175 hours after the graft was installed; no antibody appeared however, in lymph from the graft during its life. The antibody which appeared in the efferent lymph from the regional node was produced by *fixed* cells within the node and not by the blast cells that migrated into the lymph.

Lymphocytes and particularly blast cells in both the graft lymph and in lymph from the regional node synthesized large amounts of nonimmunoglobulin proteins and secreted these locally into the lymph. The elution characteristics of these proteins on Sephadex G200 columns coincided with 19S, 7S and 4S proteins, but these molecules were not immunoglobulins and had no antibody activity.

The Physiological Significance of Lymphocyte Reassortment

The processes of lymphocyte migration, the selection and activation of certain classes of lymphocytes by contact with antigen or by special relationships with certain tissues, and the proliferation and differentiation of these lymphocytes establish heterogeneous lymphoid cell populations in different regions of the lymphatic apparatus. The metabolic activities of these different lymphocyte populations also lead to differences in the biochemical composition of lymph from different regions, particularly in regard to its immunoglobulin content.

The lymphocyte population of the body is generally held to be derived initially from the thymus and the bone marrow; these organs of origin are thought to confer on lymphocytes the capacity to react in cell-mediated or humoral antibody responses. The situation is now acknowledged to be much more complex than this and other classes of "helper" or "suppressor" cells play roles in initiating and regulating the immune response. Nevertheless, the concept of thymus-derived and bone-marrow-derived cells persists as a more or less definitive distinction of lymphoid cell populations, even though there is no evidence that cells originating in either of these organs remain morphologically or functionally distinct throughout their life histories.

Functional and morphological analyses of the different lymphoid cell populations from different sites of the body demonstrate that the biological activities of these cells are not decided just in terms of a thymus or a bone marrow origin. The complex processes of reassortment going on continually in the body make each component of the total lymphocyte population different physiologically from each other at any particular moment in time. This heterogeneity in the lymphocyte population suggests that stimuli within the internal milieu act on different classes of lymphocytes to alter their migration pattern, their morphology, their metabolic activities, and their range of immunological potentialities. Regardless of any immunological precommitment that lymphocytes may possess in terms of the ideas of clonal selection, the life history of these cells will depend very much on events which happen subsequent to their release from the

organs in which they are formed. The life histories of lymphoid cells will thus be determined by the complex interactions of associated cells and a whole range of humoral stimuli derived from both the external and internal environment. This will insure that a spectrum of subpopulations of lymphocytes will be present in the lymphatic apparatus at any time and that these cells will have changing patterns of metabolism and changing patterns of physiological activity. The characteristics of a lymphocyte population will depend inevitably on exactly where the cells are located in the lymphatic apparatus. These characteristics cannot be foreshadowed in terms of the sum of the activities of the conglomerate of cells found in the blood or in the thoracic duct.

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