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Lymphocytes. 3 Distribution

Distribution of lymphocytes in health

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Twenty years ago J. L. Gowans (1959) published rigorous evidence that lymphocytes circulate from blood to tissue to lymph in the rat. This suggested a definitive solution to a problem that had been clearly posed in 1885 by Walther Flemming, the discoverer of germinal centres. When he considered previous observations that the traffic of lymphocytes leaving a lymph node via the efferent lymphatic was much greater (by a factor of 10-20) than the traffic reaching the node via the afferent lymphatics it was clear to Flemming that the vigorous mitotic activity of lymphocytes within lymph nodes, both in germinal centres and elsewhere, was one factor that could account for the discrepancy between cell influx and cell efflux. More remarkably he perceived that the *only* alternative explanation was that lymphocytes leave the bloodstream within lymph nodes and recirculate back to the blood via efferent lymph.

More than 70 years later it was shown, by exploiting tritiated thymidine, that lymphocytes recently produced by cell division within a resting lymph node could make only a minor contribution to the excess numbers leaving in the efferent lymph (Gowans, 1959; Hall and Morris, 1965a). The blood vessels from which lymphocytes entered the node in such large numbers were pinpointed by Gowans and Knight (1964) as specialised postcapillary venules in the thymus-dependent area of lymph nodes. In the 1920s histologists had been impressed by the plump endothelium of small veins in this situation. Zimmermann (1923) had tentatively suggested that the lymphocytes seen within the endothelial wall of these venules were migrating *from* the node into the blood. This view still has support based on the shape of lymphocyles as observed on histological sections. The direction in which the cells were moving before fixation has been inferred from their orientation in the vessel wall (for example, Norberg and Rydgren, 1978). The validity of this approach is questionable not just because of much other evidence in favour of the net migration of lymphocytes from the blood into the node (for example, Sedgley and Ford, 1976) but also because of contradictory results obtained by other workers applying the same method (Anderson and Anderson, 1976).

During the 1960s the astonishing diversity of the morphologically uniform small lymphocyte was gradually revealed. The diversity includes not only T and B populations but also several distinct maturational stages of each cell line. It also involves the production of clones or subsets of lymphocytes specific for each of the myriad antigens to which the body can respond. Not surprisingly, the migration of lymphocytes now seems much more complicated than could be conceived in 1959. Not only does each population show an individual migratory pattern but the migration of some lymphocytes from the blood into different organs is apparently due to distinguishable mechanisms.

Relevance of lymphocyte distribution to human disease

The insights gained into lymphocyte migration during the last two decades should almost all be credited to animal experiments, mostly on the rat, the mouse, and the sheep. A number of approaches have been followed to investigate lymphocyte migration in humans both in disease and under physiological conditions, including cannulation of the thoracic duct. The rate at which the thoracic duct output of lymphocytes declines to a basal level over eight days and the tempo with which labelled lymphocytes injected intravenously appear in thoracic duct lymph are both broadly comparable to kinetic measurements made on small rodents (Revillard *et al.*, 1968; Perry, 1968).

Another approach has been to isolate lymphocytes from venous blood, label them with radioactive isotopes *in vitro*, and reinject them intravenously. Radioactivity is measured in samples of blood taken at judiciously chosen time intervals and may also be assessed externally by devices placed so as to estimate the radioactivity in the spleen, liver, lymph nodes, and bone marrow (Hersey, 1971; Scott *et al.*, 1972; Lavender *et al.*, 1977). Again, such studies tend to confirm that lymphocyte recirculation in man is

closely comparable to the process in small rodents. In rats and mice there is a rapid localisation of intravenously injected radioactive lymphocytes in the spleen. This peaks at 2-3 hours after injection; by 24 hours the activity has fallen to about 30% of the peak value. In human studies the radioactivity over the spleen also rises very quickly to reach a peak or a shoulder at 2-3 hours after intravenous injection of radioactive lymphocytes, but the subsequent decline in activity is much slower, so that 24 hours after injection the value is about 70-90% of the peak value. One possible explanation of this difference is that higher and more damaging concentrations of radioactivity have been used for human studies. Most small lymphocytes are extremely radiosensitive and there is evidence that after a critical dose of radiation, short of that required to kill the cell immediately, lymphocytes migrate normally from the blood but fail to return to the blood from the tissues. The suggestion is that the maintained high level of radioactivity observed in the human spleen may be an artefact due to a particular form of radiation damage to lymphocytes. The alternative possibility is that lymphocytes take much longer to return to the blood from the splenic white pulp in the human than in small rodents.

Unfortunately there has been little progress for some years in methods of studying lymphocyte migration in humans. The introduction of cell labelling with indium-111-oxine chelate by Thakur *et al.* (1976) stimulated several groups to test whether it might be superior to ^{51}Cr-sodium chromate as a lymphocyte label. Provided that contamination of the oxine preparation with traces of toxic materials is painstakingly minimised indium-111 is at present the best isotope for labelling human lymphocytes. However, we have detected radiation damage when 10^8 cells are labelled with 20 μCi or more (Sharma *et al.*, unpublished results, 1978). To achieve satisfactory imaging of lymph nodes about 100 μCi must be injected in association with lymphocytes.

Although these quantitative considerations are provisional it seems likely that the ^{111}In method will require the injection of at least 5×10^8 lymphocytes from about 500 ml of blood. If this is so, then lymphocyte distribution studies in patients are likely to be confined for the foreseeable future to research on diseases where such information is thought to be crucial. Because of these frustrating technical difficulties lymphocyte migration has captured the interest of only a few clinical investigators. However, it should be remembered that lymphocyte recirculation is an essential feature of all immune responses as they unfold in the body and understanding the control of lymphocyte distribution may be important in unravelling the complexities of autoimmune diseases, the non-rejection of the fetus, and the natural history of leukaemias and lymphomas.

Model of recirculating T-cell pool

The migratory pattern that can be described with greatest confidence is that of a large population of thymus-derived small lymphocytes (Rannie and Ford, 1978a). A simple diagrammatic model of this pool of cells in a 200 g rat is represented in the Figure. This shows that about 90% of the T lymphocytes leaving the blood enter one of three major sites of lymphocyte recirculation—the spleen, the bone-marrow, or the lymph nodes. Gut-associated lymphoid tissue is included under lymph nodes because in respect of small lymphocyte migration it is qualitatively indistinguishable from lymph nodes.

Just over half of the T cells leaving the blood enter the white pulp of the spleen. They initially localise in the marginal zone, pass on into the periarteriolar sheath, and return to the venous blood within the spleen (at least, in the rat). The transit time from blood to spleen to blood is as short as 4-5 hours on average.

The time taken for T lymphocytes to traverse lymph nodes is much longer, averaging about 15-18 hours. After crossing the high-walled endothelium of postcapillary venules in 10-20 minutes they follow an ill-defined route within the paracortex to reach the medullary sinuses and the efferent lymphatic. Because of this long transit time a substantial proportion of the recirculation pool is situated within lymph nodes.

There is also a vigorous exchange of mature small lymphocytes between the blood and the bone marrow. The cells return to the blood after only 2-3 hours so that the content of recirculating lymphocytes in marrow is small (Rannie and Bell, 1979).

T lymphocytes also migrate from the blood into many non-lymphoid tissues including skin, muscle, intestine, and endocrine organs. Although the numbers are very small compared with the major sites of recirculation, this flux can be detected either by cannulation of peripheral lymphatics (Smith *et al.*, 1970) or by injecting intravenously large numbers of isotopically labelled lymphocytes (Rannie and Donald, 1977). These cells return to the regional lymph node within a few hours and pass through the node to reach the efferent lymph rather more quickly than the majority of cells circulating from blood to lymph within the node (Frost *et al.*, 1975). A question which is the subject of current experiments is whether these lymphocytes recirculating peripherally are a different population from the major recirculating pool. The assumption is reasonably made that

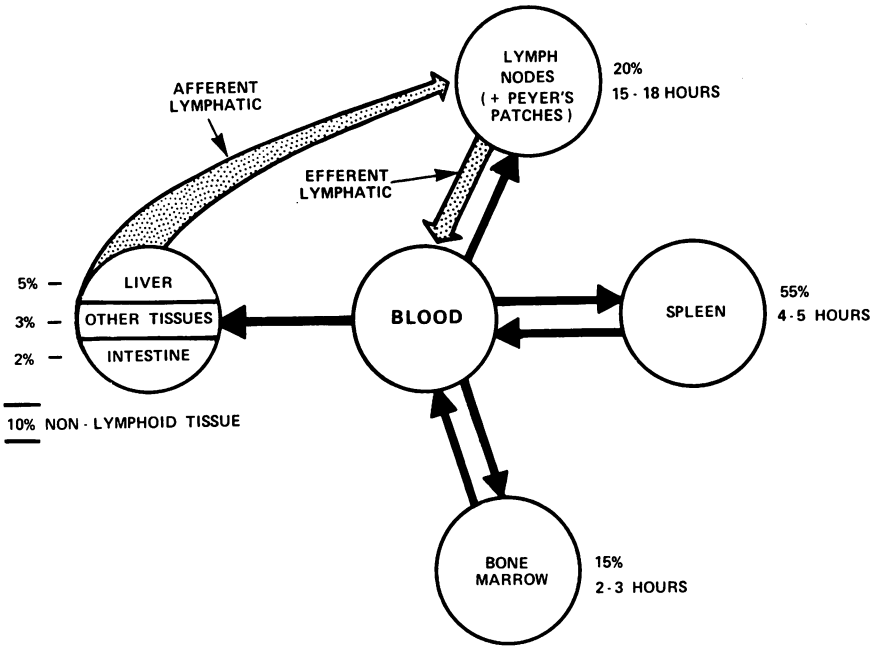

Figure *Migratory pattern of recirculating T cells.*

the same cells leave the blood for the spleen, bone marrow, or lymph nodes so that this pool of cells is redistributed between these compartments at random. There are several hints, however, falling far short of proof, that the T cells in peripheral lymph have intrinsically different properties from those in the blood. For example, the proportion of Ia-positive T cells is much higher in human peripheral lymph than in the blood (Godal and Engeset, 1978). This suggests the existence of a small pool of T cells recirculating preferentially through non-lymphoid tissue. In the sheep there is evidence for a pool of T lymphocytes that recirculate preferentially through the gut (Cahill *et al.*, 1977).

Recirculation of B lymphocytes

Many of the small B lymphocytes in blood and lymph are capable of crossing the same blood vessel walls as T lymphocytes and recirculating back to the blood from the spleen, lymph nodes, and bone marrow. Although B and T lymphocytes arrive at the spleen and lymph nodes by a common entrance they segregate within a few hours after entering the tissue (Nieuwenhuis and Ford, 1976). B lymphocytes pass on into the follicular areas, particularly the lymphocyte corona surrounding germinal centres. Probably, because B lymphocytes take a longer and more devious route, their transit time through tissue is longer than that of T cells and is also spread out over a considerable period (Howard, 1972). This is in the order of 12-48 hours and may be about the same for the lymph nodes and the spleen, although the data available for B lymphocyte recirculation between the spleen and the blood are very imprecise. Clearly the spleen has a relatively larger content of recirculating B cells than lymph nodes, suggesting that they may take several times as long to return to the blood as T cells.

Some B cells (as now defined by the detection of surface immunoglobulin produced within the cell) lack the capacity to recirculate. According to Strober's extensive data virgin B lymphocytes are non-recirculating and frequently dividing (Strober, 1975). A superficial paradox is that they are present in thoracic duct lymph. By contrast, memory B lymphocytes belong to the recirculating pool. Although thorough and careful, this work is confined to a few antigens in one species. If it is generally valid then one of the proposed functions of lymphocyte recirculation must be re-examined. During a primary response the few lymphocytes sensitive to the specific antigen are thought to be recruited from the whole recirculating pool into the antigenically stimulated organ. Possibly this applies only to virgin T lymphocytes, which apparently do recircu-

late. There is no doubt that recirculating small lymphocytes (B and T) are vectors of immunological memory, and the spread of the capacity to make a secondary response is certainly a reflection of lymphocyte redistribution (Gowans and Uhr, 1966). If this were the only function, however, there would be no need for such a dynamic recirculation.

Effect of antigenic stimulation on lymphocyte distribution

The arrival of an antigen at a lymph node or the spleen has a number of well established consequences for the recirculation of lymphocytes within that organ. At least three separate phenomena occur.

(1) There is non-specific retention or trapping of lymphocytes. As first noted by Hall and Morris (1965b), the output of lymphocytes from a lymph node diminishes within an hour of antigenic stimulation. This may proceed to almost complete arrest of release. When inspected histologically the cortical sinuses in stimulated lymph nodes are seen to be congested with lymphocytes—an appearance that has been described rather speculatively as 'plugging'. The output of cells in efferent lymph returns to normal usually after 6-24 hours. There is some evidence that the effect is mediated by a radioresistant cell, probably a macrophage (Frost and Lance, 1974). The significance of this mechanism for the function of the lymph node is uncertain.

(2) There is specific retention of the set of lymphocytes responsive to a particular antigen. Antigen specific T and B cells are sequestrated from the recirculating pool under the influence of antigen. Recently Sprent (1978) has shown that in the response to sheep erythrocytes this requires identity between T lymphocytes and radioresistant host cells, probably macrophages, at the major histocompatibility complex. Presumably antigen-laden macrophages winnow out specific T and B cells from the traffic streams. Although the histological site of this process is open to argument the T areas of the spleen and lymph nodes seem to be the most likely candidates. These areas have a resident population of interdigitating cells and a vigorous traffic of B cells.

(3) There is growth of the organ. After stimulation with sheep erythrocytes the popliteal lymph node of the rat increases in weight threefold in 3-4 days. The blood flow to the node and the lymphocyte influx from the blood both increase hand-in-glove with the increase in weight (Drayson *et al.*, manuscript in preparation, 1979). Similar increases in blood flow and lymphocyte influx have been found after lymph nodes have been stimulated by other antigens (Hay and Hobbs, 1977). This effect has probably been confused with non-specific retention (inhibition of lymphocyte release) in experiments where increased numbers of lymphocytes have been found in antigenically stimulated tissue. In general such measurements do not distinguish increased influx from decreased efflux.

Mechanism of lymphocyte migration from the blood

When lymphocytes migrate selectively into lymphoid organs under physiological conditions or into sites of inflammation selective adhesion to vascular endothelium is assumed to be the initial critical step. Because of the hydrodynamic shearing force tending to sweep cells off vessel walls and because most lymphocytes in the blood display microvilli which tend to minimise the initial area of contact between the cell and an external surface this adhesive force must be rather strong and must develop quickly (Anderson and Anderson, 1976). The adhesion must also be reversible, because after penetrating between endothelial cells the lymphocyte must lose contact with the endothelium as it insinuates itself between the layers of the basement membrane.

The mechanism of the selective adhesion of lymphocytes to specialised vascular endothelium has been approached by treating either lymphocytes or endothelium with enzymes as well as many other agents. Woodruff and Gesner (1968) made the remarkable finding that light trypsinisation of lymphocytes prevents them migrating into lymph nodes but has no effect on their migration into the spleen. This work has been extended and we know that trypsinisation also prevents migration into gut associated lymphoid tissue and an adjuvant granuloma (Rannie *et al.*, 1977). These are the same sites in which high endothelial venules have been noted. However, migration into the spleen, bone-marrow, liver, and other tissues is barely affected by trypsinisation. A number of agents, including the metabolic inhibitor sodium azide, have an effect on lymphocytes similar to that of trypsin (reviewed by Ford *et al.*, 1978). Since there is ample evidence that most of the lymphocytes recirculating between the spleen and lymph nodes belong to a common pool, the results indicate that the mechanisms of the migration of the same cells into different organs are somewhat different. So far as present knowledge extends the only way completely to inhibit intravenously injected lymphocytes from entering the white pulp of the spleen is to kill them.

Many other agents, including dextran sulphate and the lymphocytosis-promoting factor of *Bordetella pertussis*, stop lymphocytes from entering lymph nodes. These two agents may act, at least in part, on the specialised endothelial cell (Ford *et al.*, 1978). But more information is needed before such agents

can be usefully applied to manipulate immune responses.

Lymphocyte migration into the skin

So far this account has been confined to the distribution of small lymphocytes. The migratory patterns of large lymphocytes (defined operatively by their ability to incorporate RNA precursors like ^{125}IUdR *in vitro*) promise to be even more complex. This section is restricted to summarising Rannie and Ford's work (1978b) on the migration of large lymphocytes (and other populations) from the blood into the skin under three conditions—(1) inflammation induced by applying croton oil, which has no specific immune component; (2) inflammation induced by applying a contact sensitising agent (dinitrochlorobenzene (DNCB)) to a previously sensitised animal; and (3) normal skin.

The localisation in the skin of thoracic duct (TD) lymphocytes labelled *in vitro* with ^{125}IUdR was estimated at 0·5 h, 2 h, and 24 h after intravenous injection. The Table shows only the 24-hour values because at earlier time intervals significant differences were always in the same direction although they were less pronounced. Precautions were taken to remove from the samples radioactivity that had leaked from the labelled cells (Rannie and Donald, 1977).

As expected from much other work (for example, Asherson and Allwood, 1972), these blast cells localised in increased numbers in the inflammatory lesions, especially that induced by croton oil. When ^{125}IUdR blast cell localisation was compared with the localisation of ^{51}Cr-labelled TD cells (90-95% small lymphocytes) a much higher proportion of the blasts accumulated in the skin whether it was inflamed or not. More of the whole TD lymphocyte population localised in the contact sensitivity lesion than in the croton oil area, although the gross signs of inflammation were more intense in the latter. The superior localisation of large lymphocytes, *vis-à-vis* the whole population, was actually least pronounced in the case of contact sensitivity.

These results suggested that some cells in the TD population, other than large lymphocytes, have a superior ability to accumulate in immune-mediated lesions. Preliminary experiments suggested that this cell does not belong to the majority of recirculating small lymphocytes, because ^{51}Cr-labelled TD lymphocytes passaged from blood to lymph in an intermediate rat localised rather poorly in both types of inflammation. 'Long-lived' TD lymphocytes (defined by labelling a donor with ^{3}H-thymidine 3-6 weeks before transfer), however, did localise in much larger numbers in the contact sensitivity lesion. The localisation of these cells both in the normal skin and croton oil inflammation was barely above the threshold of detection.

Taken at face value, these limited results indicate that a long-lived, non-recirculating lymphocyte is capable of localising preferentially in immune-mediated lesions. This suggestion must be set in the context of our general ignorance of the train of events leading to the extravasation of mononuclear cells into inflamed sites. Possibly activated lymphocytes have no special propensity to enter immune-mediated inflammation. The low grade traffic into normal skin, however, may bring enough specific cells to a site of antigen deposition to bring about the changes in vascular endothelium which promote the emigration from the blood of the cells we have tentatively identified as localising preferentially in contact sensitivity sites.

Hall *et al.* (1978) have reported that a set of lymphocytes necessary for accelerated second-set rejection of cardiac allografts in rats is present in thoracic duct lymph and is non-recirculating. Also it is long lived, as defined by its resistance to treatment of the donor with the antimitotic drugs vinblastine and hydroxyurea for up to five days. Obviously there is an urgent need for more information about this cell which can apparently migrate into non-lymphoid tissues although it does not recirculate from blood to lymph. The possibility that it might be a monocyte has not been excluded, although macrophage precursors seem to be in a very small

Table *Per cent of injected dose/g of skin at 24 hours after intravenous injection (Rannie and Ford, 1978b)*

Skin site	*^{125}IUdR-TDL (activated cells)*	*^{51}Cr-TDL (whole population)*	*Passaged ^{51}Cr-TDL (accredited recirculators)*	*^{3}H-thymidine TDL ('long lived')*
Normal skin	0·073 (± 0·004)	0·014 (± 0·001)	0·0067 (± 0·003)	0·04 0·03
Croton-oil inflamed	0·64 (± 0·34)	0·039 (± 0·008)	0·0095 (± 0·0032)	0·04 0·04
DNCB contact sensitivity	0·30 (± 0·08)	0·069 (± 0·01)	0·0090 (± 0·0011)	0·38 0·29

Values are means ± SE except for ^{3}H-thymidine labelled TDL, where individual values are given.

minority in the rat TD lymphocyte population (Roser, 1976).

There seems to be no immediate prospect of performing analogous experiments on the migration of lymphocytes into human skin or other non-lymphoid tissues. This is simply because in experimental animals it is possible to label 50% of the recirculating pool but in humans it takes considerable effort to label 0·5% of the pool. An alternative approach might be to exploit cannulation of the peripheral lymphatic draining the foot, as Bremer *et al.* (1978) have done. This has already established that very few normal B lymphocytes recirculate through non-lymphoid tissues in the human, and, with one exception, the lymphocytes of chronic lymphocytic leukaemia patients also failed to follow this migration pathway. The traffic of cells through skin lesions may sometimes be studied by this technique and also patients with abnormal lymphocyte populations may be examined.

Conclusion

The unravelling of lymphocyte migration patterns has a long way to go. The dynamic recirculation of lymphocytes has so far made little impact on the thinking of pathologists or physicians, despite the fact that it is clearly relevant to such an everyday problem as judging the significance of a blood lymphocyte count.

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