CC/NUMBER 20
MAY 14, 1990

This Week's Citation Classic®

Gowans J L & Knight E J. The route of re-circulation of lymphocytes in the rat. *Proc. Roy. Soc. London Ser. B* 159:257-82, 1964.
[Sir William Dunn School of Pathology, Oxford, England]

A large pool of lymphocytes recirculates from the blood to the lymph by way of the lymph nodes. Lymphocytes enter the nodes from the blood via the high-walled postcapillary venules. [The *SCI*® indicates that this paper has been cited in over 1,160 publications.]

The Mystery of the Disappearing Lymphocytes

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January 5, 1990

After a year at the Pasteur Institute, I returned to the Sir William Dunn School of Pathology in Oxford in 1953 with no clear idea what to do. Howard Florey, with whom I had done a PhD before the Paris trip, suggested I work on lymphocytes, whose function and life history were then obscure. The main debate centred on the possibility that lymphocytes migrated from the blood into the bone marrow, where they became precursors of erythrocytes and granulocytes.

Florey pointed out an intriguing problem. Huge numbers of lymphocytes enter the venous blood each day from major lymphatic ducts in the neck. Since the number in the bloodstream remains constant, they must either be destroyed there or migrate to some unknown destination. The bone marrow (and the gut) were the main contenders. J.D. Mann and G.M. Higgins[1] had shown that the output of lymphocytes from a chronic thoracic duct fistula in the rat fell progressively over a few days to low levels. I confirmed their findings, and also discovered that if lymph and lymphocytes from a chronic fistula (but not lymph alone) were continuously reinfused into the blood, the fall in output could be prevented.[2] Why did this happen? Some tried to persuade me that the maintenance of lymphocyte output required the reutilization of the remnants of dead lymphocytes for new cell production. This implied that the cells in thoracic duct lymph were newly formed.

The next step was to collect lymphocytes from the thoracic duct, label them, reinfuse them into the blood, and see where they went. This was probably the most gratifying experiment I ever did: When P^{32}-labelled lymphocytes were reinfused, a large amount of cell-associated radioactivity appeared in the thoracic duct lymph. The simplest interpretation was that lymphocytes did not have a "destination"; they recirculated from blood to lymph, and thence, back into the blood. Sceptics still maintained that the labelled cells appearing in the lymph were not those that had been infused: The P^{32} had been reincorporated into new cells. This was easy to disprove. Continuous infusion of tritiated thymidine (sufficient to label all large, dividing lymphocytes) labelled only about 1 percent of the small lymphocytes. The great majority of small lymphocytes in lymph were old cells.[3]

The publication that is the subject of this commentary was the final paper in the series.[4] It was necessary to show that lymphocytic recirculation was a physiological process and to determine the route followed by lymphocytes as they passed from blood to lymph. We labelled thoracic duct lymphocytes with tritiated adenosine, infused them into rats of the same inbred strain, and determined their fate by autoradiography. The label was incorporated into the RNA of small lymphocytes and proved sufficiently stable to trace individual lymphocytes.

Autoradiography showed that the lymphocytes "homed" rapidly into the lymph nodes and Peyer's patches by way of the high-walled postcapillary venules; they also entered the white pulp of the spleen in large numbers, but not the thymus. Labelled cells also occurred in the lymphatic sinuses of the nodes, returning to the blood. When the thoracic duct was cannulated one day *after* infusion, the number of labelled cells in the lymph remained approximately constant for the next 36-48 hours, despite the usual progressive drop in total lymphocyte output: The labelled cells had mixed with the large pool of the recipient's own lymphocytes (about $1.5\text{-}2 \times 10^9$ cells). My research student, E. Julie Knight, observed that the large, dividing lymphocytes in lymph migrated preferentially into the lamina propria of the small intestine, where they became plasma cells.

Experiments in other mammals have shown that lymphocytic recirculation is a general phenomenon. We later suggested that its functional significance is to provide a mechanism by which regionally localized antigen can select specifically reactive lymphocytes from the total recirculating pool. Recent work has been concerned with different patterns of migration and distribution of lymphocyte subsets in lymphoid tissue and during inflammation elsewhere, and with the molecular nature of the recognition of endothelial cells for lymphocytes. The subject was reviewed recently by E.C. Butcher.[4]

1. **Mann J D & Higgins G M.** Lymphocytes in thoracic duct, intestinal and hepatic lymph. *Blood* 5:177-90, 1950. (Cited 85 times.)
2. **Gowans J L.** The effect of the continuous re-infusion of lymph and lymphocytes on the output of lymphocytes from the thoracic duct of unanaesthetized rats. *Brit. J. Exp. Pathol.* 38:67-78, 1957. (Cited 190 times.)
3. ————. The recirculation of lymphocytes from blood to lymph in the rat. *J. Physiology* 146:54-69, 1959. (Cited 435 times.)
4. **Butcher E C.** The regulation of lymphocyte traffic. *Curr. Topics Microbiol. Immunol.* 128:85-122, 1986. (Cited 45 times.)

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