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Splanchnic nerve stimulation increases the lymphocyte output in mesenteric efferent lymph

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Abstract. Mesenteric efferent lymph was collected from anaesthetized sheep. Lymph flow rate and leucocyte content (> 95% lymphocytes) were measured under control conditions and during stimulation of the left greater splanchnic nerve. During the first 5 min of nerve stimulation at 4 Hz lymph flow was increased by $128 \pm 57\%$ and lymph white cell count by $44 \pm 15\%$ ($P < 0.05$, $n = 8$ in both cases). This produced an overall increase in the white cell output of $228 \pm 151\%$ ($P < 0.05$, $n = 8$). The response was repeatable but short lived, with no significant differences from control being observed after the first 5 min of stimulation. There was a rise in the red cell count in arterial blood during nerve stimulation (from $3.21 \pm 0.24 \cdot 10^{12}\,l^{-1}$ to $4.48 \pm 0.22 \cdot 10^{12}\,l^{-1}$, $P < 0.05$, $n = 9$) but no statistically significant changes in the white cell count or percentage of lymphocytes. The increase in lymph white cell output could be mimicked by intravenous injection of noradrenaline while phentolamine blocked the nerve-induced increases in both lymph flow and white cell concentration. The possible mechanisms and immunological consequences of this α-adrenoceptor-mediated increase in lymphocyte traffic are discussed.

Key words: Adrenergic innervation – α-Adrenoceptors – Immune system – Lymph – Lymphocytes – Lymph node – Splanchnic nerve – Sympathetic innervation

Introduction

Whilst much research has been focussed on the activity of isolated immune cells in vitro, relatively few studies have attempted to examine their behaviour in the intact animal [22]. The reductionist approach has led to an increasing understanding of the molecular and cellular interactions between different elements of the immune system, but has not tended to emphasize possible regulation of immune behaviour by extrinsic control systems. As a consequence the ability of the nervous system to modify lymphocyte function has only recently been recognized [14, 15]. It has now been demonstrated, for example, that lymphocyte function and antibody production may be altered following experimental lesions of selected brain areas, although the mechanisms linking these events are not clear. That the lymph node is a potential site for interaction between the neurological and immune systems has been suggested by histochemical studies showing that a variety of nerves terminate on both the nodal structures and the lymphocytes within them [5, 16]. It has also been shown that field stimulation of nerves in isolated strips of mesenteric lymph node capsules produces α-adrenergic increases in contractile activity in vitro [11, 21], but the function subserved by this innervation in the living animal is unclear. One possibility is that it changes the lymphocyte population in a node or the number of lymphocytes returned to the bloodstream. This notion is supported by other studies showing that periods of emotional stress, which commonly give rise to increased sympathetic nervous activity, are associated with a relative lymphocytosis in animals [3] and man [4]. Such changes are likely to affect the continuous process of lymphocyte recirculation from blood to lymph and back again [7], which is believed to play a role in efficient immune surveillance [13].

The current study explores the possibility of neuroendocrine modulation of lymphocyte function through sympathetic nervous activity by examining the effects of splanchnic nerve stimulation on lymphocyte output in efferent mesenteric lymph in vivo. This site was chosen since the white cell output in intestinal lymph is roughly an order of magnitude higher than that in peripheral lymph (compare Fig. 1 with results in [12]), and also since something of the pharmacology of sheep mesenteric lymph node capsule responses to nerve stimulation is known [21]. The results demonstrate a short-lived α-adrenergic-mediated increase in lymphocyte output dur-

Part of this work has been communicated to the Physiological Society of Great Britain and Ireland [10]

ing splanchnic nerve stimulation which is a consequence of increases in both lymph white cell count (WCC) and lymph flow. Increases in the leucocyte count of the lymph appear to be independent of changes in lymph flow or circulating WCC, findings which are consistent with a mechanism dependent on lymph node contraction.

Materials and methods

Anaesthesia was induced in adult crossbred ewes (28–51 kg) with pentobarbitone sodium (20–30 mg kg^{-1}; i.v.) and maintained throughout the experiments with halothane (1–3% in O_2). The small intestine and mesentery were exteriorized through a right paramedian incision and wrapped in commercial foodwrap (Clingfilm, NISA, UK) to prevent dehydration. Polyvinylchloride (PVC) cannulae (dead space of < 100 µl) were pretreated for 30–45 min by filling with a 2% solution at a heparin complexing agent (Polysciences, Moulton Pk., Northampton, UK) and then flushed with heparin in saline. The efferent lymphatic draining the mesenteric lymph node chain was cannulated about 10–15 cm from its origin so that intestinal lymph could be collected. The intestines were then returned to the abdominal cavity, the incision sutured and the lymph outlet placed level with the lumbar vertebral column. The right femoral artery was cannulated via an inguinal incision and connected to a Statham P23 transducer. Arterial blood pressure was recorded using a Gould 2400 chart recorder and mean arterial pressure (MAP) was calculated using the following equation: MAP = diastolic pressure + (systolic pressure − diastolic pressure)/3.

The left greater splanchnic nerve was exposed through a paravertebral incision, tied just below the diaphragm and cut. The distal end was enclosed within an electrode filled with conducting gel allowing the nerve to be stimulated at the chosen frequency (normally 4 Hz) using a Grass S88 stimulator (0.2 ms pulse duration and 30 V nominal strength). In some animals the external jugular vein was also cannulated to allow intravenous administration of drugs. L-Noradrenaline acid tartrate (Levophed, Winthrop Laboratories) and phentolamine mesylate (Rogitine, Ciba) were used in these experiments.

Lymph was collected into pre-weighed containers anticoagulated with approximately 2 mg dry potassium ethylenediaminetetracetate (K^+ EDTA). Lymph flow rates were calculated from the weight change during timed collections, assuming a lymph density of 1.02 g ml^{-1} [24]. In some experiments 5-ml samples of femoral arterial blood were drawn off and placed in similar K^+ EDTA containers. Conventional blood and lymph cell counts were carried out using 2% acetic acid as diluent for WCC. Lymph and blood smears were also methanol fixed and stained with eosin and azur B (Diffstat; Laboratory Supplies & Instruments, Antrim, N. Ireland) to allow differential white cell counting (DWCC). In all the lymph samples examined the cells appeared to be exclusively lymphocytes both before and during stimulation, although it can be difficult to distinguish these from monocytes on the basis of morphology alone [8]. Blood lymphocyte counts were calculated using the formula: lymphocyte count = WCC × % lymphocytes/100.

Summarized results have been presented as means ± 1 SEM. The statistical significances of differences in mean values were tested using a paired Student's *t*-test except in the case of the time course results (Figs. 2, 4) for which a single factor, repeated measures analysis of variance (ANOVA) was used with Fisher's protected least significant difference test. In all cases the significance level was set at 5%.

Results

Response to splanchnic nerve stimulation

The typical effects of stimulation of the left greater splanchnic nerve (5 min at 4 Hz) are demonstrated in

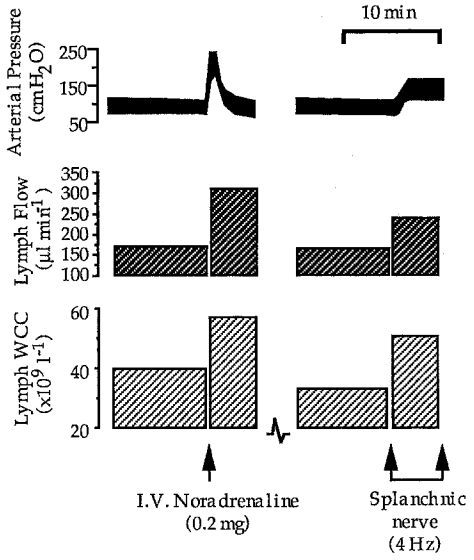

Fig. 1. Results from a single experiment showing the effects of noradrenaline (*left hand panels*) and splanchnic nerve stimulation (*right hand panels*) on femoral arterial pressure (*top record*), mesenteric efferent lymph flow (*middle panels*) and the white cell count (*WCC*) in mesenteric lymph (*bottom panels*). Lymph was collected for 10 min under control conditions. A bolus injection of noradrenaline (0.2 mg in 5 ml physiological saline) was then administered via the external jugular vein (*single arrow*) and lymph collected during the following 5 min. After a 15-min recovery period (break in ordinate) followed by a further control collection, the left greater splanchnic nerve was stimulated continuously at 4 Hz for 5 min (*double arrow*) during which time a further lymph sample was taken

results from one such experiment (Fig. 1, right hand panels). Blood pressure (top panels) rose as expected in response to sympathetic stimulation, with MAP increasing from 60 mm Hg before, to a plateau level of 93 mm Hg during stimulation. Average lymph flow (middle bar chart) was 241 µl min^{-1} over the latter period, as compared with 164 µl min^{-1} under control conditions, while the leucocyte density in the lymph (bottom bar chart) was increased from $33.2 \cdot 10^9\ l^{-1}$ to $51.2 \cdot 10^9\ l^{-1}$ by nerve stimulation. From these changes it can be calculated that the total rate of white cell output in the lymph more than doubled in response to nerve stimulation, rising from $5.44 \cdot 10^6$ min^{-1} to $12.36 \cdot 10^6$ min^{-1}. These effects were compared with those observed following a bolus injection of noradrenaline into the external jugular vein of the same animal (0.2 mg noradrenaline in 5 ml 0.9% NaCl over 2 s; Fig. 1, left hand panels). This produced a dramatic, but more transient rise in blood pressure and was followed by marked increases in lymph flow (from 169 to 313 µl min^{-1}) and lymph WCC (from $39.8 \cdot 10^9$ to $57.0 \cdot 10^9\ l^{-1}$). Consequently, lymph white cell output was increased by over 150%, rising from $6.73 \cdot 10^6$ to $17.86 \cdot 10^6$ min^{-1}. The accelerated output of lymph-borne leucocytes (almost exclusively lymphocytes) seen during splanchnic nerve stimulation can, therefore, be mimicked by circulating noradrenaline, as might be expected for an adrenergic sympathetic response.

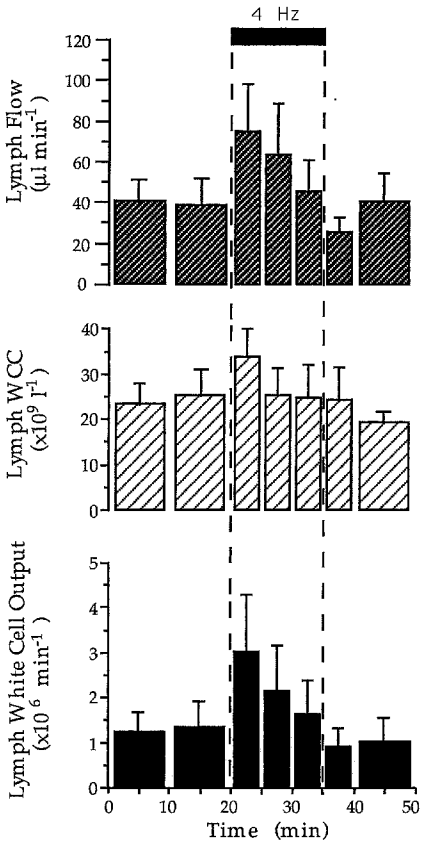

Fig. 2. Mesenteric efferent lymph responses to sustained splanchnic nerve stimulation. Lymph samples were collected before, during (*horizontal bar* and *vertical dashed lines*) and after 15 min stimulation of the left greater splanchnic nerve (4 Hz). Lymph flow (top panel) and lymph WCC (*middle panel*) were measured and used to calculate the white cell output in lymph (*bottom panel*). These summarized results plot the means ± SEM for eight sheep

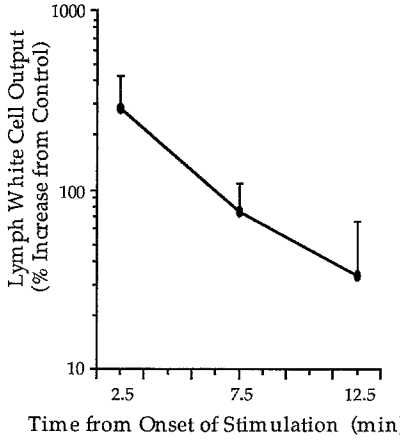

Fig. 3. Time-dependent decay of the increase in lymph white cell output during splanchnic nerve stimulation. The data from the eight experiments summarized in Fig. 2 were reanalysed with the increase in lymph white cell output for each of three samples taken during splanchnic nerve stimulation being expressed as a percentage of the output during the control period. Means ± SEM have been plotted on a logarithmic scale against the mid-time point for each collection period

Time course of splanchnic nerve effects

In order to examine the time course of the nerve mediated responses exemplified above the splanchnic nerve was stimulated continuously for 15 min at 4 Hz in nine animals. This increased MAP from 78 ± 7 mm Hg during the control period to a peak value of 113 ± 7 mm Hg during stimulation ($P < 0.0001$). In one animal lymph flow ceased completely during the stimulation period and this was excluded from the pooled data since obviously no value was available for the lymph WCC during stimulation. It was noted, however, that both lymph flow and WCC in this animal were considerably higher immediately after the stimulation period than they had been before it. When lymph collected during the first 5 min of nerve stimulation was compared with that from the preceding 10-min control period for the remaining eight animals (Fig. 2) there were increases in lymph flow (from 43 ± 14 µl min^{-1} to 82 ± 26 µl min^{-1}, $P < 0.05$), WCC (from 25.3 ± 5.7 · 10^9 l^{-1} to 33.9 ± 6.2 · 10^9 l^{-1}, $P < 0.05$) and white cell output (from 1.31 ± 0.59 · 10^6 min^{-1} to 3.02 ± 1.27 · 10^6 min^{-1}, $P < 0.05$). These responses were relatively short-lived, however, with the average lymph WCC returning to control after 5 min of nerve stimulation. Although mean lymph flow and, therefore, white cell output remained somewhat above basal levels for the next 10 min, these differences declined with time and were not statistically significant. The time course of decay in the lymph white cell output response to splanchnic stimulation is seen more clearly when the mean percentage increase above control is plotted on a logarithmic scale for the three sample times during stimulation (Fig. 3). This relationship is almost linear with a $t_{1/2}$ for the decline in the response to continuous splanchnic nerve activity of approximately 3.2 min.

Morphological examination of lymph samples showed that their leucocyte content consisted almost exclusively of lymphocytes before, during and after stimulation. Since the majority of lymphocytes enter lymph by migration out of the bloodstream [2] one possible explanation for an increased white cell output during splanchnic stimulation might be an increased rate of lymphocyte transit through the intestinal microcirculation. Decreased blood flow due to adrenergic vasoconstriction would militate against this [9] but this might be offset if there were an adequate increase in the arterial leucocyte count. Femoral arterial samples showed an increase in the mean red cell count from a control level of 3.21 ± 0.24 · 10^{12} l^{-1} to a peak of 4.48 ± 0.22 · 10^{12} l^{-1} at the end of the 15-min stimulation period (Fig. 4, $P < 0.05$, $n = 9$), presumably reflecting splenic contraction [18]. There were parallel increases in both WCC and lymphocyte counts but these changes were not statistically significant, and there was no change at all in the mean percentage of lymphocytes circulating in blood (49 ± 1% before stimulation and 49 ± 2% after 15 min stimulation at 4 Hz, $n = 6$). It seems unlikely, therefore, that the increased lymphocyte output in lymph is simply due to increased traffic of blood-borne lymphocytes through the drainage area, especially since the arterial lymphocyte count tended to increase throughout the

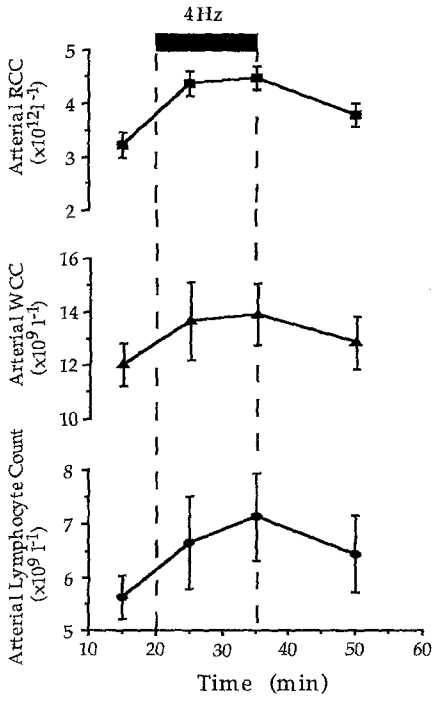

Fig. 4. Changes in arterial blood cell counts during splanchnic nerve stimulation. Red (*upper panel*) and white (*middle panel*) cell counts are plotted against time for samples of arterial blood samples taken before, during and after splanchnic nerve stimulation in the experiments summarized in Fig. 2 (data from nine sheep). In six animals a differential WCC was also performed and used to calculate the arterial lymphocyte count (WCC × %lymphocyte, *bottom panel*). Mean ± SEM is shown for each time

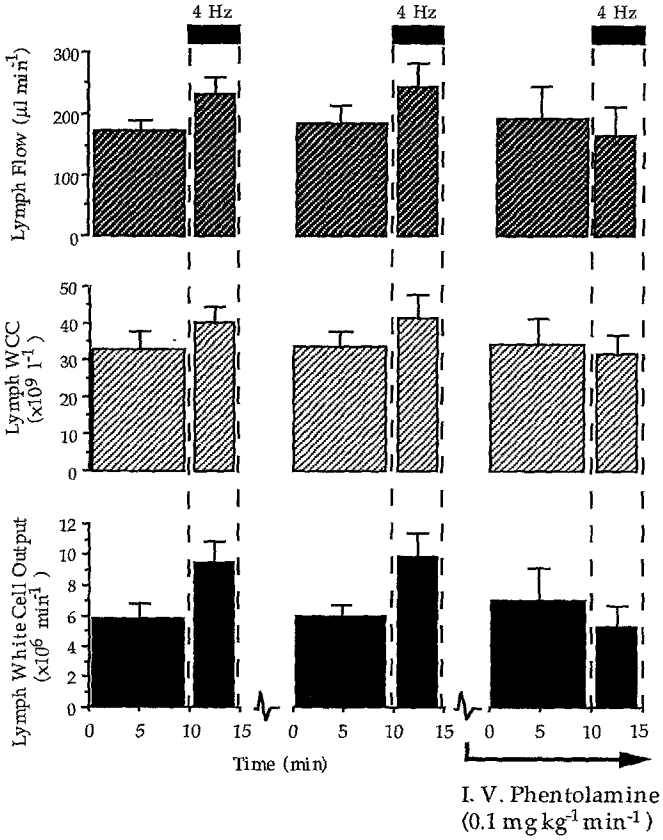

Fig. 5. Blockade of the effects of splanchnic nerve stimulation by phentolamine. Lymph was collected before and during stimulation of the left greater splanchnic nerve at 4 Hz (*horizontal bars* and *vertical dashed lines*). Lymph flow (*top panel*), lymph WCC (middle graph) and the rate of white cell output in lymph (bottom graph) were all increased during repeated 5-min stimulation periods under control conditions (*left hand* and *middle panels*), but not after 15 min infusion of phentolamine via the external jugular vein (*right hand panels* set). In each case the mean ± SEM of results from five sheep is plotted against the time from the start of lymph collection. Breaks in ordinate indicate a 15–20 min break in lymph collection

stimulation period whilst the lymph response declined (Fig. 3).

Effects of intravenous phentolamine

A series of experiments was undertaken to examine the pharmacology of the lymph responses to splanchnic stimulation using the α-adrenoceptor blocking agent phentolamine. Lymph was collected during a 10-min control period and then during a 5-min period of splanchnic nerve stimulation (4 Hz). An increase in white cell output was seen as before, again due to increases in both lymph flow and WCC (Fig. 5, left hand panels). This protocol was repeated under control conditions after a 20-min recovery period and it can be seen that there was no time- or use-dependent decay in the responses (middle panels). Phentolamine was then infused via the external jugular vein for at least 15 min, and this abolished the increases in lymph flow and WCC in response to a further period of splanchnic nerve stimulation (Fig. 5, right hand panels). Thus, while lymph white cell output was increased from $5.73 \pm 0.92 \cdot 10^6$ to $9.41 \pm 1.41 \cdot 10^6$ min^{-1} during the first stimulation period ($P < 0.05$, $n = 5$) and from $5.90 \pm 0.69 \cdot 10^6$ to $9.82 \pm 1.59 \cdot 10^6$ min^{-1} during the second stimulation period ($P < 0.05$, $n = 5$) there was no increase during the third stimulation period, which occurred during phentolamine infusion, with the mean cell output actually declining from $6.79 \pm 2.31 \cdot 10^6$ to $5.29 \pm 1.39 \cdot 10^6$ min^{-1} (NS). These results, and the ability of circulating noradrenaline to produce effects similar to those of nerve stimulation (Fig. 1), suggest that the splanchnic nerve dependent increase in lymph white cell traffic is mediated via α-adrenoceptors.

Discussion

The idea that there may be neurological regulation of the behaviour of immune cells has been increasingly current. Selective ablation of brain tissue [14] and stressful conditions [17], for example, have been shown to alter immune function. A number of observations suggest that some of this control may be mediated by sympathetic nerves. Thus, the rate of white cell production by bone marrow increases in response to stimulation of post-ganglionic sympathetic nerves [23], while chemical sympathectomy reduces the primary immune response by lymph nodes in certain strains of mice [5]. The current

results reinforce the concept of neuro-endocrine modulation of the immune system through the sympathetic nervous system. Mesenteric lymph lymphocyte output was greatly increased both by stimulation of the greater splanchnic nerve and by intravenous administration of noradrenaline (Fig. 1) and this reflected increases in both lymph flow and the white cell concentration in lymph.

The findings in the present study are consistent with early reports that the WCC in lymph collected close to a mesenteric lymph node was increased when mesenteric nerves were stimulated in anaesthetized cats [6]. More recently it has been shown that the white cell output in sheep efferent lymph is increased following painful stimuli [20] and during stimulation of the lumbar sympathetic chain [12]. It seems clear, therefore, that increased sympathetic nervous activity increases the rate of lymphocyte return from the lymphatic system to the bloodstream. It is interesting to note, in this regard, that a relative lymphocytosis has been described in rats [3] and humans [4] under conditions of emotional stress. No such change was seen in the present experiments, however, with the percentage of lymphocytes in arterial blood being almost identical before and after 15 min of splanchnic nerve stimulation. It might be surmised that this was a consequence of the experimental technique employed, with diversion of the mesenteric efferent lymphocyte traffic away from the bloodstream due to cannulation of the duct. Calculations based on the leucocyte output during the stimulation period in Fig. 2, however, indicate that fewer than $35 \cdot 10^6$ additional lymphocytes would have reached the circulation during this time had the lymphatic been intact. This represents less than 0.1% of the estimated total number of circulating lymphocytes. Acute sympathetic nervous activity, therefore, does not produce a lymphocytosis under these conditions but the effects of acute or chronic stress in an unanaesthetized animal may be quite different.

A number of possible mechanisms might account for the increased lymphocyte density seen in lymph during splanchnic stimulation. Histological studies of lymph nodes have demonstrated that sensory nerve terminals adjacent to intra-nodal lymphocytes stain positively for neuropeptides [16], while adrenergic nerve endings are found adjacent to the capsule and distributed through the parenchyma of the node itself [5]. It has also been shown that field stimulation in vitro produces nerve mediated contraction in strips of mesenteric lymph node capsule from both cattle [11] and sheep [21]. It is easy to conceive of such nodal contractions leading to lymphocyte enrichment of the efferent lymph by simple expulsion of cell rich fluid from the node. The time course of the observed response fits well with such a mechanism since one might expect any lymphocyte addition to be complete once lymph node contraction is maximal. The in vitro experiments indicate that this occurs within the first 2 min of nerve stimulation [21]. This is entirely consistent with the present experiments in which the WCC in the lymph was elevated for the first 5 min collection period only (Fig. 2). The pharmacology of the lymph node capsule contraction is also appropriate since it can be reproduced using exogenous noradrenaline (J. G. McGeown, unpublished data) and is inhibited by the α-adrenoceptor antagonist phentolamine [11, 21]. This was also the case with in vivo changes in lymph white cell traffic (Figs. 1, 5).

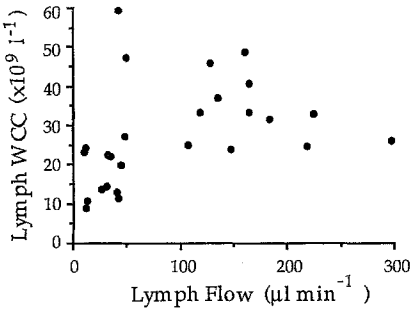

Fig. 6. Scattergram of lymph white cell count against lymph flow. Each data point represents paired measurements for a single lymph collection period under control conditions. Duplicate results from 13 different animals have been used, giving a total of 26 data pairs. Leucocyte density is only weakly correlated with lymph flow ($r = 0.37$)

The considerations outlined above make lymph node contraction a likely candidate mechanism for the production of an elevated lymphocyte output in lymph. Additional studies would, nevertheless, be required to test this more directly since it is impossible to exclude a number of alternatives on the basis of the current evidence. For example, increases in lymph flow might flush additional lymphocytes out of lymphoid tissues leading to an increase in lymph WCC. Some observations run counter to this idea, however. In particular, the lymph WCC returned to control values before lymph flow during prolonged nerve stimulation (Fig. 2), suggesting a separate, shorter-lived element to the response. As well as this discordance in time courses it should also be noted that there was little correlation between the flow rate and the lymph leucocyte count under control conditons (Fig. 6). On the other hand, nerve stimulation might alter lymphocyte recirculation from blood to lymph, perhaps by increasing the rate at which lymphocytes are presented to the lymphoid tissue. Considering that there is probably a reduction in blood flow through the splanchnic circulation during periods of sympathetic vasoconstrictor activity this seems unlikely. It might still be conceivable were there to be an adequate increase in the numbers of lymphocytes carried in blood. The average total WCC, and therefore the lymphocyte count, tended to increase in blood samples taken during stimulation, but these changes were not statistically significant and, once more, their time courses were very different from that of the increase in lymph white cell output (Figs. 3, 4). These global measurements suggest that the changes in lymph cell traffic are not secondary to changing vascular and haematological conditions. Nevertheless, some local effect on lymphocyte migration in the mesenteric nodes or Peyer's patches cannot be ruled out.

Just what immunological consequences a change in the numbers of lymph-borne lymphocytes may have remains a matter for speculation. Any factor altering the numbers and distribution of lymphocytes within lymph

nodes may alter the mechanics of immune surveillance given the important role of nodal tissue as an antigen filter for the drainage area. Just what the overall effect of such alterations on immunity would be is, however, impossible to predict. Such information as is available on the immunoregulatory influences of sympathetic activity is somewhat contradictory. Decreased immune responses have been described in some studies carried out under stressful conditions likely to be associated with increased sympathetic nervous activity [17]. The interpretation of these observations is, however, inevitably complicated by the wide range of possible neuro-humoral changes associated with stress. More direct studies of the effects of sympathetic activity have provided evidence for both sympathetically mediated enhancement [5, 23] and inhibition [1] of immunity. The fact that lymphocytes are by no means a homogeneous population, with different subsets having different migratory proclivities and immunological functions [2, 19], may help explain such differences since the responses to adrenergic stimuli may also vary on a regional and cellular level. All these aspects of neuro-endocrine regulation merit further study. Whatever the net effect, however, it seems clear that the lymph node is a potentially important site for α-adrenergic regulation of lymphocytes and, therefore, of immune function.

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