periods. Intravenous brinase (100 mg.) increased T cells from 34% to 85% after ten days, with a fall back to 34% ten days later. A lymphocyte " wash " on the separator increased T cells from 34% to 70% after eight days, but they were back again at 34% by day 12. There was no clinical improvement. A fuller report will be published later.

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MECHANISM OF LACTIC ACIDOSIS

SIR,—I appreciate the comments of Dr Cohen and his colleagues (Aug. 17, p. 405) concerning the relationship between lactate utilisation and the pathogenesis of lactic acidosis. Their suggestion that tissue utilisation of lactate occurs as the acid rather than the anion is reasonable, although I am not aware of evidence which supports that position. Not only may lactate utilisation be associated with hydrogen-ion consumption, but also the oxidation or conversion of lactate to glucose by the liver results in bicarbonate generation; thus, impaired utilisation of lactate could theoretically cause acidosis by both these mechanisms.

My letter (June 29, p. 1351) related specifically to the question of isolated hepatic impairment of lactate utilisation. I doubt whether selective hepatic inhibition of lactate utilisation would result in excess hydrogen ions or a deficit of bicarbonate and systemic lactic acidosis unless the perfusion and/or utilisation of lactate by all tissues was concomitantly impaired. While the kidneys and liver are important in lactate homœostasis the role of skeletal muscle should not be minimised. Lactate utilisation by skeletal muscle is a concentration-dependent process.[1,2] When systemic lactate concentrations are raised net lactate balance across muscle becomes positive.[2,3] This suggests that the underutilisation of lactate or overproduction of lactic acid by the liver would not produce lactic acidosis or hyperlactatæmia due to a concomitant increase in lactate utilisation by other tissues (skeletal muscle). The fact that arterial lactate concentrations do not rise excessively in dogs when hepatic lactate extraction is inhibited by hypoxæmia and hyperperfusion [4] supports such a concept. I do not know whether the above concept would apply in bacteræmic shock, but if perfusion of skeletal muscle remained intact I see no reason why it would not. I suspect, however, that the perfusion of all tissues would be reduced in bacteræmic shock as it is in other types of low-flow states, thereby impairing the uptake and/or oxidation of lactate with resulting hydrogen-ion accumulation and diminished bicarbonate generation. In patients with clinical lactic acidosis regional measurements indicate that the production of lactic acid is generalised.[5]

Thus, the evidence that Dr Cohen and his colleagues requested supports the contention that isolated impairment of lactate utilisation by the liver does not produce lactic acidosis and that lactic acidosis is predominantly an overproduction acidosis. While underutilisation of lactate may contribute to lactic acidosis when perfusion of all tissues is impaired, I am unaware of any clinical or experimental evidence that supports such a proposal.

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MINOCYCLINE: POSSIBLE VESTIBULAR SIDE-EFFECTS

SIR,—In my experience the occurrence of vestibulitis in association with minocycline (Sept. 28, p. 744) is very likely. During an epidemic of bronchitis last spring, I used minocycline almost exclusively, in large numbers of patients, for I had found other antibiotics virtually ineffective. Minocycline proved very reliable and effective, but there were many complaints of giddiness. Only as recently as this week, I prescribed minocycline for a woman with severe asthma and bronchitis, and she found that she could not tolerate it because of weakness and vertigo. It is a remarkably effective antibiotic, and I would not hesitate to use it again, since the effects are transient and pass when treatment is stopped. All patients should be cautioned, however, because they may be at risk of falling when they get out of bed.

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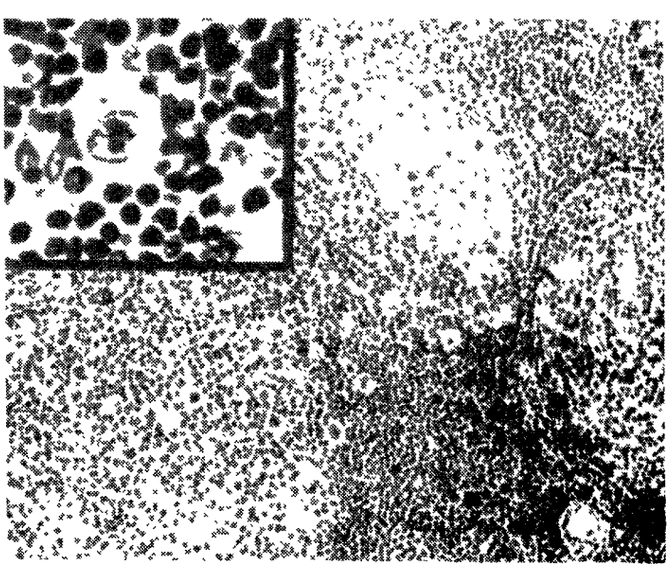
ORIGIN OF MALIGNANT LYMPHOMAS

SIR,—Professor Lennert [1] reported that the initial site of infiltration of lymph-nodes by lymphoreticular neoplasms might indicate whether they are of B or T cell origin. I wish to present evidence for the early involvement of the thymus-dependent areas of spleen and lymph-nodes in a patient with Hodgkin's disease.

A 71-year-old man had a cœliotomy because of suspected lymphoma. The spleen, which weighed 215 g., and periaortic lymph-nodes were removed. Gross examination of the spleen showed many lymphoid follicles throughout the parenchyma. Microscopical examination revealed many reactive follicles with germinal centres in the white pulp and small foci of Hodgkin's disease, which were not large enough to be seen grossly. These foci lay in the area of the perivascular lymphatic sheath (see accompanying figure), which is a thymus-dependent region. The lymph-nodes contained similar small foci of Hodgkin's disease, mainly in the paracortical or thymus-dependent zone. Both in the spleen and lymph-nodes the areas of involvement were characterised by collections of malignant-looking histiocytes (reticulum cells) including Sternberg-Reed cells, some of which had the characteristics of " lacunar cells ". In most areas the

1. Lennert, K. *Lancet*, Sept. 7, 1974, p. 586.



Part of white pulp of spleen containing follicle with germinal centre and central arteriole.

The lymphoid tissue around the central arteriole (thymus-dependent area) is partly replaced by a focus of Hodgkin's disease. Inset: Sternberg-Reed cell.

neoplastic cells were accompanied by mixtures of lymphocytes, eosinophils, and occasional plasma cells. " Focal " involvement of lymph-nodes by Hodgkin's disease has been described [2,3]; and Lukes [3] comments on the difficulty of classifying the histological type of Hodgkin's disease from such small focal lesions.

The sites of early involvement by lymphomas in lymph-nodes and spleen are of more than theoretical interest. They are of practical importance to the pathologist in the diagnosis of lymphomas, especially in detecting small early foci in tissue removed at staging cœliotomy.

According to the suggestion of Lennert that the first site of infiltration in a lymph-node (and, in this instance, also the first site of infiltration in the spleen) might give an indication of the origin of the lymphoma, a T-cell origin of Hodgkin's disease is favoured.

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PHENOLPHTHALEIN IN " ASPIRIN "

SIR,—Not everything in medical textbooks is necessarily correct. The usual teaching about proprietary preparations containing more than one drug is that these are undesirable. One reason is that flexibility of dose is removed. In practice, however, some of these mixtures are quite useful. Many compound mixtures for asthma which include both ephedrine and theophylline may be singularly successful: perhaps the drugs potentiate each other and prevent tachyphylaxis. Also taking one tablet may save the patient the trouble of coping with two or more pills.

In many cases, compounded mixtures seem to be more trouble than they are worth. Recently, one of us observed a new example of this. A 65-year-old man was seen with a fixed drug eruption. He denied taking any phenolphthalein laxatives. The only tablet he was taking was " aspirin ". This, however, was found to be a new preparation which contained phenolphthalein and codeine in addition to aspirin. We consider this to be an undesirable mixture of drugs to be taken over long periods. The continued use of irritant purgatives is hazardous and the increasing awareness of this has greatly diminished their use in clinical practice.

The incorporation of phenolphthalein into an analgesic preparation which could be taken over prolonged periods appears to be a retrograde step.

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TRAINING OF NURSES

SIR,—Your review (Aug. 10, p. 323) states baldly about Russian methods " that a system of nurse training which . . . leaves nursing administration and supervision in medical hands " is not preferable to our own system. This would be understandable if our own system were not inefficient with an inherently high wastage. Our system produces some good and some very good nurses, but there are far too many nurses who, during their training or as soon as they qualify, drop out of nursing. The major reason is the hieratic authoritarian system they have met during their training. Most of the nurses on the Salmon Committee were nurses who had foregone the care of patients and seemed at times to believe that the pursuit of administrative efficiency rather than good patient care was the *summum bonum* of the nursing service. To end the review with the suggestion that our own rigidities have been less inhibiting than those of the U.S.S.R. is to neglect to consider the sad inadequacies of the present system of nurse training in our country.

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CLASSIFICATION OF NON-HODGKIN'S LYMPHOMAS

SIR,—My colleagues and I derived great amusement from Dr Kay's letter (Sept. 7, p. 586). By all means, let us retain our sense of humour about the current controversy over the classification of non-Hodgkin's lymphomas. I find this rather difficult, however, in the face of the implications of the opening sentence in the letter by Dr Bennett and his colleagues (Aug. 17, p. 405). I clearly acknowledged their classification in my statement: " In order to reach a compromise between the concepts of Rappaport . . . those recently propounded by Lukes and those of Farrer-Brown, Bennett, and Henry in England . . ." Furthermore, it is ironical that, as far as I am aware, the only previously published report and discussion of their classification appears in a paper by Berard and me [1] and it is my understanding that a preprint of this paper was reviewed by Bennett and his associates. It is, nevertheless, some consolation to me that I have stimulated Bennett et al. to put pen to paper.

In the interest of amicable transatlantic relations, I sincerely hope that we can reach a compromise since there is no doubt about the similarity of the proposed classifications. It is equally evident, however, that there are differences of opinion which need clarification. I indicated in my previous letter that there are many who criticise the concept of " differentiation " of lymphocytes and I have thus eliminated this term from my classification. I also feel it is essential to include Burkitt's lymphoma as a distinct entity, despite accumulating evidence supporting its origin from lymphocytes bearing both B [2] and T [3] cell markers. The clinicopathological manifestations of Burkitt's lymphoma [4] and its response to therapy are so distinctive that its elimination from any histopathological classification would meet with the strong disapproval of oncologists, hæmatologists, immunologists, and many other individuals involved in the investigation of this type of lymphoma. I certainly concur with the observation that plasmacytoid differentiation may be seen in association with both small and large lymphoid lymphomas and I am thus quite happy to accept this modification. It is, however, questionable whether extramedullary plasmacytoma should be included in a classification of non-Hodgkin's lymphoma, merely on the basis of origin from B lymphocytes. Multiple myeloma is more akin to the leukæmias, and several of the leukæmias are presumed to be derived from lymphocytes of either B or T cell type. From a practical standpoint the management of myeloma and of extramedullary plasmacytoma is so different from that of the non-Hodgkin's lymphomas that these are best eliminated from this classification. I see no reason, however, to omit mycosis fungoides. Evidence is accumulating to support the concept that this disease is a distinct pathological entity and that the predominant cell is an atypical lymphocyte [5] most probably of T-cell type. This applies equally to Sezary's syndrome.[6]

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