Editorial

Lymphocytopenia in Hodgkin’s Disease

By ALAN C. AISENBERG

ALTHOUGH a depression in the blood lymphocyte count was observed by a number of early students of Hodgkin’s disease,1,2 this finding has received little comment in the recent medical literature. In the light of current concepts of lymphocyte function and the immunologic defect in Hodgkin’s disease, it has seemed worthwhile to review the implications of the profound lymphocytopenia of this condition.

To illustrate the lymphocytopenia of Hodgkin’s disease we selected 50 consecutive fatal cases seen at the Massachusetts General Hospital from 1958 to 1963 and histologically verified by the Pathology Department of this Institution (fig. 1). Patients were selected in whom at least 3 lymphocyte counts done during the last 6 months of life were available for averaging, excluding counts performed where there had been radiotherapy or chemotherapy in the prior month. Also included in figure 1, as separate entries, are the lymphocyte counts at the onset of histologically verified disease in the same 50 fatal cases, and in an additional 25 outpatient cases chosen to give a more representative spectrum of the disease.

The profound lymphocytopenia characteristic of the terminal months of Hodgkin’s disease is well illustrated in figure 1. The average lymphocyte count was in the normal range (1500-3000 per mm.3) in only 2 patients with advanced disease, whereas in 78 per cent the average was below 500 per mm.3 In contrast to the profound reduction of lymphocytes of late Hodgkin’s disease, at the onset of disease the lymphocyte count tended to be in the low normal range or only slightly depressed.

The extent to which the Hodgkin’s disease process itself rather than its therapy contributed to the lymphocytopenia is difficult to assess in view of current practices in the management of this condition. Although lymphocyte counts from the period immediately following therapy were excluded from study, it still is possible that lymphocytopenia was due in part to late effects of irradiation,3 alkylating agents,4 or adrenal corticosteroid therapy,5 all known to be lympholytic in action. However, correlation of lymphocyte count with disease course and treatment in the present series suggests that the disease itself is an important factor in the lymphocytopenia. It should also be noted that in the series of cases reported by Wiseman,2 collected prior to the use of intensive radiotherapy and chemotherapy, a depression of lymphocyte count was found in 87 per cent of the patients.

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A well-defined defect in immunologic reactivity is seen in active Hodgkin's disease (see review⁶). This is characterized by the early loss of the delayed, bacterial or cellular type of hypersensitivity⁷-¹⁰ and increased susceptibility to infection with certain fungi, mycobacteria and viruses.¹¹-¹³ Since immunologic observations from a number of laboratories¹⁴-¹⁸ over the past decade have established the importance of cells of the lymphocyte series in mediating de-
lyed hypersensitivity, it appears likely that the profound lymphocytopenia observed in advanced Hodgkin’s disease is contributory to the immunologic deficiency of this condition. However, it is unlikely that the lymphocytopenia is the sole cause of the immunologic deficiency, since a loss of delayed hypersensitivity may be seen in early, active Hodgkin’s disease, at a time when lymphocytopenia is not observed.

Realization that Hodgkin’s disease is not an immunologic entity but a clinical condition with varying involvement of the reticuloendothelial system is essential for an understanding of the immunologic status of the Hodgkin’s patient. Presumably the immunologic deficiency progresses with the advancing disease process. Quite early in the disease depression of delayed hypersensitivity is seen, manifested by negative skin tests to allergens to which a control population reacts and by inability to develop hypersensitivity following the application of dinitrochlorobenzene (DNCB). Antibody formation is essentially intact in such early patients, although a subtle defect in antibody synthesis is suggested by suboptimal primary response to certain antigens, and by an antibody response of abbreviated duration. (Further understanding of the antibody forming ability of the early Hodgkin’s patient awaits study of 7S and 19S antibody formation in these individuals). As indicated in figure 1, at this stage of the disease the peripheral lymphocyte count is usually normal or but slightly depressed. Since it is known that the lymphocyte population is not homogenous either morphologically or biochemically, it is possible that early in the course of Hodgkin’s disease a selective loss of a lymphocyte population occurs, which is undetected by simply counting the total number of lymphocytes of the peripheral blood. The only data available on this point are the observations of others and our own impression that throughout the course of Hodgkin’s disease the predominant lymphocyte remains the small mature cell. Such early Hodgkin’s patients contrast strikingly with individuals with the congenital sex-linked recessive form of agammaglobulinemia in whom there is defective antibody formation in the face of essentially normal delayed hypersensitivity.

In advanced Hodgkin’s disease it is likely that the depression of delayed hypersensitivity is more profound, though verification of this point is elusive because of the difficulty in quantitating the reaction. Since the ability to acquire DNCB sensitivity is absent in the early patient, DNCB sensitization is not a satisfactory technic for determining the intensity of anergy. However, there does appear to be a higher incidence of unresponsiveness to delayed allergens (tuberculin, Trichophyton, Candida, streptokinase-streptodornase and mumps skin test antigen) in the advanced Hodgkin’s patient, and it is in such individuals that severe mycotic infections are usually seen. In the advanced Hodgkin’s patient, depression of peripheral lymphocyte count is regularly observed and antibody formation is often depressed as well. In some regards the immunologic state of the advanced Hodgkin’s patient resembles the lymphocyte-depleted rats of Cowans, though a closer parallel is perhaps the “Swiss” form of agammaglobulinemia, a disease characterized by lymphocytopenia, thymic hypoplasia, frequent bacterial and fungal infections and early death. It should be noted that in the patient with advanced
Hodgkin's disease it becomes difficult to discriminate the anergy of Hodgkin's disease from that of a prolonged, debilitating illness.

It is reasonable to inquire into the mechanism of the anergy of early Hodgkin's disease since clearly this cannot be accounted for by lymphocytopenia. Several lines of evidence suggest that lymphocyte function is not normal in early Hodgkin's disease despite the normal peripheral lymphocyte count. First, it has been observed that transferred Hodgkin's lymphocytes fail to give the normal lymphocyte transfer reaction. Secondly, a preliminary observation suggests that Hodgkin's lymphocytes do not respond in vitro to mixed culture and phytohemagglutinin in the same manner as normal cells.

It is of some pertinence whether the anergy of early Hodgkin's disease is a central inhibition (tolerance), or a peripheral failure of the effector lymphoid cell. Depression of delayed hypersensitivity in the face of essentially normal antibody formation, and the recovery of sensitivity during disease remission, suggest an intact central mechanism. Furthermore, the failure to effect transfer of delayed hypersensitivity to Hodgkin's patients with peripheral lymphocytes from normal, hypersensitive donors is consistent with a peripheral mechanism for the immunologic defect. The most conclusive evidence for a peripheral defect would be the successful transfer of delayed hypersensitivity from the anergic but hypersensitive Hodgkin's patient to a normal individual, but our preliminary efforts in this direction have been unsuccessful. However, even in the absence of this conclusive experiment, the evidence strongly favors a peripheral lymphocyte defect.

It has been suggested recently that lymphocytes may subserve a trophic as well as an immunologic function. The evidence of this trophic function derives chiefly from observations of the fatal wasting disease that affects neonatally thymectomized animals, a disease characterized by severe depletion of the lymphocytes of both blood and tissues. If such a trophic function exists, its loss may contribute to the terminal decline of the Hodgkin's patient. (Depletion of tissue lymphocytes in Hodgkin's disease has been commented upon in the past.) However, it should be stressed that the pathogenesis of the thymectomy-wasting syndrome remains unsettled at the time of writing, as does the role of the thymus in Hodgkin's disease. The most recent evidence, i.e., the absence of wasting in thymectomized mice raised under germ-free conditions, suggests that the thymectomy-wasting syndrome may in fact be the result of terminal infection.

Finally, it should be remarked that lymphocytopenia may be observed in conditions other than Hodgkin's disease, particularly advanced carcinoma and uremia. However, it is of some significance that depressed immunologic reactivity is also frequently observed in these conditions. Regardless of the pathogenesis of the lymphocytopenia of Hodgkin's disease, or its specificity to this illness, it seems likely that the reduced lymphocyte number contributes to the immunologic defect seen in advanced Hodgkin's disease. This suggestion has received little attention in the past. In addition, recent knowledge of the immunologic significance of the lymphocyte should stimulate the investiga-
tion of lymphocyte function in other diseases where immunologic mechanisms may apply.

**SUMMARY**

The lymphocytopenia of Hodgkin’s disease has been reviewed in the light of recent knowledge of lymphocyte function. It is suggested that the anergy of early Hodgkin’s disease is a peripheral defect—a manifestation of abnormal lymphocyte function. Later in the course of the condition profound lymphocytopenia develops and most probably contributes to the more severe immunologic deficiencies of advanced Hodgkin’s disease.

**REFERENCES**


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Editorial: Lymphocytopenia in Hodgkin’s Disease

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