HODGKIN'S DISEASE

Edited by Sir David Smithers

Hodgkin's Disease

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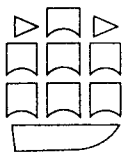

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Preface

Hodgkin's disease has long created an interest and acquired an importance out of all proportion to its frequency. Ideas about its nature, epidemiology, aetiology, modes of spread and treatment have all been changing rapidly over the past few years, and increasing success with treatment has been an added stimulus to discussion. Its study has engaged the attention of people working in many different disciplines and a series of small international meetings in Paris, Rye, London, Ann Arbor and Palo Alto have served to concentrate effort, disseminate information, agree classification and staging, secure uniformity of histological reporting and bring the subject forward in a way which could hardly have occurred so quickly or so effectively in any other. The Lymphoma Unit at The Royal Marsden Hospital, Surrey, has participated in these meetings and benefited greatly from them. Our debt to this small, varied and international group of friends and colleagues is great.

The rush of articles on Hodgkin's disease to the medical press scattered through many journals has never been so great as during the past few years. We have felt, on this account, that a more comprehensive review of the subject than can be derived from the reports of meetings is now required. This book is an attempt to set down the present position. The contributors have all worked together at one time or another and the editors have been members of a lymphoma unit. Only Dr Wilkinson and Dr Wrigley have not been employed by the Institute of Cancer Research or The Royal Marsden Hospital but Dr Wilkinson has visited the wards, seen patients for us from time to time and given us the benefit of her great experience and Dr Wrigley has contributed enthusiastically to our discussions. Close collaboration with the corresponding unit at St Bartholomew's Hospital, to which many of the authors belong, has been of inestimable benefit to our lymphoma group.

In an advancing subject such as this, books are bound to become outdated all too soon; however, general surveys need to be presented from time to time both to put the picture before those who have not been intimately concerned in its development and to allow those working on isolated parts of the problem to take a wider view. We hope we may have met some of their needs and shown that exciting progress in the understanding, and the management, of this disorder, has been taking place.

1973

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Part I. Origins and Presentation

1. Nature and Aetiology

D. W. Smithers

Seventy years after Thomas Hodgkin described the disease in 1832, Dorothy Reed (1902) wrote: 'It is discouraging to find that in the years that have passed since these early observations, our knowledge of the nature of the disease has not materially increased'. She saw no reason to believe that it was 'of the nature of a malignant neoplasm'. More than fifty years later in 1955 a leader in *The Lancet* was almost as non-committal: 'The reticuloses are placed in the dim borderland between granulomas, which may be due to infection, and true neoplasms. Hodgkin's disease itself has never been classified as a malignant disease, although rarely the disease terminates in a sarcoma-like stage—the so-called Hodgkin's sarcoma.' By 1966, *The Lancet* was beginning to reflect a changing attitude, though still with some uncertainty: 'Although the reticuloses are usually classed with malignant neoplasms, the tendency is to treat them as a separate group, both pathologically and aetiologically'. *The Lancet* leaders of 1969 and 1971 marked the continuing interest in the subject and stressed the changing views. The latter referred to the still-elusive causes and to the recent suggestion that 'the agent' might not be present in the typical nodal lesions. The 1971 leader stated that: 'The heart of the Hodgkin mystery lies in the very mixed cell response, not seen in other conditions in which these cells proliferate . . .'.

This long-standing controversy about the nature and origins of Hodgkin's disease seems to be changing direction at last. From doubt as to whether it should be considered as a granulomatous or as a neoplastic process, the concept has emerged of a progressive malignant tumour in the development of which infection may play both an initiating and a consequential role, and around which an unusual degree of mixed cell reaction develops. From a search for a single aetiological agent, investigation has turned towards attempts to understand the several stresses which may disrupt the smooth working of the lymphoid system in which these tumours arise.

Despite the uncertainties which remain, much about the nature of Hodgkin's disease has been clarified, while its treatment has become more and more successful. Uncertainty about its neoplastic nature should be abandoned. Malignant disease has only been defined in terms of the behaviour patterns it displays and Hodgkin's disease fulfils all the criteria which are required for the classification of growth disorders as malignant neoplasms. This disease process results in tumours which grow, invade and metastasise; if left untreated it proves fatal.

The habit of excluding from consideration those conditions which do not fit neatly into our preconceived notions has long been a bar to progress in the general understanding of neoplastic disorder. A full grasp of the nature of malignant disease is only possible when we admit all its particular manifestations. Concentration on the common forms of neoplasia (common because we are exposed to the same external and internal environmental influences with similar impacts on the same few organs or epithelial surfaces) restricts our view, so that the wide range of rarer tumours is neglected and too little attention paid both to the diversity of stimuli to which tissues react and to the variety of growth responses they can make. The lymphomas as a group, and Hodgkin's disease as a particular member of that group, are an integral part of malignant neoplasia; the study of the origin and behaviour of the lymphomas is just as necessary to a fuller comprehension of the malignant disease process as that of any other tumour group.

Progression

The diagnosis of Hodgkin's disease is made on histological evidence which depends on the finding of a particular marker cell (the Sternberg-Reed cell) in an appropriate cellular and architectural environment (Chapter 5). Clinically it appears as a fairly well-defined disease entity (Chapter 3), despite its varied histological appearances with their differing prognoses (Chapter 6). Some workers, however, on clinical, histological and radiological grounds (Davidson and Clarke, 1970), and others

from epidemiological considerations (Newell, Cole, Miettinen and MacMahon, 1970), have tried to distinguish two or more entities within this diagnosis (Chapter 2). One of the main pieces of evidence in favour of the view that the designation Hodgkin's disease does represent a unity lies in the observation that progression in malignancy is by way of the different histological types and that this is clearly demonstrable over a period of time in individual patients (Fig. 1.1).

Multiple lymph-node biopsy provides valuable information and is now done more frequently since the advent of pre-treatment laparotomy. By this means it has been shown that similar histological features are generally to be found in all the lymph nodes removed from a patient at any one time. Nodes differing in histological type have on occasion been removed simultaneously from one individual, but this is unusual. However, progression from one type to another, particularly from lymphocytic predominance to mixed cellularity or lymphocytic depletion, commonly takes place. Progression in malignancy has been well known as a clinical feature of Hodgkin's disease for many years; frequent serial lymph-node biopsy, which is seldom practicable, is required to demonstrate its rate histologically in any one patient; experience in those few patients in whom this evidence is available suggests that such transitions may occur either slowly over a period of a few years or take place quite rapidly. It is in the nodular-sclerosis type particularly that the histological pattern tends to remain constant over long periods (Strum and Rappaport, 1971*a*), persisting over many years in a few cases and even remaining unsuspected up to the time of death in some patients thought to be cured of the disease (Strum and Rappaport, 1971*b*).

Hodgkin's disease, then, is not only a condition of varying neoplastic activity provoking a mixed cell response, but one which has a tendency either to progress in malignancy or to be delayed or arrested in a nodular sclerosis form.

Aetiological considerations

Until quite recently, the aetiology of Hodgkin's disease has been discussed on a much too superficial plane. Old ideas that the disease was a form of tuberculosis, a granulomatous reaction to a number of infective agents, or a primary meta-

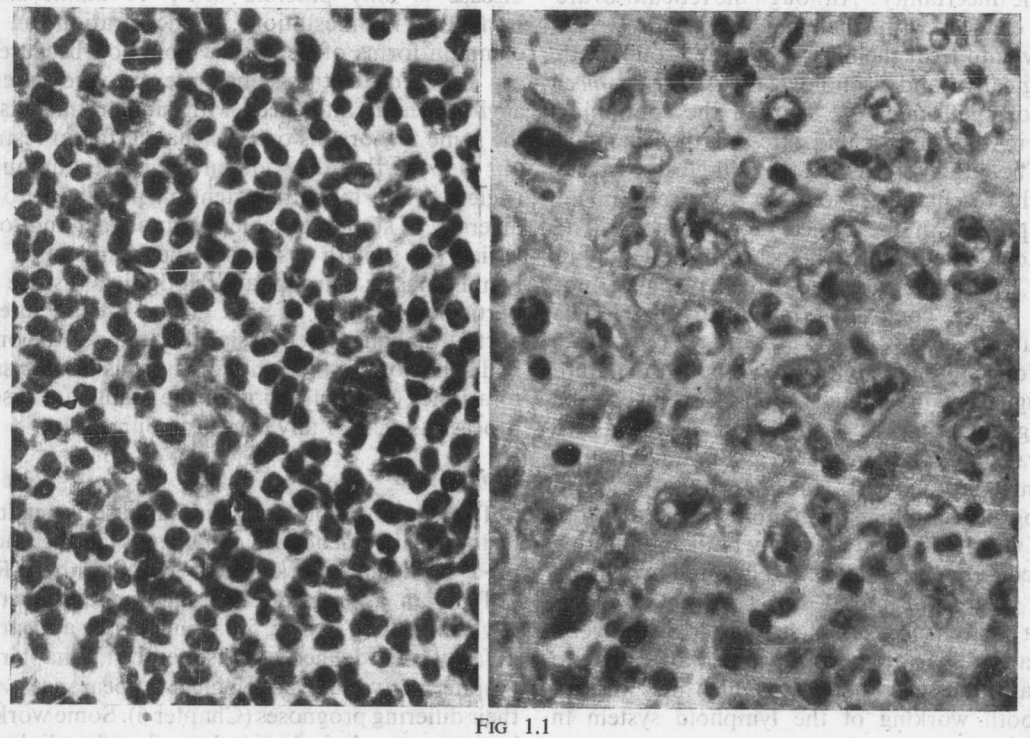

FIG 1.1

Sections of lymph nodes removed from one patient showing progression from lymphocytic predominance to lymphocytic depletion. There was an interval of 5 years between these two biopsies.

stasising tumour of the thymus failed to promote more effective investigation. The recent changes in thought which have done so, have come about mainly through two concepts: one applies generally to neoplastic disorder and the other more particularly to Hodgkin's disease.

The first of these concepts arose from a study of the incidence of malignant neoplasms. The commonest tumours, accounting for well over half the risk, arise in no more than five organs or tissues in each sex, namely the gastrointestinal, respiratory and urinary tracts, together with the skin and the prostate for men and the breast and the uterus for women. This observation emphasized the importance of environmental factors in the initiation of new growth. It became clear that the common tumour sites were those most often subjected to external demands for replacement and repair or to internal demands for cyclic growth, more especially when this did not proceed smoothly to function. Analysis of the sex, age and occupation of patients developing various tumours served to emphasize the importance of such growth demands (Smithers, 1963). Repeated or prolonged pressures on normal tissue-regulating mechanisms or the weakening of their control mechanisms were thus suspected of promoting tumour formation (Smithers, 1967*a*). Common factors in the physiological initiation of new growth, such as isolation and injury, had already been related to tumour development and to tumour incidence (Smithers, 1960).

This general concept may be briefly expressed as follows: tumour formation commonly follows repeated or prolonged demands for function, isolation from normal growth control, or both, and is the more likely when such demand is thwarted or cannot adequately be met; these demands are irregularly distributed between tissues and systems, and also within different parts of the same tissue or system, resulting in sites of predilection for tumour development and in multicentric tumour origin; the tendency towards neoplasia, once established, may then be enhanced by some single, more forceful stimulation of the normal growth response; the changes produced at different biological levels may be reversed but tend to become established and progressive.

The second concept, applying particularly to Hodgkin's disease, developed from two main studies: first, the application of the general ideas just described to the discovery of links between long-continued stimulation of the lymphoid system and its tumours; and second, that the lymphomas could be divided roughly into two groups derived respectively from the two arms of the immune system (Peterson, Cooper and Good, 1965). It further appeared that in repeated lymphoid tissue stimulation it was the aberrant immune reactions which seemed most likely to predispose to lymphoma production. This was brought out independently by Dameshek and Schwartz (1959) in relation to leukaemia, and by Kaplan and Smithers (1959) in relation to the lymphomas. These ideas were expanded by Dameshek (1965) and have been reviewed with reference to Hodgkin's disease (Smithers, 1967*b*, 1969, 1973; Kaplan, 1971).

The view of Hodgkin's disease emerging from such considerations places it more firmly than before within the generality of malignant disease while offering explanations for some of its previously unexplained peculiarities. Hodgkin's disease thus appears as a neoplastic disorder arising primarily in the cell-mediated arm of the immune system, initiated by inherited or acquired defects and by long-continued or aberrant stimulation subject to enhancement by more sudden demands resulting from infection or some interference with normal control mechanisms.

The data implicating immunological factors in the origin of lymphomas come from many sources both in laboratory animals (Chapter 9) and in humans (Chapter 10). Thymectomy, corticosteroids, antilymphocytic serum, immunosuppressive drugs, autoimmune disease and repeated antigenic stimulation can all contribute to the development of lymphomas. Confusion arises over aetiological significance because immunological disturbances not only contribute to lymphoma formation but are themselves produced as the result both of lymphoma development and of the treatment given. Pointers to the complicated dysfunctions of the cell-mediated arm of the immune system involved in Hodgkin's disease are therefore likely to come from a study of its associated disorders, such as congenital defects, lymphoid cell depletion, immune deficiency, immunosuppression, concurrent autoimmune disease, placental cell transfer, lymphocyte abnormalities and graft-versus-host reactions.

The Kaplan-Smithers hypothesis

Similarities between homologous disease in laboratory animals and certain of the manifestations of lymphoreticular neoplasia in man were discussed in the 1958 Robert Knox Lecture (Smithers, 1959). It was there suggested that some of the previously unexplained manifestations of Hodgkin's disease might be accounted for if this was a malignant tumour involving immunologically competent

cells capable of mounting a reaction against the host. At the same time, Kaplan and Rosston (1959) were making similar suggestions from the different starting-point of their work on wasting disease in laboratory animals. Professor Henry Kaplan and I then speculated together (Kaplan and Smithers, 1959) to put forward the hypothesis that tumour cells originating in lymphatic tissue might retain their capacity for immunological response, and if antigenically differentiated from normal lymphoid cells might destroy them as well as other haematopoietic cells. Further, that a two-way reaction leading to a lymphoid-depleting immunological battle might occur. It was also suggested that sustained lymphoproliferative demand, however initiated, might play an important part in the development of lymphomas.

Since then much has been learned about immunological aspects of carcinogenesis in general and about lymphoma production in particular. The role of the thymus in the development and maintenance of immunological competence has been recognized. Immunological surveillance systems for avoiding or suppressing neoplastic progression have been suggested (Burnet, 1967). Thymectomy has been shown to produce graft-versus-host type reactions and to increase susceptibility to neoplasia from oncogenic viruses (Miller, Ting and Law, 1964) and isologous thymic grafts have restored resistance to virus-induced tumours (Law and Ting, 1965). Immunosuppression has increased the viral tumour yield and mice have been rendered normally resistant again with lymphoid cells from sensitized immune donors when lymphoid cells from normal donors were ineffective (Allison, 1971).

Kaplan and Rosston had shown in 1959 that graft-versus-host reactions induced a lymphoproliferative response in the sensitized graft cells which then attacked the host cells so that profound lymphoid depletion resulted from which some animals could nevertheless recover. Survivors might then develop malignant lymphomas (Bensted, 1960; Schwartz and Beldotti, 1965) apparently derived from host cells rather than donor cells (Armstrong *et al.*, 1970). Field and Gibbs (1966) devised a method of giving large numbers of parental spleen cells to F_1 hybrids without provoking fatal graft-versus-host reactions. Field and his associates (Dawson, Cauchi and Field, 1970) then examined the tumours which resulted. Transplantation experiments suggested that these tumours were composed of hybrid cells which had suffered the loss or the suppression of many of the histocompatibility antigens of the alternate parental strain, that is, the one from which the injected spleen cells were not derived. The tumours which grew in the hybrid hosts induced a wasting syndrome indistinguishable from graft-versus-host disease, suggesting that their cells retained some immunological competence (Chapter 9). It was still uncertain whether latent oncogenic viruses were becoming active in immunologically suppressed animals or whether it was a sustained demand for lymphoproliferation that was leading to neoplasia or whether both mechanisms might be acting together. The work of Stanley and his group (Stanley and Walters, 1966; Stanley *et al.*, 1966; Stanley and Keast, 1967) was inconclusive but suggested (by way of virus-induced immune disorder and injected spleen cells) that autoimmune disease, induced in mice by viruses or by other means, could lead to lymphoproliferative preparation for tumour formation, which then might be promoted into neoplasia by viruses or by other means.

Hirsch *et al.* (1972), again in mouse experiments, showed that mixed lymphocyte cultures *in vitro* can activate leukaemic viruses normally present in a repressed form just as graft-versus-host reactions can do *in vivo*. That the lymphocyte-lymphocyte interactions of mixed lymphocyte culture and of graft-versus-host disease can both activate leukaemic virus is another observation to be accounted for in sorting out the sequence of events which lead to lymphoma development.

Schwartz (1972) attempted to relate these two themes of immune response and oncogenic viruses by postulating a normal mechanism for preventing the expression of the virogene in lymphocytes. His hypothesis, based on the discovery that latent oncogenic viruses can be activated immunologically suggested that either partial immunosuppression or sustained immunisation could interfere with feedback control so allowing viral activation and replication in transformed lymphocytes. In this way he hoped to account for lymphoma development in autoimmune disease, graft-versus-host disease and in persons infected with malaria.

The Kaplan-Smithers hypothesis implied that Hodgkin's disease had its origin in sustained lymphoproliferation and might produce a tumour-versus-host reaction. The hypothesis has received some support from the work of Cole and Nowell (1970), who followed single sublethal doses of whole-body irradiation with injections of parental strain bone marrow (or of cells in the liver and spleen recently migrated from the shielded bone marrow) producing two years later a high incidence

of lymphoid tumours which were of donor origin. Fialkow *et al.* (1971) reported the case of a 16-year-old girl with acute lymphoblastic leukaemia who had 1 000 rads whole-body irradiation and bone marrow from her brother, and who developed recurrent leukaemia of donor-type cells after 62 days; various explanations have been submitted to account for this (Fisher, 1971; Moore and Heyden, 1971; Parker, 1971). Grifoni and his co-workers (1969) have detected anti-lymph-node antibodies in the serum of patients with Hodgkin's disease. They found antibody-releasing and antibody-coated lymphoid cells in the same individual, suggesting the presence of two lymphocyte populations in conflict, one of which was playing 'the tumour' role. Stuart and Regunathan's work (1971) on the allergic macrophage of graft-versus-host disease has also been of interest. They showed that macrophages taken from runts are auto-aggressive: when these cells are mixed with normal syngeneic lymphocytes they cause massive adherence and necrosis. The reaction is highly specific and clearly cellular.

On the clinical scene, patients with some of the rare immunological deficiencies have been found to be prone to lymphoid tumours (Fraumeni, 1969). An infant has been reported having Hodgkin's disease with an associated thymic aplasia (von Bernuth *et al.*, 1970). Patients immunosuppressed following renal transplants have been found to have a heightened tumour risk, particularly one for lymphomas (McKhann, 1969; Starzl *et al.*, 1970), with an unusual brain incidence of particular interest since it may indicate that even more of these tumours might have appeared at more usual and accessible sites had the immunosuppressive drugs not also been effective tumour chemotherapeutic agents (Smithers and Field, 1971).

The relationship of infectious mononucleosis to Hodgkin's disease (Massey, Lane and Imbriglia, 1953; Kenis, Dustin and Peltzer, 1958; Pacini *et al.*, 1968), the likelihood that the Epstein-Barr (EB) virus is the cause of infectious mononucleosis (Henle, Henle and Diehl, 1968), the finding of Sternberg-Reed-like cells in this disease (Lukes, Tindle and Parker, 1969), the evidence of altered antigenicity in cultured lymphoid cells from patients with infectious mononucleosis (Steel and Hardy, 1970), the elevated antibody titres to EB virus in Hodgkin's disease (Levine *et al.*, 1971), the establishment of the malignant potential of a cell line isolated from the peripheral blood in infectious mononucleosis (Adams *et al.*, 1971), and the case-to-case and case-contact-case spread of Hodgkin's disease (Chapter 2), form a fascinating collection of observations which should before long fit into a recognizable pattern. EB virus increases the proliferative capacity of lymphoid cells and may make it easier for antigenically-altered cells to survive, to mount an anti-host reaction, and possibly to become neoplastic. Order, Porter and Hellman (1971) and Order, Chism and Hellman (1972) have demonstrated the presence of common tumour-associated antigens in Hodgkin's disease. The evidence of immunological defects and viral infections in the development of this disorder has been increasing steadily.

Virus-associated immunopathology is a rapidly developing subject summarized in a World Health Organization Bulletin in 1972. The relationship between viruses, immunology and lymphomas must be a complex one. Viral infections of cells of the immune system offer particular complications in that they may inhibit or enhance their function while provoking attacks upon themselves through their surface antigens by other normal defence cells. Immune suppression and autoimmune disease will favour both chronic lymphocytic stimulation and survival of cells carrying foreign antigens. There are many possible variations on such a theme. The Kaplan-Smithers hypothesis of chronic stimulation of immunocompetent cells allied to immunological warfare in Hodgkin's disease has acquired much supporting evidence over the last 15 years.

Susceptibility

Whatever its aetiological background, Hodgkin's disease exhibits irregularities of attack not only between individuals in a community but also between lymph-node groups within an individual. These observations suggest that varying susceptibilities as well as varying exposures may play a part in tumour development. Some interesting variations that have been found in age, sex and racial incidence are discussed in Chapter 2.

Variation in susceptibility to such a disease process may be due to inherited or acquired defects, and also to the accessibility of inciting agents to susceptible individuals or lymph nodes. A familial tendency may be due to inherited susceptibility or to a shared exposure; in this case the factors of inheritance and environmental risk may both play a part.

The irregular, though roughly symmetrical, distribution of first-detected lymph-node involvement in Hodgkin's disease (Chapter 11), led to the suggestion (Smithers, 1967*b*, 1969) that initiating

influences were unevenly distributed and that the regions from which lymph normally flows to the lymph nodes of the lower neck might provide the main port of entry for the agents inciting this disorder. It was further suggested (Smithers, 1970) that these non-random patterns of origin and of spread might have their basis in a varying lymph-node susceptibility (possibly induced by previous infection) acted on by inciting factors one of which might be a virus.

Observing a rise in Hodgkin's disease mortality from the age of 11 years, Miller (1966) thought that this might be related to a faulty involution of lymphoid tissue in childhood, particularly that of the oropharynx. McVay (1964) had found a relatively high rate of previous appendicectomy among patients with carcinoma, notably of the colon; he suggested that the appendix might provide some protection against viruses initiating malignant change, and advocated similar studies with regard to tonsillectomy. Gross's findings (1966) on the association between past appendicectomy and tonsillectomy in patients with neoplastic disease were inconclusive, but Bierman (1968) and Hyams and Wynder (1968) noted high rates of previous appendicectomy among patients with Hodgkin's disease, and Bierman also among patients with carcinoma of the colon, breast and ovary and with granulocytic leukaemia. Bierman said that his data suggested a systemic as well as a local effect in about one-third of his patients with neoplastic disease. Vianna, Greenwald and Davies (1971*a*) stated that tonsillectomy in their series of cases increased the liability to the development of Hodgkin's disease by a factor of 2·9 times. These workers (Vianna, Greenwald and Davies, 1971*b*) went on to suggest that Hodgkin's disease might be initiated by a virus of low virulence, the entrance of which via the oral-respiratory tract portal was facilitated by the removal of a protective barrier allowing immune-complex material to escape and evoke the distinctive reaction in the draining lymph nodes. However, as Player (1971) pointed out, Vianna and his colleagues had no absolute controls in patients with infected tonsils who needed tonsillectomy but did not have the operation done. It may well be that infection increases the risk of Hodgkin's disease and that treatment, even tonsillectomy, may help to prevent it.

Some explanation is required of the irregularities of origin by race, environment, sex, age and lymph-node involvement. These irregularities could result from freely distributed inciting agents acting preferentially on the basis of established susceptibility patterns both in different individuals within a population and in different lymph nodes within an individual. They could also result from varying exposure of susceptible individuals or lymph-node groups to inciting agents through close personal contacts or through the modification of portals of entry by surgical or other means. It is likely that the observed irregularities result from varying combinations of factors such as exposure to infection, ease of access, induced susceptibility, and the severity or the long-continued nature of the demands for growth made on the system involved.

Disturbances of immunologically competent cells may arise in Hodgkin's disease from two directions. Impaired host reaction may set the scene or abnormalities may appear in immunocompetent cells. EB virus, with its lymphoproliferative action and its liability to oral transmission (Pereira *et al.*, 1972) is the infective agent most likely to be concerned on present evidence. A graft-versus-host reaction and host-versus-graft response may be the stimulus which leads to tumour formation. Speculations about the origins of Hodgkin's disease have changed, we are still speculating, but the new ideas account for the facts far better than the old.

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