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Editorial

Is Hodgkin's Disease Infectious?

S. Grufferman

BEGINNING IN the last century, generations of distinguished clinicians and researchers have suspected that Hodgkin's disease might have an infectious aetiology. In 1898, Sternberg suggested that Hodgkin's disease might be an atypical manifestation of tuberculosis [1]. In the early part of this century, numerous papers appeared in the literature suggesting that Hodgkin's disease might be caused by bacteriological agents such as "*Corynebacterium granulomatosis maligni*" and *Bacillus hodgkini* [2, 3]. There was even a diagnostic test, the Gordon test, which was based on injection of tissues from patients into animals [4]. As late as the 1940s, Hodgkin's disease was classified as an infectious disease and was assigned code number 44 in the *International List of Causes of Death*, Fourth Edition. This code number was shared with venereal diseases (except gonorrhea and syphilis) and mumps [5]. The important question that these reports raise is why so many leading clinicians and scientists of their day thought that Hodgkin's disease might have an infectious aetiology. And why does this notion persist? Certainly, the clinical picture of Hodgkin's disease with its enlargement of lymph nodes, remitting fevers, nightsweats, and other constitutional symptoms often mimicked an infectious disease.

Epidemiological research on Hodgkin's disease was greatly stimulated when MacMahon in 1966 reported that, on epidemiological grounds, Hodgkin's disease appeared to be three separate diseases, a childhood, young adult and an old adult disease [6]. He hypothesised that the young adult disease was a prime suspect for having an infectious aetiology and that the old adult disease was a true malignancy. His work stimulated several statistical studies of time–space clustering of Hodgkin's disease with conflicting, but usually negative, results [7, 8]. Time–space clustering would, of course, be a characteristic of many infectious diseases.

Interest in the infectious aetiology of Hodgin's disease was further increased by the report of Vianna and associates in 1971, of a remarkable cluster of 31 Hodgkin's disease cases centred around a single graduating class of a high school in New York State [9, 10]. What was important about this cluster was not only its large size, but the fact that it was defined by shared exposures of the involved individuals during the period of their high school attendance rather than by clustering at the time that their disease was diagnosed years later. This finding was consistent with an infectious disease process. It also provided a possible explanation of why the earlier statistical studies of time–space clustering were equivocal in their results, since they dealt with clustering at the time of diagnosis of the disease. The Albany, New York study was followed by a better designed study by Vianna and Polan [11]. They found that among students attending high schools in which diagnosed Hodgkin's disease cases were in attendance, there was a remarkably increased risk of Hodgkin's disease. Here was strong evidence to support what many had previously suspected, that Hodgkin's disease could be transmitted from person to person. The two school studies evoked a great deal of epidemiological research on Hodgkin's disease as an infectious disease. As is so often the case with exciting new scientific findings, Vianna's findings could not be confirmed in studies conducted in Oxford and Boston [12, 13]. The Boston study was an exact replication of the Vianna study and included additional analyses as well [13]. It showed absolutely no increased risk of Hodgkin's disease in students exposed to Hodgkin's disease cases in the high school setting. These negative studies seemed to have put the issue of Hodgkin's disease transmissibility to rest once again.

Interest in the possibly infectious aetiology of Hodgkin's disease was rekindled by some fascinating studies on the relationship between the Epstein-Barr virus (EBV) and the disease. It had been well known that patients with Hodgkin's disease had significantly higher antibody titres against the EBV when compared to healthy controls [14]. It is also well known that patients with Hodgkin's disease have impaired immune function. A difficult "chicken and egg" dilemma arose as to which came first, the EBV infection or Hodgkin's disease? Several cohort studies of patients with infectious mononucleosis, which had been discovered to be caused by EBV, rekindled interest in viruses as the possible cause of Hodgkin's disease [15]. It is now well established that people with serologically confirmed infectious mononucleosis have approximately a 3-fold increased risk of developing Hodgkin's disease [15]. Again, one could not be certain whether the infectious mononucleosis was the result of immune impairment due to early or as yet undetected Hodgkin's disease. This issue was laid to rest by the very clever "nested case–control" studies of Evans and Comstock [16] and Gutensohn and colleagues [17]. They found that people destined to develop Hodgkin's disease had significantly higher antibody titres against the virus than did healthy controls and well in advance of their development of Hodgkin's disease.

Until recently, it was believed that EBV could not be detected

Correspondence to S. Grufferman at the Department of Family Medicine and Clinical Epidemiology, M-200 Scaife Hall, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261, U.S.A.
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in Hodgkin's disease tumour samples. This was refuted by the development of newer molecular biological techniques, such as *in situ* hybridisation and the polymerase chain reaction. It is now well established that anywhere from 15 to 33% of Hodgkin's disease tumour samples are found to contain EBV genomic material [18, 19]. While there appear to be strong associations between the histological subtypes of Hodgkin's disease and EBV presence in tumours, the relationship between the detection of EBV in patient's tumours and epidemiological risk factors remains to be explained.

Another line of research, supportive of the infectious aetiology of Hodgkin's disease, is that of the issue of the "poliomyelitis" or "late host response" model [15, 20]. This model is based on the pattern of occurrence of paralytic poliomyelitis during the prevaccination era. In less developed countries, exposure to the poliomyelitis virus was very common and usually occurred early in life. Infection during early childhood usually led to unapparent or mild disease and only rarely to paralytic poliomyelitis. In developed countries, with higher levels of hygiene, exposure to the polio virus was sporadic, if not rare. In developed countries, where most people had no immunity to the virus, infection with the polio virus during adolescence or young adulthood led to a different host response which was the paralytic form of the disease. The analogy for Hodgkin's disease would be that Hodgkin's disease might be caused by an unknown but common infectious agent and that people who do not develop immunity to this agent early in life were then at risk of developing Hodgkin's disease during adulthood. A considerable body of evidence has been collected to support this notion. Most notable are the findings suggesting that people with young adult Hodgkin's disease have had fewer of the usual childhood infectious diseases than did their matched controls [21, 22]. Young adult cases were also more apt to come from more privileged social classes which led to their being reared in less crowded environments, living in single family dwellings, and having fewer early childhood playmates than did matched controls [22]. An unresolved question arising from this line of reasoning is that of how to explain the occurrence of childhood cases of Hodgkin's disease in developed countries.

The paper by Alexander and associates in this issue of the Journal (pp. 1479–1486) is both the logical next step in the investigation of the infectious aetiology of Hodgkin's disease and also an innovative new direction in research. While there have been independent investigations of clustering, of antibody titres against EBV and other herpes viruses, and of the detection of EBV genomic material within Hodgkin's disease cells, this study is perhaps the first to integrate all three approaches into a unified investigation. The traditional epidemiological approach has been to investigate potential risk factors for a disease by collecting past histories in cases and matched controls to try to identify differences between the two groups. Only recently have epidemiologists begun to consider risk factors identified by traditional approaches in relationship to some biological markers or other characteristics which serve to identify subsets of the disease. I believe that traditional, purely questionnaire-based, epidemiological approaches have "skimmed the cream" off the pool of epidemiological findings and have made gradually diminishing contributions to new knowledge. It is by the use of innovative approaches, such as those of Alexander and associates, that epidemiology can again produce exciting new aetiologic leads. Their paper also attests to the fact that this new approach to epidemiological research is not going to be easy, nor will it be inexpensive. They simultaneously evaluated case-clustering, serum antibodies to EBV and human herpes virus-6, and presence of EBV genomic material in cases tumours. When one pursues multiple avenues of investigation simultaneously, larger numbers of subjects are needed to produce meaningful results. Additionally, the application of newer technologies to cancer aetiological research increases the expense and complexity of such research. Nevertheless, the approach exemplified by Alexander and colleagues is the way that epidemiological research on cancer aetiology needs to proceed. They have chosen for their investigation a promising area for uncovering a possibly infectious aetiology of a human cancer—namely, Hodgkin's disease. They have identified a priority area for future epidemiological research.

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