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Oncogenic Viruses and their Tumours

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Epidemiology of Burkitt's Lymphoma

The train of events which led to the belief that Burkitt's lymphoma may be caused by a virus is now well known. I shall merely outline the epidemiological evidence and explain the hypothesis of etiology which is most consistent with all available knowledge.

The initial recognition of a clinical syndrome (Burkitt 1958, 1962*a*) which was subsequently identified as a pathological entity (O'Conor 1961, O'Conor & Davies 1960) prompted a geographical study of tumour distribution. This was first undertaken in Africa (Burkitt 1962*b*, *c*) but was later extended to New Guinea (Booth *et al.* 1967) and other parts of the world (Burkitt 1967).

These studies indicated that the regions where the tumour was endemic were characterized by certain climatic conditions and that warmth and moisture were essential factors (Haddow 1963). This led to the belief that some biological agent, probably an insect vector, must be implicated in the causation of this tumour. The similarity between the geographical pattern of Burkitt's lymphoma and certain vector-transmitted diseases in Africa (Burkitt 1963) strengthened this conviction, as did the climatic dependence of the tumour demonstrated in New Guinea (Booth *et al.* 1967).

The question then arose: 'What can an insect, possibly a mosquito, carry that can cause cancer?' The obvious answer was 'viruses', although none of the viruses demonstrated to be oncogenic in animals was known to be insect vectored. Professor J N P Davies had suggested near the beginning of the investigations the possibility of a virus etiology, but it was Professor M A Epstein, Professor R J Harris and Dr Gilbert Dalldorf who recognized the opportunity afforded by the demonstrated climatic dependence of this tumour to search for a causative virus.

The virus first discovered by Epstein & Barr (1964) seems the favourite candidate, and Epstein (1970) and Epstein & Achong (1970) have reviewed the evidence which incriminates it as the cause of infectious mononucleosis and possibly of this lymphoma.

The epidemiological and experimental evidence pointing to a virus as a possible cause of Burkitt's lymphoma is enhanced by the remarkable results of chemotherapy, which suggest a high degree of antigenicity consistent with experience in virus-induced tumours in animals. Further evidence of an infective process is the time and space clustering of patients with Burkitt's lymphoma demonstrated by Pike *et al.* (1967) and Morrow *et al.* (1971).

Later investigation showed that the vectored-virus theory, which led to the discovery of viruses in the tumour, could not be substantiated. It now seems that the right goal was reached by taking the wrong road.

Not only did it become evident that there were large moist tropical areas where this tumour rarely, if ever, occurred, but cases began to be reported from many non-tropical regions throughout the world. Moreover, the EB virus, apparently always associated with this tumour, is not normally vector-transmitted and is equally prevalent in areas of high or low incidence of Burkitt's lymphoma. This led to an awakened interest in the suggestion originally made by Dalldorf (1962) that malaria infection might be related to tumour endemicity. Subsequent epidemiological studies have confirmed a very close relationship between the incidence of Burkitt's lymphoma and the occurrence of hyperendemic and holoendemic malaria (Burkitt 1969, Kafuko & Burkitt 1970). This geographical relationship has been strengthened by the relationship between the distribution of this tumour and that of other manifestations of chronic malaria such as 'big spleen disease' (Hamilton *et al.* 1965) and the nephrotic syndrome (Kibukamusoke *et al.* 1967).

Further evidence lies in the demonstrated reduced incidence of AS hæmoglobin in patients with this tumour (Pike *et al.* 1970). Since this hæmoglobinopathy gives some protection against malaria it might be expected also to provide thereby some protection against Burkitt's lymphoma.

The epidemiological evidence suggesting the incrimination of intense persistent malarial infection has been strengthened by experimental

work indicating a relationship between lymphomas and malaria in mice (Jerusalem 1968, Wedderburn 1970).

Current Concept

A hypothesis of causation which is consistent with all available evidence is that the EB or other virus acting on normal lymphoid tissue is usually non-pathogenic, occasionally causes non-malignant lymphoid proliferation (infectious mononucleosis) and only very rarely gives rise to malignant lymphoid proliferation.

The same viruses, acting in lymphoid cells which have been subjected to intense chronic malarial or possibly other infection, would still usually be non-pathogenic and occasionally give rise to infectious mononucleosis, but might be much more likely to result in malignant change than when acting on normal cells.

Confirmation that the EB virus plays a causative role in this disease will be difficult to establish, but convincing evidence might be obtained if an effective vaccine against EB virus infection could be made and given to a large community of children in an area where this tumour is known to be common. Any reduction in the estimated number of tumours would suggest a causative relationship between the tumour and the virus.

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The following papers were also read:

Virus Leukæmia in Domestic Mammals
Professor W F H Jarrett

Virus Etiology for Human Cancer?
Professor M A Epstein

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Epstein M A
(1969) In: Proceedings of Quadrennial International Cancer Conference, Perugia. Ed. G Klein & G Weinhouse **4**, 771
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Meeting November 3 1970

A Laboratory Meeting was held at The Mathilda and Terence Kennedy Institute of Rheumatology, London W6. Demonstrations were given.

Meeting December 1 1970

A Laboratory Meeting was held at the North London Blood Transfusion Centre, Edgware, Middlesex. Demonstrations were given.

Meeting February 2 1971

A Laboratory Meeting was held at the Westminster Medical School, London SW1. Demonstrations were given.

Meeting March 2 1971

A Laboratory Meeting was held at St Bartholomew's Hospital, London EC1. Demonstrations were given.