Epstein-Barr virus as the cause of a human cancer

from M. A. Epstein

BURKITT'S first account of the malignant lymphoma which now bears his name (Burkitt *Brit. J. Surg.* **46**, 218; 1958) attracted little attention. However, Burkitt's lymphoma soon acquired outstanding significance when Burkitt showed that its distribution in Africa is determined by climate; for, the fact that the incidence was influenced by temperature and rainfall suggested that a biological agent such as an oncogenic virus was concerned in causation (Burkitt *Brit. med. J.*, **ii**, 1019; 1926; *Nature* **194**, 232; 1962), although the original hypothesis as to how this might be has required revision.

The concept of a viral aetiology for endemic Burkitt's lymphoma has gained steadily in strength with the discovery of Epstein-Barr virus (Epstein *et al. Lancet* **i**, 702; 1964) and the gradual demonstration of its close association with the tumour (Epstein *Prog. exp. Tumor Res.* **21**, 72; 1978), paralleling the relationship of known oncogenic animal DNA viruses to the tumours they induce. Thus, Burkitt's lymphoma patients have high titre antiviral antibodies with a specific pattern varying with disease events, and every tumour cell carries the virus DNA with at least one molecule linearly integrated into the host cell genome giving expression of virus-coded neoantigens; in addition, the virus transforms normal human cells *in vitro* into continuously growing lines and induces malignant tumours experimentally in subhuman primates (Epstein & Achong *A. Rev. Microbiol.* **31**, 421; 1977). Although Epstein-Barr virus therefore seems to be the cause of endemic Burkitt's lymphoma, ethical constraints make direct proof of this hard to obtain in humans. In any case, the virus cannot act alone in the aetiology of the tumour, since the virus occurs throughout the world (Henle & Henle *Prog. exp. Tumor Res.* **21**, 19; 1978) whereas a high tumour incidence is restricted to parts of Africa and New Guinea with specific weather patterns. A climate-dependent cofactor seems essential in determining the distribution of the tumour, and observations of many kinds indicate that this cofactor is hyperendemic malaria (Burkitt *J. natn. Cancer Inst.* **42**, 19; 1969; *A. Rep. Internat. Agency Res. Cancer, Lyon*, 78, 1977).

Strong new support for a causative role for Epstein-Barr virus in endemic Burkitt's lymphoma has now been provided by an important prospective study in a high incidence area for the tumour in which WHO's International Agency for Research on Cancer has been following 42,000 children serologically since 1972 in the West Nile District of Uganda (de Thé *et al.*, this issue of *Nature*, page 756). The scale of the undertaking and the efficiency of the modest logistics employed are remarkable, while the absence of interruption in this particular region provides an unusual criterion of WHO prestige.

This prospective study has demonstrated that children destined to develop endemic Burkitt's lymphoma have long been infected by the virus and show an important difference in their response to it, namely unusually high titres of antibodies to the virus capsid antigen compared with controls. The data on these high antibody titres have permitted the calculation of the risk factor attached to such a response to the infection—the risk of developing endemic Burkitt's lymphoma was approximately 30 times higher for children with a virus capsid antigen antibody titre two doubling dilutions or more above those of the control population.

Such a risk factor is very striking and is indeed appreciably greater than that accepted as establishing an aetiological relationship between heavy smoking and carcinoma of the bronchus (Doll & Peto *Brit. med. J.*, **2**, 1525; 1976; *Roy. Coll. Physicians London, 3rd Rep. Smoking or Health*, Pitman Medical, London, 54, 1977).

The ways in which the virus may interact with the essential climate-dependent cofactor of hyperendemic malaria to bring about malignant transformation have become clearer through other kinds of investigation. It is well known that only B lymphocytes have receptors for the virus (Pattengale *et al., Lancet* **ii**, 93; 1973; Jondal & Klein *J. exp. Med.* **138**, 1365; 1973), and also that malaria is both immunosuppressive and a stimulator of B cell proliferation (Salaman *et al. J. gen. Microbiol.* **59**, 383, 1969; O'Conor *Am. J. Med.* **48**, 279; 1970; Greenwood *et al. Lancet*, **i**, 169; 1972); persistent malaria might therefore stimulate and maintain an unusual supply of lymphoid cells especially liable to undergo malignant change when infected by the virus. Such cells could be a specific type of B cell or B cells at a particular early stage of differentiation. There is evidence now that certain subclasses of B lymphocytes constitute a special target for transformation by Epstein-Barr virus *in vitro* (Katsuki *et al. Virology* **83**, 287; 1977; Steel *et al. Nature* **270**, 729; 1977), whilst the lack of differentiation shown by the cells from acute leukaemias (Greaves *et al.* in *Immunodiagnosis of leukaemias and lymphomas* (ed. Theirfelder, Rodt, Thiel) Lehmans Verlag, Munich, 1977; Janossy *et al. Leukaemia Res.* **1**, 289; 1977) suggests that cells malignantly transformed to give endemic Burkitt's lymphoma might likewise be at an early stage in differentiation.

Where Burkitt's lymphoma is common Epstein-Barr virus affects everyone at an early age and hyperendemic malaria affects over 50% of children, yet of these doubly-infected individuals only a rather small number develop tumours, perhaps because of genetic predisposition, or very early infection, or a particular sequence in the timing of infection in relation to the acquisition of malaria.

Direct proof that Epstein-Barr virus causes Burkitt's lymphoma can only be obtained by showing that vaccination against the virus decreases tumour incidence. The new data lend added support to this proposal and to attempts to control by vaccination the numerically more important Epstein-Barr virus associated human tumour, nasopharyngeal carcinoma. □

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International study of short-term carcinogenicity tests

AN international study, now in progress, is looking at the reliability of various *in vitro* assay systems such as the Ames test in predicting carcinogenicity.

In this study, which is supported by the UK Medical Research Council, UK Health and Safety Executive, ICI, the US National Institute of Environmental Health Sciences and the US Environmental Protection Agency, the response of about 25 assays (see box) will be determined for 42 carcinogens and non-carcinogens. Investigators will be unaware of the identity of the chemical they are testing. All available carcinogenicity data on the selected compounds will be reviewed by an independent panel, as the definition of non-carcinogenicity is central to the study. It is recognised that the results of this study might possibly cause re-evaluation of the carcinogenicity of some chemicals.

The Salmonella reverse mutation assay (the Ames assay) has gained prominence as a test of carcinogenic potential and will be concentrated on both in this study and in a related study organised by the US National Cancer Institute—in which a smaller number of assays are being evaluated with a larger range of chemicals. Be-