the future, possibly techniques might be developed which would use the ability of certain undamaged non-haemopoietic cells in the marrow, such as fibroblasts, to undergo division, and to direct their maturation towards the erythroblast, granulocyte, and megakaryocyte pathways.¹¹

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For Debate

EB Virus and the Treatment of Lymphomas

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Summary

The high incidence of EB virus infections (and possibly of other viruses) in patients with African lymphoma and, to a lesser extent, in patients with lymphosarcoma in the temperate zones, is thought to be due to its being a passenger virus which persists in the human body and, since it is lymphotropic, presents an opportunistic infection of proliferating lymphoid cells. The thesis is put forward that by entering the cell nucleus, the virus renders malignant lymphoid cells more vulnerable to cytotoxic drugs. Hence a deliberate policy of EB virus inoculation before starting chemotherapy might achieve a more rapid response and longer remissions in indigenous lymphomas of the temperate zones, and might possibly render drug-resistant cases once more drug-sensitive.

The African lymphoma (Burkitt tumour) is characterized by the following four features: (1) a typical morbid anatomical distribution affecting the large viscera, deep abdominal lymph nodes, and the skeleton, without involvement of the peripheral lymph nodes, lungs or spleen; (2) the typical histological appearances of a uniform "starry sky" pattern; (3) cultural and serological evidence of an EB virus infection; and (4) a very definite, and sometimes dramatic, response to cytotoxic drugs.

These features merit a more detailed consideration.

Macroscopical Manifestations

A clear-cut distinction between African lymphoma and childhood lymphosarcoma in the temperate zones cannot be made as no single feature can be considered as diagnostic.¹ Nevertheless, in tropical Africa the combination of tumours of the major viscera associated with tumours of the skeleton—especially the disfiguring tumours of the jaws—constitute a diagnostic

clinical picture. The frequency of bone involvement of the clinical syndrome is impressive and is at present unexplained.

In contrast, the indigenous lymphosarcomas elsewhere tend to affect the peripheral lymph nodes and the spleen in a large proportion of cases.²⁻⁵ Neoplastic disease of the bones also does occur, but this presents either as diffuse lymphoid infiltrations or as nodular lymphomatous tumours of the cancellous bone; expansive and distorting tumours of the facial bones and adjacent soft tissues as seen in the African lymphoma are rare.

Histological Features

Microscopically the Burkitt tumour shows diffuse sheets of lymphoid cells with uniformly distributed cells of reticulum-cell type with much clear cytoplasm producing a "starry sky" pattern—a feature which is otherwise seen only in the reactive centres of lymph nodes.⁴ Nevertheless, occasional cases of African lymphoma may lack this characteristic feature.⁶

A similar histological variant of lymphosarcoma has been observed in many parts of the world, including the United States,⁶⁻⁹ in Papua and New Guinea,¹⁰ in South America,^{11,12} and in Southern India.¹³ Squire¹⁴ reported feline lymphomas with "starry sky" patterns. Among our own material 14 out of 78, or 18%, of lymphosarcomas showed similar histological features, though in most cases the distribution of the swollen reticulum-type of cells was less definite and was patchy rather than uniform. Moreover, in several cases the "starry sky" reaction was present exclusively in the subcapsular peripheral zones of the neoplastic lymph nodes, suggesting that this phagocytic reaction was of recent origin and represented a response to toxic stimuli reaching the lymph nodes via the afferent lymphatics.

In retrospect it would appear quite likely that a proportion of lymphomas, diagnosed in the past as Hodgkin's paraganuloma, may have been lymph nodes reacting to a viral infection, such as an EB virus infection, which would explain the favourable clinical course of some cases in this group.

Evidence of Viral Infection

Cases of African lymphoma generally show evidence of an EB virus infection. This evidence is both direct and indirect. The

virus itself has been isolated from the Burkitt tumour and from lymphoblastic cell lines from tumour tissue, but the virus has also been isolated from cell lines from other lymphomas, from cell lines from patients with rheumatic fever, as well as from healthy individuals.¹⁵ Serological evidence of an EB virus infection has been obtained in patients with African lymphoma but, similarly, also in patients with lymphosarcoma in the temperate zones with and without a "starry sky" pattern, in patients with nasopharyngeal carcinomas, sarcoidosis, and rheumatic fever, and in healthy persons.^{16 17} In general, nearly all African patients give positive EB serological reactions, whereas negative EB reactions have been obtained in an appreciable proportion of similar lymphomas elsewhere.¹⁶ When positive, the titres are usually lower than in Africa, though occasionally they may be raised to the same order.^{16 18} A point of great practical importance is that there is no correlation between antibody titre and the course of the disease in either African or non-African patients.¹⁶

The EB virus is commonly regarded as a member of the herpes group.¹⁹ It is of universal distribution and its presence has been shown in healthy individuals in Africa, in the United States, in members of a South American Indian tribe, and in Iceland.¹⁹ Like other members of the herpes group the EB virus may lie dormant and persist in the body in an inactive form. It is lymphotropic,¹⁷ entering the nuclei of both normal and neoplastic proliferating lymphoid cells, in which it replicates.¹⁹ This affinity for lymphoid cells appears to be the reason why evidence of an EB virus infection has also been obtained in cases of nasopharyngeal carcinomas which provoke an appreciable lymphocytic reaction, and in cases of sarcoidosis and rheumatic fever.^{16 17} To date the EB virus has not been shown to have any oncogenic properties.¹⁹ Thus it must be regarded as a passenger virus which, being lymphotropic, finds a favourable culture medium in the cells of actively growing lymphomas, especially lymphosarcomas.

One interesting observation is that evidence of an EB virus infection is most definite in tropical Africa where malaria is endemic. This observation led first to the suggestion that the agent causing the African lymphoma might be spread, similarly to malaria, by an insect vector, and later to the speculation that malaria itself might in some way be connected with the Burkitt tumour.¹⁷ Both these theories are unlikely as typical cases of Burkitt tumour have been observed outside the endemic regions of Africa. On the other hand, previous or chronic malarial infections may well explain the high incidence of EB virus infection in sub-Saharan Africa, for it is known that malaria may impair the function of the reticuloendothelial system. Such impaired function might well facilitate a massive EB virus infection with subsequent EB antibody production of high titre.

The EB virus is not the only virus which has been implicated. A reovirus has been isolated from an African lymphoma, and antibodies against reovirus have been shown in a series of patients with African lymphoma.²⁰ Furthermore, virus particles of type C murine leukaemia, and mycoplasma (pleuropneumonia-like organisms) have also been demonstrated in a variety of lymphomas.²¹

Response to Cytotoxic Drugs

The prompt response to chemotherapy was the property which, more than any other, established the African lymphoma as a

clinical entity. A variety of cytotoxic drugs, especially cyclophosphamide alone or in combination, have achieved complete regression and long remissions in early cases with small tumours, and have evoked a moderate to good response in more advanced cases.^{6 12 22 28} The rapidity of the response, observed in many instances, is regarded as unique in the treatment of tumours, virtual destruction of the neoplastic tissue having been observed within 72 hours.²⁴

Conclusion

It would appear that the EB virus (and possibly other lymphotropic viruses) is a passenger virus which is widely distributed throughout the world; that it may persist in many individuals; that it may be reactivated by a variety of benign as well as malignant processes which are associated with lymphocytic proliferation; and that the virus enters the nuclei of such lymphoid cells, where it replicates. Since the African lymphoma is, on the one hand, almost invariably associated with high EB antibody titres, and usually shows, on the other hand, a remarkably response to cytotoxic drugs, the conclusion seems inescapable that it is the intranuclear virus which renders the African lymphoma so susceptible to chemotherapy.

It follows that a deliberate infection with the EB virus (and possibly also with other lymphotropic viruses) before starting chemotherapy might achieve a more effective therapeutic result in the treatment of indigenous lymphomas in the temperate zones, and especially of lymphosarcomas. Such procedure might even prove to be efficacious in those cases of lymphomas which have become resistant to cytotoxic drugs.

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