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Malignant Lymphomas of African Children

(lymphoblastic leukemia/Burkitt lymphoma/malaria/(Epstein–Barr virus/cancer survey)

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ABSTRACT **Clinical, pathologic, and epidemiologic observations of malignant tumors of children in sub-Sahara Africa suggest alternative theories of causation, and give insight into environmental influences that may play a large role in the etiology and form of malignant lymphatic tumors and cerebral neoplasms of infants.**

Malignant lymphomas account for nearly half of the cancers of young children, but there are striking geographic differences among the several types. In northern hemispheres the malignant lymphomas are commonly lymphoblastic leukemias, but in central, sub-Sahara Africa and in New Guinea they are almost always solid, multicentric tumors, the so-called Burkitt type of lymphoma. In Brazil, and probably in South Africa as well, the ratios are intermediate, and in both areas hybrid forms have been conspicuous. Indeed, the pattern of Burkitt tumor in North America is notably different from that in Africa as, for example, in the frequency of leukemia and of jaw tumors.

The Burkitt tumor has been intensively investigated (1) during the past dozen years, largely because its distribution in Africa resembles the geographic pattern of arbovirus infections; these studies led to the suggestion that the tumor might be caused by a mosquito-borne virus (2). A miscellany of agents have since been recovered from African tumors and one, a herpes virus, is still being exhaustively studied because of its intimate association with the tumor. Whatever the role of this virus may prove to be, it is now quite evident that it is just as intimately associated with various other diseases, which include infectious mononucleosis, cancers of the postnasal space, and Hodgkin's disease. The elevated antibody levels to the virus, which attracted much attention when they were first associated with the Burkitt tumor, are also present in these and other circumstances; elevated antibody levels are now thought to be an expression of impaired cellular immunity, rather than indicative of a casual relationship (3).

Furthermore, the Epstein–Barr (EB) virus is distributed worldwide and, therefore, offers no explanation of the uneven distribution of the Burkitt tumors. In addition there is little in the known natural history of EB virus infection to distinguish it from other herpes viruses, especially the cytomegalo viruses and virus III, which is a passenger of the Brown–Pearce tumor of rabbits. On the other hand, a herpes virus is believed to be the cause of a lymphatic malignancy in primates, and herpes viruses have been related to cancers of the cervix and uterus; continued exploration of the role of all these agents is surely in order.

An environmental factor that plays a significant role in determining the geographic pattern of the lymphomas is tropical malaria—holo- or hyper-endemic malaria. The association of malaria of this kind, in which repeated infections during the first year of life induce a severe and uninterrupted struggle with the parasite was originally recognized epidemiologically (4) and has been repeatedly confirmed. Initially, it was simply postulated that the pre-existing malaria transformed acute leukemia into a restricted, localized, subacute, or chronic disease. Both processes, the malaria and the leukemia, compete within the reticuloendothelial system; it was presumed that the leukemia cell is greatly disadvantaged by the malaria and survives and grows only in distant loci, such as the jaw bones and ovaries, the favorite sites of the African tumors. This view of pathogenesis also provided an explanation of the somewhat later peak-age incidence of the Burkitt tumor and its greater response to chemotherapy. The concept was further reinforced by the observation that myeloid leukemia at times behaves in a more chronic fashion in Africa than in European children, and that chloromatous deposits are more frequently seen in Africa than elsewhere (5).

If the Burkitt tumor bears such a relationship to acute, lymphoblastic leukemia, then the reciprocal ratios of the two are easily understood and the lessons of the Oxford survey, which revealed that childhood leukemia is initiated during gestation and that its prolonged latency is characterized by extreme susceptibility to various infections (6), may be pertinent to the Burkitt tumor as well. The first of these two observations, the origin during gestation, is critical to the proposition that the Burkitt lymphoma is caused by a postnatal virus infection, such as that associated with EB virus. The second observation is a reminder of deficiencies in the developing countries of adequate vital statistics. We cannot measure the mortality among the young that is due to holoendemic malaria, or measure the relationship between deaths during infancy that are caused by malaria and by leukemia.

We found no answers to these questions during a recent survey that spanned central Africa, but we did benefit from the firmly established and expertly directed cancer registries in Ibadan, Kampala, and Nairobi. Selected, combined notifications from these three registries are shown in Table 1 in parallel with the 1962–1965 notifications from England and Wales. Table 1 (which assumes the population at risk is unknown for the African series) recognizes two types of lymphatic neoplasm, two types of solid tumors, and three age

TABLE 1. *The relative frequency of different types of cancer in African and European children*

	Age at notification, years							
	0–4		5–9		10–14		All ages	
Diagnosis	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*
Leukemia	23 (7)	671	37 (19)	375	38 (29)	258	98 (15)	1304
Lymphomas	131 (186)	137	493 (614)	156	288 (253)	221	912 (345)	514
Neural tumors	36 (10)	629	27 (13)	404	16 (10)	314	75 (11)	1347
Other cancers	302 (92)	640	142 (119)	231	185 (102)	352	629 (100)	1223
Leukemia + lymphomas	154 (37)	808	530 (194)	531	326 (132)	479	1010 (108)	1810
Neural and others	334 (51)	1269	169 (52)	635	201 (59)	666	704 (53)	2570
Total	488 (46)	2077	699 (117)	1166	527 (89)	1145	1714 (76)	4388

A, a consecutive series of cancer notifications from Ibadan, Kampala, and Nairobi Cancer Registries (1966–1969).

B, cancer notifications, England and Wales. The Registrar General's Cancer Supplement 1962–1965.

The Standardized Incidence Ratios are shown in parentheses. Standard equals 100.

groups. The numbers of leukemias, solid lymphomas, neural tumors, and other cancers are shown in the upper lines and immediately beneath (in parentheses) the incidence ratios when the 1852 solid tumors, other than neuroblastomas, are allowed to set the standard of comparison (i.e., when the A:B ratio for solid tumors other than neuroblastomas equals 100).

For all forms of cancer the A:B ratio was 76, and for the lymphatic neoplasms and solid tumors the ratios were 108 and 53, respectively. The slight excess (8%) of lymphatic tumors in Series A was accompanied by an 85% deficit of leukemia and a 89% deficit of neural tumors. For children under 5 years of age the corresponding figures were 93 and 90%, respectively, and for children over 10 years they were 71 and 90%, respectively.

These observations suggest that the central African environment, perhaps due to the repeated attacks of malaria during infancy that are characteristic of the regions in question, have several consequences for children who are incubating malignant diseases: (*i*) the malaria may make survival difficult, hence the relative deficit in the youngest age group, (*ii*) the masking effect of true incidence may be disproportionately large on cancers with short latent periods, such as leukemia and neuroblastoma, (*iii*) the acquisition of resistance to malaria among the survivors may determine the switch from leukemia to the multifocal form of lymphoma.

The problem of underreporting has long been recognized as a worrisome aspect of the leukemia problem in Africa; during our recent survey, special attention was given to the evidence regarding leukemia. It seems more and more certain that the acute forms of lymphoblastic leukemia are seldom seen among young children in the countries we visited. The deficiency of acute leukemias of all forms is most marked among the youngest age groups. Thus, Essien (7) provided convincing evidence in Ibadan—where interest is high and pediatric hematologic consultations are commonplace. Of the 91 cases of acute leukemia Doctor Essien had personally studied, 37 were younger than 15 years, but only 5 of these were below 10 years of age. Essien calculated the incidence of acute leukemia in Ibadan to be 0.35/100,000 per annum, but only 0.19/100,000 in children younger than 15 years (7). Equally thorough studies in Kampala (8) provided similar evidence.

Of special interest to us during the 1972 survey were clues in Kampala and Nairobi that acute lymphoblastic leukemia may now be emerging as a more common disease among young children than was true even a few years ago. The Kampala evidence is based on an intensive, 11-month search for instances of acute leukemia among clinic patients that revealed eight cases, of which three were lymphoblastic (9). The authors also reviewed recent hospital records; they concluded that underreporting had occurred. The possibility of increasing incidence due to environmental changes and the relationship of leukemia to the solid lymphatic tumors was not discussed.

In Nairobi, 13 cases of acute, lymphoblastic leukemia alone had been observed during the past 2 years, a striking increase over our experience in the same community 12 years before, when such illnesses were rarely seen in young children. Some of the evidence was found in the cancer registry, but others were brought to our attention by Dr. R. B. Barr, who had personally documented the nature of many of the illnesses.

The records of the Nairobi patients were searched for evidence of malarial infection, along with the records of an equal number of patients of similar ages who were currently being treated for Burkitt lymphomas in the same hospital. All but one of the Burkitt's lymphoma patients in whose records malaria was mentioned was infected, but evidence of malaria was completely lacking in those who were leukemic; nine of the leukemic patients had laboratory notations of the absence of plasmodia, or malarial pigment, or both. Unfortunately, the comparison of the two groups could not be extended to their geographic origins since the Burkitt patients had been drawn from all parts of Kenya to the Kenyatta National Hospital, which has long been a study center of such tumors, while the leukemia patients had largely lived in or near Nairobi.

Both Kampala and Nairobi are in the midst of striking social changes, and there was evidence in both places of increasing control of malaria. In Nairobi the use of malarial prophylactics has increased, and improvements in housing, sanitation, and nutrition are conspicuous. The situation in Kampala is believed to be similar, and the leukemias that occur there will hopefully be critically examined for evidence of malaria. Much more detailed evidence will be needed to determine whether tropical malaria alters the pattern of the malignant lymphomas of young children, and to explore the mechanisms that may be involved, but the experience of the past decade is testimony to the value of clinical epidemiologic studies of the natural history of malignant diseases.

Tumors resembling the African variety occasionally occur in many places where malaria is rarely or never seen. They are less frequent and often less distinct, but it is clear that other environmental influences than malaria need to be considered.

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