An alternative and perhaps more likely explanation for the synergism of levodopa and anticholinergic drugs is that levodopa therapy, while producing repletion of striatal dopamine, still cannot completely redress the dopaminergic/cholinergic imbalance and that a central anticholinergic effect is still required to produce a maximum therapeutic effect.

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Burkitt's Lymphoma: A Time-space Cluster of Cases in Bwamba County of Uganda

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Summary

Seven cases of Burkitt's lymphoma have to date (March 1971) been diagnosed in the county of Bwamba in Uganda. All these patients had the clinical onset of their tumour in the 27 months from October 1966 to December 1968; five of them in the last six months of this period. Two of the patients were full sibs living in the same house. This is the most discrete time-space cluster of the disease yet recorded and provides further evidence for a role in the aetiology of Burkitt's lymphoma of an infective agent with a relatively short latent period.

Introduction

The space-time clustering of Burkitt's lymphoma cases which has been demonstrated in the West Nile District of Uganda (Williams *et al.*, 1969) suggests that an infective agent is involved in the development of the tumour. The West Nile clustering pointed to a few months and 10 to 20 kilometres as the pertinent units of time and distance between clustered cases.

Chronic intense malaria infection seems to play a crucial background role in the genesis of Burkitt's lymphoma (Burkitt, 1969); and it is well established that all patients with Burkitt's lymphoma have antibodies to Epstein-Barr virus, the majority at high titres (Henle *et al.*, 1969). A combination of infection with malaria and Epstein-Barr virus is the currently most favoured hypothesis concerning the cause of the disease. The principal epidemiological evidence for a role for malaria is the close geographic coincidence of falciparum malaria and Burkitt's lymphoma (Kafuko and Burkitt, 1970). Experimental support is provided by the finding that mice infected with a murine plasmodium, *P. berghei yoelii*, are more susceptible to lymphoma development when challenged with Moloney leukaemogenic virus (Wedderburn, 1970). The supporting

evidence for an oncogenic role for Epstein-Barr virus includes the following: it has been found in virtually every Burkitt's lymphoma tissue culture; it causes lymphocytic transformation and stimulates lymphoproliferation; Burkitt tumours immunologically react with each other and are strongly antigenic; and there are other members of the herpes virus group that are causally related to animal tumours—Marek's disease of chickens (Churchill and Biggs, 1967), frog kidney carcinoma (Mizell *et al.*, 1969), and malignant lymphoreticular proliferation in primates (Melendez *et al.*, 1969).

However, to account for Burkitt's lymphoma space-time clustering on the basis of these two highly prevalent endemic infections is very difficult.

Malaria is hyperendemic and holoendemic in West Nile (Kafuko *et al.*, 1969) and Epstein-Barr virus infection is so common that 85% or more of children have detectable antibodies to it by the age of 3 years (Henle *et al.*, 1969; East African Virus Research Institute, 1970). Moreover, the interaction between Epstein-Barr virus and malaria would be expected to be maximal at very young ages, when malaria is producing its greatest stress. The incidence of Burkitt's lymphoma is, however, at a peak round age 7, with a wide age range.

With our present knowledge of malaria and Epstein-Barr virus infection, and requiring a latent period of five years with a lot of variability, the observed space-time clustering of tumour cases would not be expected on the basis of any interaction between the two agents alone. Though it may be possible to build a hypothetical model for clustering dependent on some postulated peculiarity—for example, an unusual route of entry for Epstein-Barr virus at a critical time—there is no evidence at present to support such a model. Thus the clustering evidence stands as a challenge to this hypothesis.

However, the space-time clustering which continues to be observed in West Nile (Kafuko *et al.*, 1971) may be a sociological phenomenon, as yet not understood, peculiar to the West Nile District, rather than a biological aspect of Burkitt's lymphoma. Since the above difficulty with the simple Epstein-Barr virus plus malaria hypothesis is based only on the West Nile clustering, it is clearly important to confirm it in other areas.

We report here a time-space cluster of cases of Burkitt's lymphoma in Bwamba County of Toro District in Uganda.

Data

The map shows a part of Toro District in Uganda with the inhabited area of Bwamba County, the Ruwenzori Mountains, and the road from the district capital of Fort Portal to Bwamba. (Bwamba County is bordered by the Congo (Kinshasa) on

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Map of part of Toro District, Uganda. The area shown between the Ruwenzori Mountains and the forest is the inhabited area of Bwamba County. The place of onset of the seven known Burkitt's lymphoma cases are marked with a numeral in time sequence of occurrence (see Table II).

the west and by Lake Albert on the north.) The population figures for Bwamba (Uganda Census, 1959, and provisional figures for Uganda Census, 1969) are given in Table I.

TABLE I—"African" Population of Bwamba County

	Males	Females	Total
1959 { Total	28,609	30,496	59,105
Under 16 years	13,549	13,461	27,010
1969 Total			68,165*

Total population increase 1959 to 1969 = 15%.

* This provisional figure is for all persons irrespective of ethnic group—it is unlikely this figure overestimates the "African" population by more than 0.5%, and probably it is by less than 0.1%.

The population of Bwamba, most of whom are subsistence farmers, is concentrated to the west of the Ruwenzoris in the narrow strip between the mountains and the Semliki forest shown at an altitude of between 600 and 1,000 metres. Access to Bwamba from Fort Portal is by a difficult road across the foot of the mountains. Though there are regular bus services to Fort Portal, it remains the most isolated county in Uganda.

Malaria is hyperendemic (McCrae, 1968) and 39% of the people have sickle-cell trait (Lehmann and Raper, 1956).

Until late in 1969 medical care in the area was provided by a medical assistant at a Government dispensary at Bundibugyo (eastings/northings 173/78, see Map) and by a sister who visited weekly from Virika Mission Hospital in Fort Portal. Both services were stable for more than a decade though there were intermittent civil disruptions from 1962 to 1965 in the area. In late 1969 the dispensary was replaced by a new Government hospital.

TABLE II—Burkitt's Lymphoma in Bwamba County. All cases ever recorded* in order of date of onset of symptoms

Case No.	Age	Sex	Month and Year of Onset	Place of Onset. Eastings/Northings
1	5	M.	October 1966	174/84
2	4	M.	December 1967	170/72
3	3	F.	July 1968	168/81
4	5	F.	August 1968	175/78
5	6	M.	September 1968	164/75
6	3	M.	November 1968	172/84
7	9	M.	December 1968	168/81

* To 10 March 1971.

Table II gives details of all known patients with Burkitt's lymphoma from Bwamba (see also map). Six of the seven patients were diagnosed at Virika Hospital—the hospital that runs the weekly clinic in Bwamba. No one from this hospital could recall another case. All the histology for Uganda is done at Makerere Medical School in Kampala. By using these histological records plus Mr. Burkitt's list of suspected lymphoma patients, all cases of Burkitt's lymphoma (proved and suspected) diagnosed in Uganda since the late 1950s have been recorded in the Kampala Cancer Registry. There is no record of any Burkitt's lymphoma patient from Bwamba in the Registry before these seven and there have been none since (March 1971). The first patient developed clinical symptoms in October 1966, the second in December 1967, and the remaining five between July and December 1968. (The incidence for 1968 was 16.1 per 100,000 population under age 16 years.) All seven patients lived within an area 15 km square.

The diagnosis of Burkitt's lymphoma in all seven patients was confirmed histologically. The series excludes an additional patient (clinical onset in September 1968) from the same area of Bwamba, whose clinical symptoms and response to therapy were characteristic of Burkitt's lymphoma but whose histological diagnosis was that of histiocytic lymphoma.

Two patients (Cases 3 and 7) are full siblings living in the same house. Dalldorf *et al.* (1964) reported Burkitt's lymphoma in two sisters in Kenya, but provided no other details. We have previously recorded two first cousins who lived in the same house complex and who had their clinical onset of Burkitt's lymphoma within two months of each other (Morrow *et al.*, 1971), but this Bwamba pair is the first occurrence recorded in full siblings in Uganda.

So far as we have been able to ascertain nothing dramatic happened in late 1967 and through 1968 to account for this cluster of cases.

This is the most obvious space-time cluster of cases since the Aliba "outbreak" in West Nile (Pike *et al.*, 1967) when five patients presented in the space of two years from a single small village.

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