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SPACE-TIME CLUSTERING OF BURKITT'S LYMPHOMA IN THE WEST NILE DISTRICT OF UGANDA: 1961–1975

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Summary.—Epidemiological data relating to all 202 patients diagnosed with Burkitt's Lymphoma (BL) in the West Nile District of Uganda in the period 1961 to 1975 have been reviewed and analysed. Statistically significant evidence of space-time clustering of cases, first reported for the period 1961–65, was also present during 1972–73, but not during other periods. The patients involved in such clusters were found to be older than other patients ($P<0{\cdot}001$). The average annual incidence of BL in the District was $2{\cdot}45\times10^{-5}$ and overall there was no change in the incidence during the study period. However, there were statistically significant changes in incidence in different counties, which could not be explained as case-ascertainment artifacts. One sib pair of patients with BL was found and the series also included 7 instances of BL in two cousins.

It is suggested that study of variation in the intensity and type of malarial infestation in different areas at different times may help explain the epidemiological findings and suggest what, if any, aspects of this infection are critical for inducing BL.

An important feature of the epidemiology of Burkitt's Lymphoma (BL) has been the occurrence of "space-time clusters" of patients with the disease in areas endemic for BL. Pike, Williams and Wright (1967) first reported this phenomenon for patients diagnosed in the West Nile District of Uganda in the period 1961–1965. Patients with clinical onset in 1966 and 1967 displayed similar clustering relative to the earlier cases (Williams, Spit and Pike, 1969) and a remarkable "outbreak" of BL was noted (Morrow *et al.*, 1970) in Bwamba county in Toro District of Uganda (Fig. 1). This tendency, for patients whose date of clinical onset of disease are close in time, to live closer together than would be expected by chance, has given much support to the view that an infective agent may be involved in the aetiology of the tumour and that there is a relatively short latent period between infection and clinical onset of BL. The observation of seasonal variation in the date of presentation of new patients with BL, consistent from year to year, in the West Nile District, also favours such an hypothesis (Williams, Day and Geser, 1974). However, recent studies have failed to find evidence of space-time clustering of patients with BL in the Mengo and Acholi and Lango Districts of Uganda (Morrow *et al.*, 1976*a*; 1977) and in the North Mara District of Tanzania (Brubaker, Geser and Pike, 1973) (Fig. 1). Furthermore, a reduction in this effect has been reported for patients in the West Nile District for the period 1966 to 1971 (Smith, 1974).

In view of these apparently conflicting findings it seemed appropriate to review the data that has been collected on all newly diagnosed patients with BL in the West Nile District over the 15-year period 1961–75 to determine whether the space-time clustering observed only in this area of Uganda represents a real biological phenonemon, or whether the earlier results

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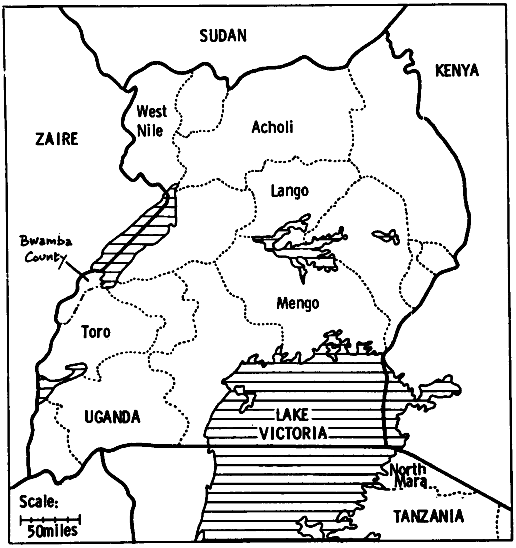

FIG. 1.—Map of East Africa showing areas from which studies of space-time clustering have been reported.

may have been a chance finding or have arisen artifactually due to some biased method of case ascertainment.

POPULATION AND METHODS

The West Nile district is in north-west Uganda on the borders of both Zaire and Sudan, the eastern boundary of the District being mainly along the Nile river. The population was estimated to be about 570,000 in 1969(Uganda Government, 1971) at which time the District was divided into 10 administrative counties (Fig. 2). There is a general rise in elevation from about 2,000 feet in the east near the Nile to around 4,000 feet in the more densely populated western areas. The south western part of Okoro county is the only area in the District rising above 5,000 feet (Uganda Government, 1967).

Since 1961, an attempt has been made by one of us (EHW) to register all new cases of BL in the District. A careful search of hospital records was made for all patients diagnosed in the period 1961 to 1965 (Pike *et al.*, 1967) and, since 1966, a mobile team has been established to locate accurately the homes of all newly diagnosed BL patients and to maintain regular contact with hospitals in and around the District in order that all new cases of BL should be registered. Regular checks have also been conducted with the Lymphoma Treatment Centre of the Uganda Cancer Institute and the Uganda Cancer Registry (both situated in Kampala) for BL patients who may have escaped registration in the District. Since 1972 the detection of BL cases in the entire West Nile district has been carried out as part of a large prospective epidemiological study of BL in the northern part of the District (Geser and de Thé, 1972).

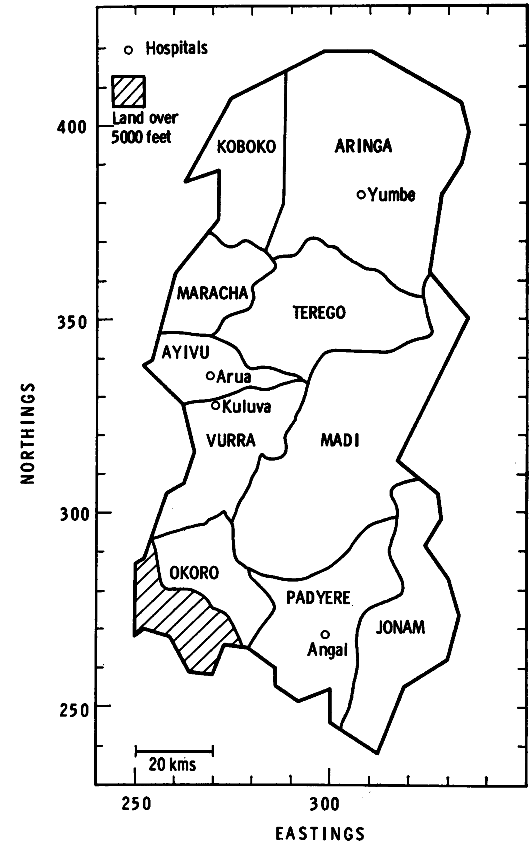

FIG. 2.—Map of West Nile District of Uganda showing county boundaries, hospitals and areas over 5,000 feet in altitude. Yumbe Hospital was opened in 1970 and two other hospitals were opened in 1973 at Maracha (co-ordinates 269/359) and Nebbi (286/275).

Microscopic proof of diagnosis has been sought wherever possible. In most cases where a histological section was obtained the material was examined in the Department of Pathology, Makerere University Medical School. From 1966 diagnosis of BL has also been based on touch preparations made at the time of biopsy. More recently the touch preparations have been supplemented by aspirations of tumour cells through a 21-gauge needle, and also histological sections have been reviewed by a panel of pathologists under the auspices of the International Agency for Research on Cancer. In this report cases are classified as histologically confirmed if diagnosed on the basis of a histological section, a touch preparation or a tumour aspiration.

A total of 202 cases of BL have been recorded with onset in the West Nile District in the 15-year period from 1961–75. For 39 (19%) patients the diagnosis of BL was based on clinical criteria only, the remainder having histological proof of the disease.

Details of the patients are given in the Appendix.

RESULTS

In Fig. 3 are shown the number of patients with onset of BL in the years 1961–75. Estimates of the District population in each year of the study period were derived from the 1959 (383, 926) and 1969 (573, 762) census reports for the District (Uganda Government, 1959; 1971) assuming an exponential increase, and these have been used to determine the annual incidence of BL over the 15 years of the study. The data are consistent with a uniform incidence over time (χ^2 (14 d.f.)$=20{\cdot}15$; $P=0{\cdot}13$) and, in particular, there is no evidence of an increase in incidence in the later years (χ^2 trend (1 d.f.)$=0{\cdot}03$; $P=0{\cdot}86$).

Fig. 4 shows the average age-specific annual incidence of BL, for males and females separately, over the study period. The proportion of the District population in single-year age groupings by sex was taken from the 1969 census data (unpublished tabulation). The peak incidence is at age 5 years for males and 7 years for females. Overall, 63% (127) of the patients were male and 37% (75) female, the male excess being less marked in the older children.

In order to consider possible temporal changes in the epidemiological characteristics of BL in the West Nile district, we have divided the 15-year study period into 3

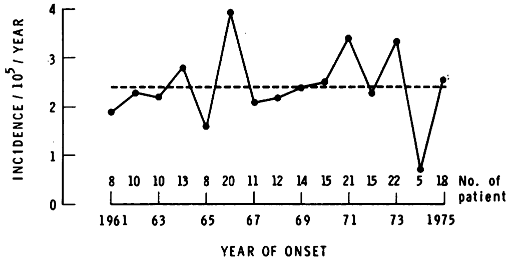

FIG. 3.—Incidence of BL by year 1961–75.

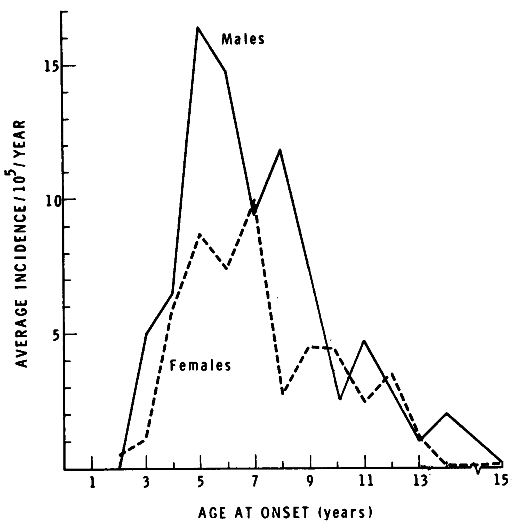

FIG. 4.—Average annual age-specific incidence of BL (1961–75).

quinquennia and the age and sex distribution of patients with onset of disease in these periods is shown in Table I. The ratio of males to females remained reasonably constant over time, but there is a decline in the proportion of older females, 50% of female patients being 9 years or older at onset in 1961–65, whereas less than 20% of patients presented at these ages in the subsequent decade (χ^2 (2 d.f.)$=7{\cdot}64$; $P=0{\cdot}02$; however, the significance may derive from the number of comparisons). There is also an increase in the proportion of older males in 1971–75, but this is not statistically significant. The percentage of patients with histologically proven BL were 71%, 72% and 94% respectively in the 3 quinquennia.

TABLE I.—*Age at Presentation of BL Patients in the West Nile District by Sex and Onset*

Age at presentation (years)	Year of onset 1961–65 Male	Female	1966–70 Male	Female	1971–75 Male	Female
2–5	10 (7)*	5 (2)	19 (15)	13 (11)	17 (16)	9 (8)
6–8	14 (11)	4 (2)	20 (14)	9 (6)	20 (19)	16 (15)
9–15	7 (5)	7 (6)	5 (3)	5 (2)	11 (10)	5 (5)
16+	—	2 (2)	1 (1)	0	3 (3)	0
Total	31 (23)	18 (12)	45 (33)	27 (19)	51 (48)	30 (28)

* The number of patients with histologically confirmed BL is included in the number of cases but is also shown in parentheses.

TABLE II.—*Average Annual Incidence of BL by County*

County	Number of patients with BL 1961–65	1966–70	1971–75	1961–75*	Estimated Mid 1968 population	% Increase in population 1959/69	Average annual incidence of BL/10^5/year 1961–75
Koboko	1	2	6	9·2	35454	71	1·73
Aringa	7	11	13	32·6	55003	39	3·95
Maracha	4	9	12	25·9	58403	26	2·96
Terego	6	16	12	35·4	55777	34	4·23
Ayivu	9	5	22	38·0	73892	38	3·43
Madi	3	10	2	15·7	44442	66	2·35
Vurra	2	6	6	14·5	34253	28	2·81
Okoro	1	1	2	4·2	75153	63†	0·37
Padyere	4	5	3	12·9	72060		1·19
Jonam	3	7	3	13·7	46303	95	1·97
Total	49*	72	81	202	550741	49	2·45

* 9 patients with unknown county of residence in 1961–65 have been divided between counties in proportion to those patients with known county of residence in 1961–65.

† Okoro and Padyere were not separate counties at the time of the 1959 census.

There is significant variation in the average annual incidence of BL between the 10 administrative counties of the District over the whole study period (Table II) and significant differences remain if Okoro, the county with a substantial proportion of land over 5,000 feet, is excluded (χ^2 (8 d.f.)=26·16; P=0·001) though when the adjacent county of Padyere is also excluded, the remaining counties do not quite show significant variation (χ^2 (7 d.f.)=13·34; P=0·06).

Space-time clustering

The data suggested that space-time clustering of cases of BL may be occurring on two different time scales. There seemed to be considerable variation in the incidence of BL within counties over a period of years, and there was also evidence of the kind of clustering previously described by Pike *et al.* (1967) which involved a much shorter time scale. We have examined these two aspects separately.

(i) *Variation in incidence by county in quinquennial periods.*—Fig. 5 shows the location of the home of all patients with disease onset in each of the 3 quinquennial periods. Particularly noticeable are the changes over the last 2 quinquennia; in 1971–75 there was a considerable reduction in the number of cases from the eastern and southern parts of the District, but a marked increase in patients living in the area in and around Ayivu county. The changes in the distribution of places of residence between these two time periods is statistically significant when considered by county (Table II: χ^2 (8 d.f.)=20·44 (combining the two adjacent southern counties of Okoro and Padyere); P= 0·009) a large increase was observed in cases in Ayivu county (from 5 to 22) and a

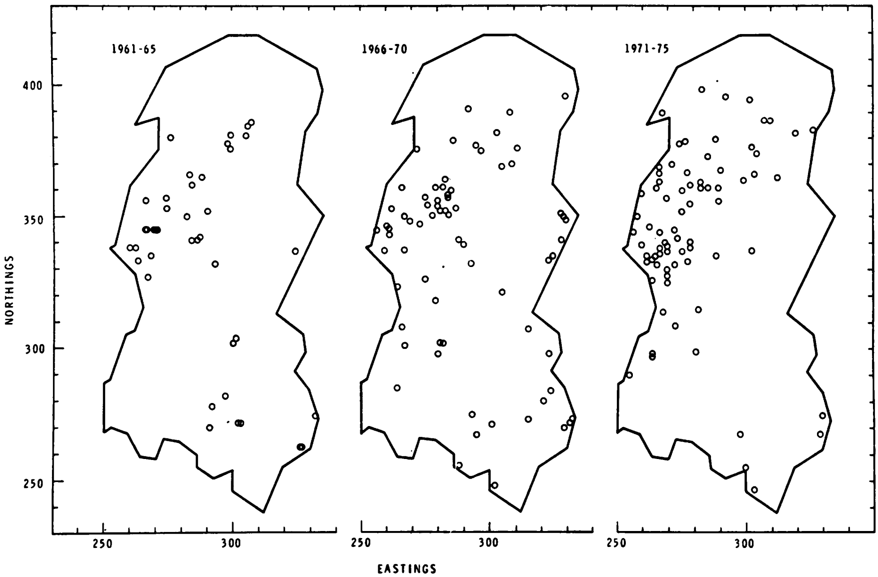

FIG. 5.—Location of homes of patients with onset of BL in each of the periods 1961–65, 1966–70 and 1971–75.

reduction in Madi county (from 10 to 2). We have no direct measure of changes in the size of the county populations over this period, but between the 1959 and 1969 censuses the population of Madi increased proportionately more than did Ayivu, and we know of no large-scale movements of population within the District in recent years that could account for the apparent changes in the distribution of places of residence of patients with BL.

(ii) *Clustering over shorter time periods.*—To eliminate the effects of the large-scale space-time clustering phenomenon, described above, analysis of clustering over shorter time periods was performed within each of the quinquennial periods. In Table III the results of the Knox (1964) test for space-time clustering within each of these periods is shown, using "critical" time periods of 30, 60, 90, 120, 180 and 360 days and "critical" space distances of 2·5, 5·0, 10·0, 20·0 and 40·0 km. Table IIIa displays the observed and expected numbers of pairs of patients within the various critical time and space distances for the period 1961–65. The results confirm, with the reviewed data, the findings of Pike *et al.* (1967) of strong evidence of clustering in time and space in this period. However, there is little evidence of such clustering in the period 1966–70 (Table IIIb) and the observation of two sets of results significant at the 5% probability level among the 30 sets examined is certainly compatible with chance, assuming no space-time clustering to have been present in this period. There is also little evidence of clustering in 1971–75 (Table IIIc). We further subdivided the ten years 1966–1975 into 5 two-year periods and applied the Knox test in each period, with the same critical time and space distances. In 4 of the periods there was essentially no evidence of clustering, but for patients with onset in 1972–73 there was a highly significant excess of "close pairs" at a number of time and space distances (Table IV).

(iii) *Characteristics of individuals in local clusters.*—Fig. 6 shows the locations of the homes of patients with onset of BL during the two time periods (1961–65, 1972–73) in which there was striking evidence of space-time clustering as indicated by the Knox test. Examination of Tables IIIa and IV

TABLE IIIa.—*Observed and Expected Numbers of Pairs of Patients with Onset of BL "Close" in Space and Time, Patients with Onset 1961–65* (n=*35*†)

Critical distance (km)		Critical time (days)						Total
		<30	<60	<90	<120	<180	<360	
< 2·5	Obs.	0	1	1	2	4*	4	7
	Exp.	0·24	0·48	0·71	0·95	1·29	2·49	
< 5·0	Obs.	1	2	2	4	6**	8*	12
	Exp.	0·40	0·83	1·21	1·63	2·22	4·28	
<10·0	Obs.	6**	7*	8*	11*	15**	21*	39
	Exp.	1·31	2·69	3·93	5·31	7·21	13·90	
<20·0	Obs.	8*	13*	15	21	32**	49**	105
	Exp.	3·53	7·24	10·59	14·29	19·41	37·41	
<40·0	Obs.	15*	29*	36*	53***	70***	112**	262
	Exp.	8·81	18·05	26·42	35·67	48·44	93·35	
Total		20	41	60	81	110	212	595

TABLE IIIb.—*Patients with Onset 1966–70* (n=*72*)

Critical distance (km)		Critical time (days)						Total
		<30	<60	<90	<120	<180	<360	
< 2·5	Obs.	1	1	2	2	3	7	15
	Exp.	0·45	0·90	1·36	1·80	2·83	5·13	
< 5·0	Obs.	2	3	5	5	9	22	51
	Exp.	1·54	3·07	4·61	6·13	9·64	17·44	
<10·0	Obs.	5	8	13	24	36	70*	171
	Exp.	5·15	10·30	15·45	20·54	32·31	58·47	
<20·0	Obs.	15	27	37	57	87	161*	425
	Exp.	12·80	25·61	38·41	51·05	80·31	145·32	
<40·0	Obs.	30	58	90	123	198	351	1000
	Exp.	30·13	60·25	90·38	120·11	188·97	341·94	
Total		77	154	231	307	483	874	2556

TABLE IIIc.—*Patients with Onset 1971–75* (n=*81*)

Critical distance (km)		Critical time (days)						Total
		<30	<60	<90	<120	<180	<360	
< 2·5	Obs.	1	1	3	4	6	8	27
	Exp.	1·01	1·93	3·06	3·97	5·81	9·56	
< 5·0	Obs.	1	5	8	13	19	24	81
	Exp.	3·02	5·80	9·18	11·90	17·43	28·68	
<10·0	Obs.	11	23	42*	53*	78**	104	286
	Exp.	10·68	20·48	32·40	42·02	61·53	101·25	
<20·0	Obs.	28	56	96	129	185	269	781
	Exp.	29·17	55·92	88·47	114·74	168·01	276·48	
<40·0	Obs.	70	131	217	280	404	647	1837
	Exp.	68·60	131·54	208·08	269·88	395·18	650·32	
Total		121	232	367	476	697	1147	3240

* $P<0\cdot05$
** $P<0\cdot01$
*** $P<0\cdot001$

Statistical significance levels were computed assuming a Poisson distribution, except where the expected value exceeded 30, in which case a normal approximation was employed using the computed expectation and variance. The Poisson approximation is likely to yield conservative estimates of significance levels.

† Excludes 5 patients for whom only the year of onset was known and 9 patients whose homes were not located.

suggested that the smallest time and space distances at which there was strong evidence of clustering in both periods were 10 km and 180 days, and also indicated in Fig. 6 are those patients involved in such "close pairs". It is notable that in the 1972–73 period the patients in these pairs came from only two areas, whereas in the 1961–65 period the linked patients were more diffusely spread throughout the District.

An interesting incidental finding was

TABLE IV.—*Observed and Expected Numbers of Pairs of Patients with Onset of BL "Close" in Space and Time. Patients with Onset 1972–73* (n=*37*)

Critical distance (km)		Critical time (days) <30	<60	<90	<120	<180	<360	Total
< 2·5	Obs.	1	1	3	3	4	5	5
	Exp.	0·38	0·83	0·31	1·72	2·42	4·07	
< 5·0	Obs.	1	5	7	11*	14*	16	17
	Exp.	1·28	2·81	4·47	5·85	8·24	13·83	
<10·0	Obs.	6	16	25*	34**	50***	58*	62
	Exp.	4·65	10·24	16·29	21·32	30·07	50·46	
<20·0	Obs.	15	31	56**	74***	107***	142*	159
	Exp.	11·94	26·26	41·78	54·67	77·11	129·40	
<40·0	Obs.	33	71	117*	151*	211*	335	397
	Exp.	29·80	65·57	104·32	136·51	192·54	323·08	
Total		50	110	175	229	323	542	666

TABLE V.—*Age at Onset of BL Patients during Periods of Space-time Clustering Divided According to whether or not Patients were Involved in "Close" Pairs* (i.e. *Onsets within 10 km and 180 Days*)

	Date of onset							
	1961–65				1972–73			
Age at onset (years)	BL cases in "close" pairs		Other BL cases		BL cases in "close" pairs		Other BL cases	
2	1		—		—		—	
3	—		—		2		3	
4	—	5 (26%)	3	12 (75%)	—	6 (29%)	3	11 (69%)
5	2		5		2		2	
6	2		4		2		3	
7	—		1		8		3	
8	5		—		—		1	
9	3		1		2		1	
10	2		—		1		—	
11	2	14 (74%)*	—	4 (25%)*	2	15 (71%)**	—	5 (31%)**
12	1		1		1		—	
13	—		—		—		—	
14	—		—		1		—	
15+	1		1		—		—	
Total	19		16		21		16	

* χ^2 (1 d.f.) = 6·22; $P = 0·01$ (Wilcoxon test: $P = 0·02$).
** χ^2 (1 d.f.) = 4·28; $P = 0·04$ (Wilcoxon test: $P = 0·01$).
Combined χ^2 (1 d.f.) = 11·96; $P = 0·0005$ (Wilcoxon text: $P = 0·0006$).

that the patients involved in "close pairs" tended to be older than the other patients with onset in the same time period (Table V). In both time periods about 70% of patients involved in clusters were aged 7 years or over at onset of BL, whereas only about 30% were so aged among those not in clusters. This difference in the age distribution of patients was statistically significant in both time periods.

(iv) *Contact between patients.*—Evidence of contact between BL patients prior to diagnosis has not been systematically sought throughout the study period. However, cases in related individuals were noted. Patients 134 and 197 (see Appendix) were sibs and lived in the same house, though their disease onsets were separated by 4 years. Six pairs of cousins (sharing 2 grandparents) are also included in the series (Patients 30, 57; 50, 100; 123, 162; 124, 125; 130, 151; 154, 158). Five of these pairs lived in close proximity to each other, but their respective dates of onset were

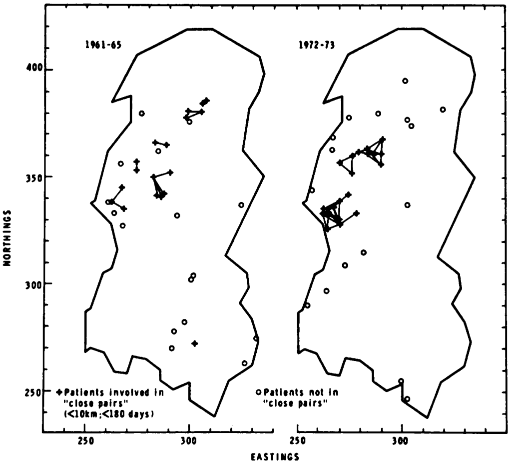

FIG. 6.—Location of homes of patients with onset of BL in the periods 1961–65 and 1972–73 showing pairs of patients whose disease onset was within 10 km and 180 days of each other.

from 1 to 4 years apart, with the exception of Pair 6 who were estimated to have had onset of BL the same day, and Pair 4 whose onsets were a month apart. An additional patient (161) was cousin to the sib pair with BL and had onset 17 months after onset of the first of the sibs to develop BL. He lived close to the sib pair.

DISCUSSION

Space-time clustering of patients with BL in the West Nile district seems to have been occurring in two distinct ways during the period 1961–75. Firstly, the kind of clustering originally described by Pike *et al.* (1967) for cases with onset during 1961–65 was also present during 1972–73, although it was not apparent at other time periods. This clustering was most evident among pairs of patients with onset of disease within 6 months or so of each other and whose places of residence were less than 10 km apart, and it was too strong to be dismissed as the maximum of a random sequence.

The additional finding that patients involved in clusters are, on average, older than other patients, supports the notion that the clustering is a real phenomenon and is probably not attributable to some artifact of case ascertainment. However, we have no satisfactory explanation which accounts for this age difference. In the districts of Uganda where detailed epidemiological studies have been conducted, the average age at onset of BL is lowest in those districts in which the incidence of the disease is highest (Morrow *et al.*, 1977). It might therefore be expected that in areas where there is a locally high incidence, as in a space-time cluster, the average age at onset of BL would tend to be lower, rather than higher, than that of other patients. A possible explanation is that if the precipitating event leading to the onset of BL is chronic and severe infection with malaria (Dalldorf *et al.*, 1964; Morrow, Gutensohn and Smith, 1976*b*) a local increase in the intensity of malarial infection in part of a district might give rise to a crop of BL cases and, if chronic infection *over several years* is a necessary precondition for onset of the disease, the cases arising in such a situation might be expected to be older than other cases in the District, as only the older cases would have been chronically infected with malaria for the necessary period prior to onset. It should be noted that only one of the 7 patients in the Bwamba cluster (Morrow *et al.*, 1970) was aged more than 6 years. However, the situation in Bwamba was rather unusual in other ways also, as no patients with BL had been diagnosed in this area prior to this cluster.

The clustering in 1972–73 occurred among two groups of cases in the adjoining counties of Maracha, Terego and Ayivu, whereas that in 1961–65 involved groups of patients scattered more widely in the district (Fig. 6). This suggests that whatever local factors precipitated a cluster of cases, these were distributed differently in these two periods.

The second kind of space-time clustering occurred over a longer time interval, the incidence of BL varying considerably within counties in different quinquennia. Although case detection has been good in the West Nile over the study period, it might be argued that some of the variation in incidence may be attributable to this cause. In general, ascertainment is likely to have been poorest in the southern part of the district. The low incidence in Okoro is most likely to be due to a substantial proportion of the county being over 5000 feet in altitude, where it is known that BL is much less common, but the low rates in Padyere and possibly Jonam also (Table II) may be due to cases being missed. The disappearance of cases from the eastern part of Madi district in 1971–75, a period of social instability in Uganda (Fig. 5, Table II) might possibly be similarly explained, but such reasoning cannot account for the marked increase in cases from Ayivu county in the same period. The two major hospitals in the district are both situated in this area (Arua and Kuluva hospitals) and the detection of new cases is very likely to have been considerably better in this county than in other parts of the District throughout the study period. There is therefore good reason to suppose that this "macro" space-time clustering is a real effect. It suggests that the intensity of the precipitating factor which leads to onset of BL varies from county to county (*i.e.* over wide areas) with time. Thus, if as has been argued elsewhere (Morrow *et al.*, 1976*b*) chronic severe infection with malaria is this factor, then it is to be expected that the intensity or type of malarial infection among persons within a county should show considerable variation from year to year. The ongoing prospective serological and epidemiological study in the District should provide data on this issue.

The detection of all new cases of BL in a rural African community is a difficult undertaking, and it is therefore surprising that the incidence of the disease appears to have remained reasonably constant over a 15-year period (Fig. 3) during which time it might be supposed that case ascertainment should have improved considerably because of increasing epidemiological activity in the district. It should, however, be noted that the proportion of patients with histologically confirmed disease was lowest in 1961–65, and we have little data on some of the patients diagnosed in this period.

The present and other studies have identified a number of distinct features of the epidemiology of BL. The first, and most important, was Burkitt's (1962) observation that within tropical Africa occurrence of the disease is limited by both altitude and rainfall, and this suggested the possibility of a mosquito-borne virus as the causative agent. Most of the other purely epidemiological observations are consistent with this hypothesis. Space-time clustering, both on small and larger time scales, seasonal variation in the incidence of BL (Williams *et al.*, 1974) and the observations on BL among immigrants from high altitude areas to areas endemic for BL (Morrow *et al.*, 1976*a*) may all be possibly explained by variation in exposure to mosquitoes in different places and at different times, though the decline in the incidence of BL in the Mengo districts of Uganda is more difficult to explain on this basis. However, the Epstein-Barr virus (EBV) which has been strongly implicated by serological (Henle *et al.*, 1969) and nucleic-acid-hybridization studies (Zur Hausen *et al.*, 1970) is not known to be arthropod-borne, and the epidemiological observations cannot be explained by assuming EBV to be the sole causative agent. This has led to the hypothesis that, in addition to EBV infection, exposure to chronic severe infection with malaria is a necessary precondition for developing the disease (O'Conor, 1970) and it is this infection which precipitates onset of BL (Morrow *et al.*, 1976*b*) (except for the few sporadic cases reported from non-malarious areas, which may have a quite different aetiology). We do not know enough of the variation in malaria over time and in different localities to be sure that the epidemiological data can be explained on this basis (Pike and Morrow, 1972). The precipitating event, be it infection with malaria or exposure to some other agent, must vary in intensity (or frequency) in different areas over long time periods, to give the long term variation in incidence of BL, but there must also be local "pockets" of intense exposure to the agent for a limited period which gives rise to subsequent space-time clusters. The period between the critical exposure and the onset of BL is also likely to be short, perhaps a year or less, otherwise it is unlikely that either space-time clustering or seasonal variation in disease incidence would occur. Direct person-to-person transmission of BL seems unlikely, otherwise it might be expected that space-time clustering would be found more consistently both over time and in different areas. The finding of a sib pair with BL and 7 pairs of cousins with the disease is certainly compatible with an agent which is transmitted between individuals. However, in most instances disease onsets in related individuals occurred a year or more apart, and this is not in line with a short latent period. We have not been able to assess whether the number of cases in related individuals is more than would be expected by chance, but polygamy is common in the District and the average family size is large so that 7 instances of the disease in cousins may not be excessive.

The case for the involvement of malarial infection in the aetiology of BL is far from proven. However, if severe and chronic infection with malaria is the cofactor with EBV infection which leads to the development of BL, and it is the former which primarily determines the time of onset, then study of the variation in intensity and type of malarial infection in different areas at different times may help explain the epidemiological findings and may suggest what aspects of this infection are critical for inducing BL.

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APPENDIX

Patient number	Date of diagnosis	Date of onset	Co-ordinates east	Co-ordinates north	Age	Sex	County	Diagnosis category	Reference number
1	/ /61		269	345	6	M	05	1	WN028
2	17/ 6/61	17/ 4/61	291	270	5	M	09	0	WN041
3	26/ 6/61	26/ 5/61	326	263	12	F	10	1	WN034
4	17/ 7/61	17/ 5/61			8	M	NK	1	J130
5	17/ 7/61	17/ 2/61	300	302	22	F	06	1	WN027
6	20/12/61	20/11/61	299	376	6	M	02	0	WN042
7	/ /62		269	345	7	M	05	1	WN029
8	/ /62		267	345	4	F	05	0	E5
9	/ /62		326	263	6	F	10	0	WN033
10	/ /62		269	345	4	M	05	0	WN030
11	31/ 3/62	31/12/61	267	327	4	F	07	1	WN043
12	4/ 5/62	27/ 4/62	266	356	6	M	03	1	WN044
13	11/ 6/62	21/ 5/62	267	345	10	F	05	1	WN031
14	7/ 8/62	10/ 7/62	268	335	8	F	05	1	WN045
15	21/ 9/62	7/ 9/61			14	M	NK	1	K95
16	24/ 9/62	27/ 8/62			5	M	NK	1	K180
17	18/10/62	18/ 6/62	262	338	10	F	05	1	WN047
18	26/ 2/63	8/ 2/63	335	275	6	M	10	1	WN074
19	19/ 3/63	19/ 9/62			12	M	NK	1	J187
20	5/ 5/63	5/ 4/63	302	272	6	M	09	1	WN035
21	29/ 5/63	29/ 4/63	301	304	5	F	06	1	WN048
22	9/ 6/63	9/ 5/63	302	272	8	M	09	1	K123
23	20/ 6/63	20/ 5/63			12	M	NK	1	K125
24	19/ 8/63	19/ 7/63			7	M	NK	1	J212
25	15/ 9/63	15/ 8/63	324	337	4	M	06	1	WN073
26	22/11/63	22/10/63			13	M	NK	1	K186
27	31/ 1/64	31/10/63	260	338	5	M	05	1	WN071
28	13/ 3/64	12/ 2/64	284	362	7	M	04	1	WN076
29	20/ 3/64	20/ 1/64	306	385	9	M	02	1	WN075
30	27/ 4/64	29/ 3/64	293	332	4	F	07	0	WN049
31	16/ 6/64	26/ 5/64	263	333	5	M	05	1	WN077
32	15/ 7/64	3/ 6/64	307	386	12	F	02	1	WN072
33	16/ 7/64	16/ 4/64	274	353	11	M	03	0	WN121
34	15/ 8/64	15/ 7/64	274	357	6	M	03	0	WN037
35	15/ 9/64	15/ 8/64	297	282	6	M	08	0	J256
36	22/ 9/64	22/ 8/64	288	365	5	M	02	1	WN050
37	24/ 9/64	10/ 9/64	283	366	8	M	03	1	WN051
38	15/12/64	15/11/64			8	M	NK	1	K222
39	8/ 1/65	18/12/64	284	341	9	M	04	0	WN054
40	16/ 1/65	16/12/64	290	352	8	F	04	1	WN055
41	13/ 4/65	15/12/63			5	M	NK	1	J238
42	25/ 5/65	25/ 3/65	286	341	5	M	04	1	WN101
43	30/ 6/65	9/ 6/65	282	350	2	F	04	0	WN056
44	19/ 7/65	19/ 6/65	292	278	9	F	09	0	WN052
45	25/ 8/65	11/ 8/65	305	381	25	F	02	1	WN078
46	15/ 9/65	12/ 9/65	287	342	11	F	04	1	WN058
47	15/ 9/65	15/ 8/65	298	378	8	F	02	0	E1
48	20/ 9/65	6/ 9/65	299	381	9	F	02	1	WN079
49	4/ 1/66	4/10/65	276	380	5	M	01	0	WN080
50	1/ 2/66	18/ 1/66	273	347	5	F	04	1	WN081
51	24/ 3/66	24/ 1/66	284	357	4	F	04	1	WN059
52	17/ 4/66	17/ 2/66	266	361	5	M	03	1	WN060
53	22/ 4/66	22/ 3/66	285	360	5	F	04	1	WN099
54	30/ 4/66	31/ 3/66	278	350	5	M	04	1	WN064
55	13/ 6/66	13/ 1/66	261	345	7	M	05	1	WN061

Patient number	Date of diagnosis	Date of onset	Co-ordination east	Co-ordination north	Age	Sex	County	Diagnosis category	Reference number
56	7/ 7/66	7/ 6/66	305	321	7	M	06	0	WN082
57	23/ 7/66	9/ 6/66	293	332	10	M	07	0	WN088
58	5/ 8/66	5/ 7/66	332	273	5	M	10	1	WN090
59	14/ 8/66	1/ 7/66	297	375	9	M	02	0	WN063
60	16/ 8/66	16/ 7/66	256	345	6	M	05	1	WN062
61	23/ 8/66	21/ 8/66	286	379	9	F	01	0	WN086
62	30/ 8/66	16/ 8/66	267	301	6	F	07	0	WN065
63	8/ 9/66	8/ 8/66	275	357	8	M	03	1	WN083
64	9/ 9/66	9/ 8/66	267	350	4	M	03	0	WN070
65	28/10/66	24/10/66	322	332	6	F	06	0	WN087
66	29/11/66	15/11/66	278	349	5	M	04	0	WN069
67	1/12/66	17/11/66	280	356	7	M	04	1	WN067
68	22/12/66	8/12/66	276	354	5	F	03	1	WN068
69	20/ 1/67	20/12/66	261	343	5	M	05	1	WN066
70	1/ 3/67	1/ 2/67	323	298	7	F	10	1	WN085
71	1/ 4/67	1/ 3/67	260	346	4	F	03	1	WN084
72	2/ 5/67	2/ 3/67	283	352	6	M	04	0	WN102
73	12/ 5/67	12/ 4/67	308	390	10	F	02	0	WN103
74	14/ 6/67	14/ 3/67	282	361	5	M	04	0	WN091
75	8/ 8/67	8/ 6/67	331	272	4	M	10	1	WN092
76	9/ 8/67	4/ 8/67	280	354	5	F	04	1	WN093
77	29/ 8/67	29/ 7/67	266	308	3	M	07	1	WN094
78	15/11/67	1/ 9/67	301	271	5	M	09	1	WN097
79	19/11/67	19/ 5/67	293	275	8	M	09	1	WN100
80	28/12/67	28/11/67	279	361	9	F	03	1	WN098
81	15/ 7/68	15/ 4/68	292	391	6	F	02	1	WN105
82	1/ 8/68	15/ 7/68	315	307	6	M	06	1	WN106
83	2/ 9/68	19/ 8/68	323	333	5	F	06	1	WN107
84	15/10/68	15/ 8/68	282	302	6	F	06	1	WN108
85	26/10/68	15/ 3/68	321	280	8	F	10	0	WN132
86	8/11/68	8/ 9/68	330	349	8	M	02	0	WN109
87	2/12/68	15/ 8/68	269	348	8	M	03	1	WN104
88	19/12/68	19/11/68	330	396	3	M	02	0	WN110
89	24/12/68	19/12/68	264	323	3	M	07	1	WN111
90	26/ 1/69	10/12/68	328	341	5	M	06	1	WN112
91	14/ 2/69	30/12/68	303	382	5	M	02	1	WN113
92	19/ 2/69	11/11/68	281	302	4	F	06	1	WN115
93	3/ 3/69	24/ 2/69	328	351	7	M	06	0	WN116
94	20/ 3/69	15/ 1/69	264	285	17	M	08	1	WN129
95	27/ 3/69	5/ 2/69	329	350	7	F	02	1	WN117
96	31/ 3/69	28/ 2/69	284	351	5	F	04	0	WN118
97	21/ 4/69	21/ 1/69	259	337	11	F	05	1	WN119
98	5/ 6/69	15/ 5/69	309	370	8	M	02	0	WN122
99	7/ 7/69	15/ 6/69	329	270	6	M	10	1	WN123
100	28/ 7/69	15/ 6/69	273	347	3	M	04	1	WN124
101	16/ 9/69	31/ 8/69	262	353	5	F	03	1	WN126
102	1/10/69	1/ 8/69	295	267	7	M	09	1	WN127
103	24/10/69	10/10/69	281	352	5	M	04	1	WN128
104	16/12/69	16/10/69	325	335	5	F	06	1	WN130
105	23/12/69	23/11/69	288	341	9	M	04	1	WN131
106	30/ 1/70	15/12/69	302	248	6	M	09	1	WN135
107	9/ 2/70	9/ 1/70	315	273	8	M	10	0	WN134
108	16/ 4/70	10/ 2/70	295	377	6	M	02	1	WN136
109	30/ 4/70	5/ 3/70	284	358	7	F	04	1	WN137
110	1/ 6/70	1/ 5/70	272	376	3	M	01	1	WN138
111	3/ 7/70	3/ 6/70	279	318	8	M	07	1	WN139
112	18/ 7/70	18/ 5/70	305	369	9	M	02	1	WN157
113	10/ 8/70	10/ 7/70	290	339	4	M	04	1	WN140
114	28/ 8/70	14/ 8/70	267	337	11	M	05	1	WN141
115	8/10/70	15/ 7/70	311	376	4	M	02	1	WN154
116	19/10/70	18/ 7/70	324	284	6	F	10	1	WN145
117	3/12/70	15/ 7/70	288	256	6	M	09	1	WN146
118	3/12/70	17/11/70	287	353	6	M	04	1	WN142
119	8/12/70	20/11/70	283	364	5	F	03	1	WN144
120	29/12/70	29/11/70	275	326	4	F	07	0	WN148

Patient number	Date of diagnosis	Date of onset	Co-ordinates east	Co-ordinates north	Age	Sex	County	Diagnosis category	Reference number
121	7/ 1/71	7/11/70	280	298	9	F	06	0	WN149
122	6/ 4/71	31/ 3/71	273	332	9	M	05	1	WN151
123	11/ 5/71	11/ 4/71	283	363	4	M	03	1	WN153
124	31/ 5/71	26/ 4/71	304	366	6	M	02	1	WN155
125	4/ 6/71	4/ 3/71	313	365	6	F	02	1	WN156
126	19/ 7/71	19/ 5/71	308	387	6	M	02	1	WN160
127	9/ 8/71	26/ 6/71	330	275	6	F	10	1	WN162
128	15/ 8/71	3/ 3/71	281	299	28	M	06	1	WN181
129	15/ 8/71	15/ 7/71	329	268	7	M	10	1	WN165
130	25/ 8/71	18/ 7/71	274	342	6	M	04	1	WN164
131	26/ 8/71	14/ 7/71	268	314	5	F	07	1	WN163
132	6/ 9/71	6/ 8/71	286	373	8	M	02	1	WN166
133	20/ 9/71	17/ 9/71	269	340	4	F	05	0	WN167
134	13/10/71	13/ 9/71	265	335	8	M	05	1	WN168
135	16/10/71	30/ 9/71	260	359	7	M	03	0	WN169
136	20/10/71	29/ 8/71	263	346	8	M	05	1	WN170
137	23/10/71	9/ 7/71	289	335	12	F	05	1	WN171
138	27/10/71	27/ 6/71	260	339	12	M	05	1	WN172
139	15/12/71	15/11/71	279	355	7	F	04	1	WN175
140	17/12/71	1/12/71	270	337	5	M	05	1	WN173
141	18/12/71	18/11/71	284	399	4	M	01	1	WN174
142	20/ 1/72	1/ 1/72	267	363	3	M	03	1	WN176
143	24/ 1/72	3/ 1/72	320	382	5	M	02	1	WN177
144	1/ 3/72	28/ 2/72	282	315	7	F	07	0	WN178
145	7/ 4/72	15/ 7/71	264	298	36	M	08	1	WN179
146	19/ 6/72	19/ 4/72	303	377	8	M	02	1	WN182
147	21/ 7/72	1/ 7/72	303	337	6	F	06	1	WN183
148	25/ 8/72	20/ 6/72	264	297	4	M	07	1	WN184
149	13/ 9/72	2/ 9/72	270	330	11	M	05	1	WN185
150	7/10/72	11/ 9/72	262	335	10	M	05	1	WN187
151	31/10/72	12/ 9/72	274	342	7	F	04	1	WN188
152	27/11/72	/ 5/72	303	247	5	M	09	1	WN193
153	6/12/72	14/11/72	267	369	7	F	03	1	WN190
154	15/12/72	13/11/72	262	333	7	F	05	1	WN191
155	19/12/72	21/11/72	255	290	4	F	08	1	WN192
156	4/ 1/73	/ 8/72	289	380	7	M	02	1	WN194
157	24/ 1/73	3/ 1/73	273	309	3	F	01	1	WN195
158	27/ 1/73	13/11/72	262	333	3	M	05	1	WN189
159	30/ 1/73	16/ 1/73	270	328	11	M	07	1	WN197
160	22/ 2/73	1/ 2/73	270	339	6	M	05	1	WN196
161	12/ 3/73	27/ 2/73	265	334	7	M	05	1	WN190
162	4/ 5/73	20/ 4/73	283	363	9	M	03	1	WN200
163	8/ 5/73	15/ 3/73	276	352	9	M	04	1	WN201
164	9/ 5/73	10/ 4/73	276	360	5	F	03	1	WN202
165	6/ 6/73	23/ 5/73	278	333	7	F	05	1	WN205
166	23/ 6/73	23/ 4/73	305	374	3	M	02	1	WN203
167	10/ 7/73	19/ 6/73	302	395	6	M	02	1	WN204
168	/ 8/73	/ 6/73	257	344	9	M	05	0	WN215
169	3/ 8/73	19/ 7/73	279	362	7	F	03	1	WN207
170	7/ 8/73	2/ 1/73	267	336	14	M	05	1	WN206
171	24/ 8/73	24/ 4/73	264	326	7	F	07	1	WN208
172	4/ 9/73	4/ 8/73	300	255	6	F	09	1	WN209
173	6/ 9/73	15/ 7/73	290	361	12	F	04	1	WN210
174	20/ 9/73	20/ 5/73	286	361	5	M	04	1	WN211
175	21/ 9/73	10/ 9/73	290	356	7	F	04	1	WN212
176	21/ 9/73	11/ 9/73	291	368	3	F	02	1	WN213
177	3/10/73	3/ 7/73	275	378	4	F	01	1	WN214
178	5/12/73	20/11/73	283	361	6	F	04	1	WN216
179	29/ 1/74	22/ 1/74	270	325	5	M	07	1	WN217
180	13/ 2/73	/ 8/73	270	357	7	M	03	1	WN218
181	9/ 4/74	27/ 3/74	266	332	5	F	05	1	WN220
182	11/ 9/74	28/ 8/74	267	367	6	F	03	1	WN221
183	16/ 9/74	2/ 9/74	300	364	4	M	04	1	WN222
184	5/10/74	5/ 9/74	268	390	8	M	01	1	WN223
185	11/ 2/75	11/ 1/75	276	337	3	M	05	1	WN225
186	21/ 2/75	27/ 1/75	273	345	10	F	04	1	WN226

Patient number	Date of diagnosis	Date of onset	Co-ordinates east	north	Age	Sex	County	Diagnosis category	Reference number
187	28/ 2/75	21/ 2/75	267	338	5	M	05	1	WN227
188	17/ 3/75	17/ 1/75	293	396	16	M	02	1	WN228
189	29/ 4/75	10/ 4/75	278	367	10	F	03	1	WN229
190	21/ 5/75	1/ 5/75	266	332	6	M	05	1	WN230
191	5/ 7/75	14/ 6/75	266	361	8	M	03	1	WN234
192	5/ 7/75	21/ 6/75	267	344	5	M	05	1	WN233
193	12/ 7/75	12/ 6/75	279	340	10	M	04	1	WN235
194	4/ 8/75	20/ 4/75	298	268	13	F	09	1	WN237
195	25/ 8/75	2/ 7/75	272	370	6	M	01	1	WN240
196	28/ 8/75	/ 4/75	310	387	6	M	02	1	WN241
197	9/ 9/75	7/ 9/75	265	335	12	M	05	1	WN242
198	18/10/75	1/10/75	310	387	4	M	02	0	WN244
199	13/11/75	2/10/75	279	339	5	M	04	1	WN247
200	24/11/75	24/10/75	258	350	5	F	03	1	WN246
201	12/12/75	12/ 8/75	327	383	6	M	10	1	WN248
202	31/12/75	4/10/75	277	379	7	F	01	1	WN250

Codes

County:

01 Koboko
02 Aringa
03 Maracha
04 Terego
05 Ayivu
06 Madi
07 Vurra
08 Okoro
09 Padyere
10 Jonam

Diagnosis Category:

0 Clinical diagnosis only
1 Histological proof