PAPERS AND ORIGINALS

Levodopa in Parkinsonism: the Effects of Withdrawal of Anticholinergic Drugs

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Summary

The results are reported of a trial in which 34 patients receiving a stable dose of levodopa for the treatment of idiopathic Parkinsonism, as well as anticholinergic drugs which they had been taking before the introduction of levodopa, underwent withdrawal of their anticholinergic remedies. Withdrawal was gradual over four weeks in 17 patients (group 1) and abrupt in the remaining 17 (group 2).

Only 11 out of 34 patients on stable levodopa therapy were able to tolerate withdrawal of anticholinergic drugs for more than eight weeks. The main reasons for the resumption of these remedies were subjective increases in slowness in 20 (59%), tremor in 15 (44%), and recurrence of hypersalivation in 5 (15%). Hypersalivation was the single feature which was most significantly and adversely influenced by anticholinergic withdrawal in patients on levodopa irrespective of whether withdrawal was sudden or gradual. It is suggested that the synergism which seems to exist between anticholinergic remedies and levodopa may be due to inhibition of dopamine inactivation by anticholinergic drugs, thus ensuring continual utilization, or alternatively, to a primary central anticholinergic effect.

Objective and more severe subjective deterioration occurred only on sudden withdrawal. Hence we would advise that if for any reason anticholinergic drugs are to be withdrawn in patients receiving a stable dosage of levodopa this must be done slowly. Conversely it would appear from our results that the introduction of anticholinergic drugs in patients treated initially with levodopa is likely to produce additional benefit, particularly when the maximum tolerated dose of levodopa is small.

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Introduction

Before treatment with levodopa became available anticholinergic drugs were the mainstay of drug treatment in Parkinsonism and produced an estimated 20% improvement (Yahr *et al.*, 1969), mainly in the features of rigidity and tremor; hypersalivation was also considerably improved in many cases. The advent of levodopa with its beneficial effects of varying degrees in all types and all aspects of Parkinsonism has raised the important question of whether anticholinergic drugs should be continued in patients receiving levodopa therapy or whether they should be given in addition when levodopa is used as the primary treatment. It is well known that rapid deterioration in the Parkinsonian state may occur when anticholinergic drugs, used as the only treatment, are withdrawn. It seemed important therefore to determine whether continued anticholinergic therapy was necessary in addition to levodopa therapy, whether any synergism existed between the two forms of treatment, and to delineate those clinical features, if any, which responded preferentially to anticholinergic drugs.

A study was therefore designed in order to analyse the effects of withdrawal of anticholinergic drugs in a group of patients receiving a stable dosage of levodopa. In view of the likelihood that sudden withdrawal would be followed by non-specific side effects patients were allocated to two groups in one of which such withdrawal was sudden and in the other gradual.

Patients and Methods

Thirty-six patients with paralysis agitans (idiopathic Parkinsonism) (20 male, 16 female) who had been receiving a constant amount of anticholinergic therapy for a number of years, and who had responded to levodopa which they had been taking in stable dosage for two months or more, were admitted to the trial. The duration of disease in these patients varied from 3 to 28 years.

Most of the patients were receiving benzhexol (Artane) or orphenadrine hydrochloride (Disipal) either alone or in combination with bztropine (Cogentin) and had been taking these drugs for at least five years. Patients were allocated to the gradual (group 1) or sudden (group 2) withdrawal groups in such a way that the doses and combinations of anticholinergic drugs were matched as closely as possible in each group (Table

TABLE I—Prewithdrawal Dosages of Anticholinergic Drugs and Levodopa

Case No.	Anticholinergic Drugs (Daily Dosage)				(Daily Dosage) (g)
	Benzhexol (Artane) (mg)	Orphenadrine HCl (Disipal) (mg)	Levodopa Benzotropine (Cogentin) (mg)	Others	
Group 1					
1 ..	—	200	4	—	1.2
2 ..	—	200	2	—	1.5
3 ..	—	—	—	Chlorphen-oxamine HCl 400 mg	4.0
4 ..	6	—	—	Methixene HCl 15 mg	1.5
5 ..	6	150	4	—	3.0
6 ..	15	—	—	—	2.0
7 ..	6	150	—	—	1.0
8 ..	—	200	—	—	0.6
9 ..	6	—	—	—	3.0
10 ..	—	200	2	—	2.5
11 ..	—	150	—	—	6.0
12 ..	2	—	—	—	3.0
13 ..	8	—	4	—	3.5
14 ..	6	—	4	—	3.0
15 ..	—	150	—	Biperiden HCl 6 mg	2.0
16 ..	—	150	2	—	3.5
17 ..	—	150	2	—	3.0
18*	6	—	—	—	—
Group 2					
19 ..	10	—	—	—	0.75
20 ..	—	150	4	—	1.2
21 ..	8	250	—	—	4.0
22 ..	8	200	—	—	1.0
23 ..	8	200	—	—	1.5
24 ..	—	100	2	—	1.5
25 ..	—	150	2	—	3.0
26 ..	—	150	2	—	3.5
27 ..	6	—	—	—	2.5
28 ..	9	—	2	—	1.2
29 ..	—	150	2	—	5.5
30 ..	—	150	2	—	2.5
31 ..	7.5	—	2	—	3.5
32 ..	—	100	—	Phenglu-tarimide HCl 20 mg	4.0
33 ..	6	—	2	—	5.0
34 ..	—	100	2	—	4.0
35 ..	15	150	—	—	2.0
36*	—	200	2	—	—

*Withdrawn from final analysis (see text).

I); the groups were also matched so as to include equal numbers of patients who had undergone previous stereotaxic surgery. There were 18 patients in each group.

In group 1 anticholinergic drugs were reduced by one-quarter of the total dose per week, so that at the four-week stage these drugs had been discontinued; and in group 2 the drugs were stopped abruptly. In each group clinical assessments were carried out immediately before the trial and at two-weekly intervals thereafter for eight weeks. The patients were assessed clinically by one of two of us (R.C.H. and J.G.P.) by the methods described in a previous study (Hughes *et al.*, 1971). On this occasion, however, particular note was also made of emergent mental symptoms or autonomic release phenomena—for example, disturbances of micturition, perspiration, salivation, visual symptoms, etc. The opinions of the patients and their relatives regarding any changes were sought at each attendance and patients were told before the trial that deterioration might occur but that this was unlikely. In the event of any change occurring patients were asked if possible neither to recommence anticholinergic drugs nor to increase their dosage until they had been reassessed clinically.

Results

Two patients were eventually excluded from the study on the grounds of insufficient attendances in one case and variation of levodopa dosage in the other. Thirty-four patients therefore completed the trial period but only 16 of them were able to tolerate withdrawal of anticholinergic drugs for the whole of the eight-week trial period, and five of these 16 resumed these drugs immediately after the eight-week stage. Since then a further four patients have returned to anticholinergic therapy.

PATIENTS' AND RELATIVES' ASSESSMENT

Twenty-five patients felt they were worse on withdrawal of anticholinergic drugs, and their complaints, which were confirmed by their relatives, are listed in Table II. It can be seen that increasing bradykinesia, increasing tremor, or both were the commonest complaints, though in three patients gross hypersalivation was the main indication for resumption of their previous drugs. Three patients (Cases 14, 29, and 30) noted a reduction in duration of effects of individual levodopa doses from 3½-4 hours to 2½ hours or less; redistribution of their levodopa—that is, an increased number of doses of lesser amount—served only to reduce further the effectiveness of individual doses. This was completely reversed when anticholinergic drugs were resumed. The only factor common to these patients was that each patient was receiving benzotropine (in combination with orphenadrine in two patients and benzhexol in one); other patients receiving this drug did not note

TABLE II—Complaints of 25 Patients who Claimed to be Worse on Anticholinergic Withdrawal

	Group 1 Slow Withdrawal	Group 2 Sudden Withdrawal	Total
Increased bradykinesia ..	6	14	20
Increased rigidity ..	2	2	4
Increased tremor ..	8	7	15
Hypersalivation ..	2	3	5
Deterioration of speech ..	1	2	3
Dysphagia ..	1	1	2

similar effects. It is worthy of note, however, that two patients (Cases 24 and 28) who noted gross deterioration on withdrawal were also receiving benzotropine; the deterioration in Case 28 was completely reversed by restarting benzotropine alone. These findings are in accordance with the accepted fact that benzotropine is the most potent anticholinergic drug in general usage. Two patients felt they were improved on withdrawal, particularly with regard to speech, and in one of these walking was said to be improved; these impressions could not be confirmed clinically.

Of the 17 patients in group 1 five said they felt no change, two felt better, and 10 felt worse. The number of patients noting deterioration is statistically significant ($P < 0.05$). Of the 17 patients in group 2, two said they felt no change, none felt better, and 15 felt worse. This again is significant ($P < 0.01$).

STATISTICAL ANALYSIS

The assessment of the four main clinical features—namely, bradykinesia, rigidity, tremor, and gait—together with the results of the four timed tests previously described (Hughes *et al.*, 1971) were analysed. The change in score from pre-withdrawal to each two-weekly assessment was the measure of improvement or otherwise in the patient. Groups 1 and 2 were considered separately by these within-patient comparisons and the mean change for the group at each time interval was tested against zero (Tables III-VI).

In both groups 1 and 2 the numbers of patients able to tolerate anticholinergic withdrawal decreased progressively at each assessment interval. This was particularly so in group 2 where only four patients were able to tolerate withdrawal to the eight-week stage compared with 12 in group 1. One patient did not attend for assessment at the eight-week stage.

In group 1 there was on average a non-significant deterioration in bradykinesia, rigidity, and tremor and a non-significant improvement in gait when assessments of these features were compared with those obtained before withdrawal. Of the timed tests, repeated handgrips and rising from a chair showed on average a non-significant deterioration and restacking books a non-significant improvement. Walking a set distance, however, showed on average a significant improvement at two weeks which was maintained at the later assessments (see Table III).

TABLE III—Group 1 Patients: Walking Set distance. Within-patient Comparisons from Prewithdrawal to Two-weekly Assessments

	2 Weeks	4 Weeks	6 Weeks	8 Weeks
Number of patients	17	14	12	11
Prewithdrawal mean	8.64	8.71	8.22	8.35
Mean improvement	0.89	0.94	0.77	0.86
Standard error of change ..	0.283	0.392	0.246	0.333
	P<0.01	P<0.05	P<0.01	P<0.05

TABLE IV—Group 2 Patients: Rigidity. Within-patient Comparisons from Prewithdrawal to Two-weekly Assessments

	2 Weeks	4 Weeks	6 Weeks	8 Weeks
Number of patients	12	9	6	4
Prewithdrawal mean	0.75	0.83	0.58	0.63
Mean deterioration	1.08	1.06	0.50	0.75
Standard error of change ..	0.379	0.556	0.50	0.479
	P<0.02	P>0.05*	P>0.3*	P>0.2*

*Not significant.

TABLE V—Group 2 Patients: Rising from a Chair. Within-patient Comparisons from Prewithdrawal to Two-weekly Assessments

	2 Weeks	4 Weeks	6 Weeks	8 Weeks
Number of patients	12	9	6	4
Prewithdrawal mean	5.49	5.72	6.08	6.75
Mean change*	+8.33	+3.84	-1.12	+7.30
Standard error of change ..	4.197	3.812	0.931	6.921
	P<0.05	P>0.3†	P>0.3†	P>0.3†

*A positive sign indicates a deterioration.

†Not significant.

TABLE VI—Group 2 Patients: Repeated Handgrips. Within-patient Comparisons from Prewithdrawal to Two-weekly Assessments

	2 Weeks	4 Weeks	6 Weeks	8 Weeks
Number of patients	12	9	6	4
Prewithdrawal mean	6.03	6.03	6.12	5.55
Mean deterioration	1.81	1.02	0.22	0.53
Standard error of change ..	0.406	0.552	0.549	0.384
	P<0.001	P>0.1*	P>0.7*	P>0.2*

*Not significant.

No reason other than anticholinergic withdrawal could be found to account for this improvement, but it should be noted that this result is in agreement with the non-significant gait improvement noted at each assessment period. It is possible that continuing improvement due to levodopa was responsible for this finding.

In group 2 patients there was on average a non-significant deterioration in all four main clinical features at two and four weeks with the exception of rigidity, which was significantly worse at two weeks (Table IV). All timed tests showed a deterioration at the two-week stage which was significant for rising from a chair ($P < 0.05$) (Table V) and highly significant for repeated handgrips ($P < 0.001$) (Table VI). At the later stages when patients unable to tolerate withdrawal had returned to taking anticholinergic drugs, and hence could not be included in the further analysis, the changes were not significant.

When groups 1 and 2 were compared with respect to clinical features and timed tests there was a significant difference between changes noted in gait, walking a set distance, and repeated handgrips, the changes being more favourable for group 1 patients. The differences, however, were significant only at the two-week stage when there was a maximum difference between the amount of anticholinergic drugs being taken by the two groups (Tables VII-IX). After two weeks there was no significant difference between the groups in any clinical feature or timed test. For some of the timed tests the variability of the changes experienced by the two groups was significantly different, and when this was observed the Mann-Whitney U test (instead of Student's t test) was used to compare the groups (Siegel, 1956) (Table VIII).

TABLE VII—Gait. Comparing Slow Withdrawal (Group 1) and Sudden Withdrawal (Group 2) in Terms of Changes from Prewithdrawal to Each Assessment Period. (Numbers of Patients are shown in Parentheses)

	2 Weeks	4 Weeks	6 Weeks	8 Weeks
Mean slow withdrawal changes	-0.35 (16)	-0.21 (14)	-0.33 (12)	-0.36 (11)
Mean sudden withdrawal changes	+0.82 (11)	+0.78 (9)	-0.50 (6)	-0.50 (4)
Difference between changes	+1.17	+0.99	-0.17	-0.14
Standard error of change	0.565	0.659	0.640	0.638
	P<0.05	P>0.1*	P>0.7*	P>0.8*

*Not significant.

TABLE VIII—Walking Set Distance. Comparing Slow Withdrawal (Group 1) and Sudden Withdrawal (Group 2) in terms of Changes from Prewithdrawal to Each Assessment Period. (Numbers of Patients are shown in Parentheses).

	2 Weeks	4 Weeks	6 Weeks	8 Weeks
Mean slow withdrawal changes	-0.89 (17)	-0.94 (14)	-0.77 (12)	-0.86 (11)
Mean sudden withdrawal changes	+10.08 (12)	+0.30 (9)	-0.63 (6)	-0.88 (4)
Difference between changes	+10.97	+1.24	+0.14	-0.02
Standard error of change	—	—	0.448	0.682
	P<0.05	(Non-parametric tests)*	P>0.7*	P>0.9*

*Not significant.

TABLE IX—Handgrips. Comparing Slow Withdrawal (Group 1) and Sudden Withdrawal (Group 2) in terms of Changes from Prewithdrawal to Each Assessment Period. (Numbers of Patients are shown in Parentheses)

	2 Weeks	4 Weeks	6 Weeks	8 Weeks
Mean slow withdrawal changes	+0.21 (17)	+0.34 (14)	+0.13 (12)	-0.01 (10)
Mean sudden withdrawal changes	+1.81 (12)	+1.02 (9)	+0.22 (6)	+0.53 (4)
Difference between changes	+1.60	+0.68	+0.09	+0.54
Standard error of change	0.564	0.861	1.032	1.257
	P<0.01	P>0.3*	P>0.9*	P>0.6*

*Not significant.

When the numbers of patients returning to anticholinergic therapy in group 2 were compared with those in group 1 the difference was significant at each trial interval (Table X).

TABLE X—Number of Patients in whom Anticholinergic Drugs were Reintroduced

	Group 1		Group 2		
	Total in Group = 17		Total in Group = 17		
	No.	%	No.	%	
At 2 weeks	0		5	29	P = 0.044
At 4 weeks	1	6	7	41	P = 0.039
At 6 weeks	4	24	11	65	P < 0.05
At 8 weeks	5	29	13	76	P < 0.05

MENTAL CHANGES

Twenty-six patients noted no emergence of mental symptoms on withdrawal; seven had insomnia, which was associated with extremely vivid dreaming in three; and increased somnolence was noted by another patient. Four patients commented on an increase in lethargy. Depression, agitation, and confusion each occurred in two patients. Emergent mental symptoms occurred with equal frequency in groups 1 and 2 with the exception of sleep disturbance and vivid dreaming which was exclusive to group 2.

AUTONOMIC "RELEASE" PHENOMENA

An increase in salivation occurred in 15 patients; in most of these this relieved the levodopa-induced symptom of dryness

of the mouth previously noted (Hughes *et al.*, 1971), but in five patients frank hypersalivation occurred. An increase in perspiration occurred in seven and was excessive in three. Six patients noted alteration of vision—blurring of vision occurring in three and excessive epiphora in three. Changes in bowel or bladder function occurred in seven patients, four noting relief of constipation and three complaining either of incontinence of urine or frequency and hesitancy of micturition. The urinary symptoms were relieved completely on resumption of anticholinergic therapy. When his anticholinergic drugs were withdrawn one patient developed a recurrence of ulcer dyspepsia which had been quiescent for many years.

DYSKINESIA

A reduction in dyskinetic movements was noted by five patients and an increase by one patient.

ANTICHOLINERGIC DOSAGE

Twelve of the 19 patients who restarted anticholinergic drugs before the eight-week stage found it necessary to revert to their previous dosage (100%) in order to attain their prewithdrawal status; seven, however, were able to regain this state, taking a considerably reduced dosage, the range of reduction being 23-77%.

LEVODOPA DOSAGE

The average daily dose of levodopa for the patients in the two groups was equal at 2.7 g, and in group 2 (sudden withdrawal) the dosage of levodopa being given in individual cases bore no relationship to the degree of deterioration. In group 1, however, patients who noticed no change or showed improvement on withdrawal were taking an average dose of 3.1 g compared with 2.2 g in those patients who resumed anticholinergic drugs because of deterioration. This finding is supported by a significant association between the dosage of levodopa and the degree and direction of clinical change at the eight-week stage of slow withdrawal. The scores of the four main clinical features were combined and changes at eight weeks were plotted against

FIG. 1—Group 1. Change in the combined scores of four clinical features, from prewithdrawal of anticholinergic drugs to the 8th week, related to dosage of levodopa ($r = -0.634$, $P < 0.05$).

FIG. 2—Group 1. Change in the combined scores of four timed tests, from prewithdrawal of anticholinergic drugs to the 8th week, related to dosage of levodopa ($r = -0.875$, $P < 0.01$).

the dosage of levodopa (r with 9 D.F. = -0.634 $P < 0.05$) (Fig. 1). When changes in the combined timed tests at the

eight-week stage were plotted against levodopa dosage (Fig. 2) the association was significant at the 1% level. These results suggest that patients tolerating lower doses of levodopa may benefit even more than those receiving a higher dosage from the addition of anticholinergic drugs.

Previous stereotaxic surgery, either bilateral or unilateral, did not appear to influence the need to restore anticholinergic therapy, nor did the duration of the Parkinsonian syndrome.

Discussion

The fact that anticholinergic drugs could be withdrawn in only 11 of the 34 patients on stable levodopa therapy and the spectrum of symptoms which emerged during withdrawal suggest that there is a synergism between levodopa and anticholinergic drugs and that some features of Parkinsonism, especially hypersalivation, respond equally well or even preferentially to anticholinergic drugs. The increased slowness noted by 20 patients after withdrawal is surprising, since it is bradykinesia and akinesia that respond best to levodopa. However, gross deterioration in this feature was noted by only four patients. We were able to verify this clinically in one patient whose writing also showed a pronounced deterioration (Fig. 3). The other three

FIG. 3—Handwriting—effect of anticholinergic withdrawal: (a) Anticholinergic drugs alone. (b) Levodopa and anticholinergic drugs (constant dose for one year). (c) One week after anticholinergic drug withdrawal (levodopa continued). (d) One week after (c)—anticholinergic drugs reintroduced.

had recommenced anticholinergic therapy, because of gross deterioration, before they could be reassessed. The fact that only three patients were able to tolerate withdrawal beyond the eight-week stage in group 2 compared with eight in group 1 suggests that rapid withdrawal was a factor in determining these numbers, particularly since the four patients who exhibited gross deterioration on withdrawal were all in group 2. Nevertheless, even in group 1 nine patients had to return to anticholinergic therapy (which in one patient had consisted of only 2 mg of benzhexol a day) at or before the end of the trial and a further three have recommenced such treatment since the termination of the trial.

Information in the literature regarding the combined use of levodopa and anticholinergic drugs is relatively sparse, though a number of authors have commented that anticholinergic drugs were not discontinued when levodopa therapy was initiated. A possible reason why levodopa and anticholinergic drugs act synergistically is that the dopamine formed from levodopa may be inactivated by the neuronal membrane uptake system which in turn is inhibited by anticholinergic drugs as suggested by Coyle and Synder (1969). The prevention of dopamine inactivation by anticholinergic drugs gains some support from the following clinical observations noted on withdrawal of such treatment: (1) the complaints of increased slowness in 59% of patients and of increased tremor in 44%, (2) an apparent reduction in the duration of the effect of individual doses of levodopa in three patients, and (3) decrease in levodopa-induced involuntary movements in five patients. All of these effects were reversed by the resumption of anticholinergic drugs.

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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