Papers and Originals

Burkitt's Tumour in the West Nile District of Uganda 1961-5

M. C. PIKE,* PH.D. ; E. H. WILLIAMS,† M.B., B.S. ; BARBARA WRIGHT‡

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African malignant lymphoma (Burkitt's tumour) has been shown to have an irregular distribution within Africa as a whole (Burkitt, 1962), and also within Uganda (Burkitt and Wright, 1966). These broad patterns have led to a number of aetiological hypotheses, the best-known one—and, at the moment, still the most plausible one—being that the tumour is induced by a mosquito-borne virus.

Within Uganda the area with the highest apparent incidence is the West Nile District,¹ though it is impossible to be sure of rates in a country with, as yet, very scattered medical facilities, and where the influence of traditional medical practice remains strong though on the wane. Different biopsy rates in the outlying hospitals and frequent changes of staff add a possibly large error to the figures. Also, Mr. Burkitt made frequent tours to different parts of Uganda (to the end of 1965) looking for cases of African malignant lymphoma, and the influence of these tours on the reporting of cases from different areas may have been considerable.

A more detailed study of the cases in a much smaller area, such as the West Nile District, might permit of a narrower and more testable hypothesis concerning the aetiology of the disease—for example, implicating a particular species of mosquito—or it might suggest a completely new hypothesis.

The oft-mentioned theory that the disease is virus-induced suggested to us that we should in particular look to see whether on a more detailed scrutiny of the cases in the West Nile District it would be possible to show evidence of "contagion" or "infection."

This paper reports on all the known—that is, microscopically proved—and suspected cases of Burkitt's tumour in the West Nile District with date first seen at hospital or date of onset of symptoms in the five-year period from 1 January 1961 to 31 December 1965. The study period was started in January 1961, as it was about this time that the disease became well known in Uganda, and we could legitimately hope that very few cases reaching hospital would be misdiagnosed from this date. The end of 1965 was chosen as the closing date for cases to enable us to include cases presenting up to nine months after the onset of symptoms (the calculations in this paper were begun in October 1966).

Data

Fig. 1 shows the county boundaries and hospitals of the West Nile District of Uganda.

There are three hospitals actually within the district: Angal Mission Hospital, Arua Government Hospital, and Kuluva

* Medical Research Council's Statistical Research Unit, University College Hospital Medical School, London W.C.1, on secondment to Department of Pathology, Makerere Medical School, P.O. Box 2072, Kampala, Uganda.

† Kuluva Hospital, P.O. Box 28, Arua, Uganda.

‡ Kampala Cancer Registry, Makerere Medical School, P.O. Box 2072, Kampala, Uganda.

¹ In the extreme north-west of Uganda; bordered by the Sudan in the north, by the Congo on the west and south, and by the Nile on the east.

Mission Hospital. Moyo Government Hospital at easting/northing 357/404 (see Fig. 1) is also fairly accessible from the area, but no African malignant lymphoma cases from the West Nile District have been reported from this hospital.

Communications within West Nile District are quite good, and all roads lead to the capital, Arua. There are eight district bus routes, all operating daily both ways and spread roughly evenly over the entire area.

There were 51 known and suspected cases of Burkitt's tumour with date first seen or date of onset of symptoms in the five-year period 1961-5.² The data on these cases are rather incomplete. Twelve of the cases are *not* microscopically proved, and there are certainly legitimate grounds for disagreement about the validity of the diagnosis in at least some of them. For four of the cases we have managed only to fix on the year of their first attendance at hospital (one in 1961, three in 1962); the records at Arua Hospital are unfortunately not obtainable for any year before 1965. These four patients all lived in the same village of Aliba (subcounty Aroi; county Ayivu); one other patient also lived in this village, and presented to Arua Hospital on 11 June 1962 with a three-weeks history. These five cases make up the "Aliba outbreak" (Goma, 1965). We do not know the addresses of 10 of the cases.

Fig. 2 shows the onset distribution of these cases in time and in space.

Analysis of "Contagion"

The occurrence of all human cancers—with the possible exception of acute leukaemia in children—is thought, in "normal" circumstances, to be random in the sense that *where* the disease occurs and *when* it occurs are independent of one another. This would not hold if a strong carcinogen—for example, a mobile x-ray unit with very faulty equipment—was introduced into a small area for a short time; but this can hardly be regarded as a normal circumstance.

The randomness does not hold, for example, for measles or chicken-pox or mumps; in these diseases cases tend to occur in time-space "clusters." That is, cases which occur close together in time tend also to occur closer together in space than one would expect on a purely random distribution of the places of onset *vis-à-vis* the times of onset. In the case of measles, for example, the disease might move through one school then on to a neighbouring one, possibly returning to the first area after the reappearance of nonimmune children.

In well-known common infectious diseases the occurrence of these time-space clusters is so striking that no statistical analysis is needed for their nonrandom nature to be firmly established. In rare diseases the proof of the excess of clustering

² A table exists giving for each patient: hospital of presentation, whether microscopically proved, date first seen, date and place of onset of symptoms, age, sex, and ethnic group. It can be obtained from the M.R.C. Statistical Research Unit, 115 Gower Street, London W.C.1. This table also gives the basis for inclusion of the clinically diagnosed cases.

requires more elaborate methods. *It is not sufficient simply to observe an "anomalous" clustering situation—such as two cases living next door to one another getting the disease within a week of each other—it is necessary to test whether such anomalous clusters happen more often than one should expect purely by chance.*

This testing is done in the standard statistical manner—the distribution of a "measure of clustering" is worked out on the basis of the random allocation of places of onset to times of onset, and the observed value of the measure of clustering is then compared with this distribution. The only difference between the various tests so far proposed is in their definition of measure of clustering. We have applied two methods.

Statistical Methods

The first (Knox, 1963, 1964) considers each possible pair of patients and counts the number of pairs whose onset dates were within some specified time of one another (say, T days), and whose places of onset were within some specified distance of one another (say, D kilometres); the choice of T and D is discussed below. The test is then whether the number of cluster-pairs observed is greater than one should expect on the basis of chance alone.

The second (David and Barton, 1966) first divides the cases into different groups on a time-clustering basis only, and then tests whether the spatial variation within these groups, compared with the overall spatial variation of the cases, is less than may be attributed solely to chance. The time-only clusters are defined as consisting of a chain of cases, all but the last of which are followed by another occurring within a specified time interval (say, A days); the choice of A is discussed below.

More formally stated, these methods suppose that there are N cases of the disease with dates of onset— $t_1, t_2, \dots, t_i, \dots, t_N$ —in increasing date order, and with respective places of onset measured in kilometres eastings and northings— $(x_1, y_1), (x_2, y_2), \dots, (x_N, y_N)$. The number of cluster-pairs in the Knox test is then obtained as follows: consider each possible pair of patients—patient i and patient j ; $i=1, 2, \dots, (N-1)$ and

$j=i+1, i+2, \dots, N$ —and count the number of them such that both $(t_j - t_i) < T$ and $(x_j - x_i)^2 + (y_j - y_i)^2 < D^2$. While the time-only cluster groups of the David and Barton test are obtained as follows: the first group consists of patient 1 (with date of onset t_1) plus patient 2 if $(t_2 - t_1) < A$, plus patient 3 if $(t_3 - t_2) < A$, and so on to patient i , the first for whom $(t_{i+1} - t_i) \geq A$; then the first group consists of patients 1, 2, $\dots, i$. The second group starts with patient $(i+1)$ and is formed in exactly the same manner as the first group. This process is continued until all the N cases have been assigned to groups—we suppose that there are n groups in all, where the value of n depends, of course, on A .

These methods are independent of the population structure of the area under study so long as it is only changing proportionally, and in this respect they would appear to be peculiarly well adapted to the problem we are dealing with here. We note also that the methods are not dependent on all cases being reported except in so far as the cases missed should not invalidate the basic assumption of unchanging (or proportionally changing) effective population structure. The effective population comprises, of course, those people who would use the hospitals. Missing cases can then only reduce the chances of detecting any epidemic characteristics.

Results

Tables I and II give the results of applying these two tests to the 36 cases with known dates of onset 1961–5 and known addresses. We have done the calculations in four ways with each method by considering all cases or only microscopically proved cases, and all cases or only the cases presenting at Arua Hospital or Kuluva Hospital. This latter split was thought necessary owing to the fact that Angal Hospital is known to send some biopsy material to elsewhere than Makerere Medical School and it may be that we have a biased sample of cases from them.

Table II shows the general picture most clearly. Over a wide choice of time-only cluster divisions the David and Barton test gives very significant results. With the choice of A =average time interval between cases, which David and Barton suggested

FIG. 1.—Counties (with reference numbers) and hospitals of West Nile District. FIG. 2: All known and suspected cases of Burkitt's lymphoma, with known addresses in West Nile District and with dates of onset between 1 January 1961 and 31 December 1965. A tail attached to the symbols signifies a non-microscopically proved case. FIG. 3: All known and suspected cases of Burkitt's lymphoma in West Nile District, with dates of onset between 1 January 1966 and 31 September 1966.

should be used if there was no strong theoretical reason for using any other,³ the probability of obtaining such extreme results (or even more extreme ones) by chance alone is less than 1% for all four categories of cases (maximum probability = 0.008 for category ii cases).

TABLE I.—“Significance” Levels* of Observed Time-Space Clustering Obtained with Knox's Method. Cases with Known Addresses and Dates of Onset. The Number of Cluster-pairs is Given in Parentheses

T = Critical Time Apart in Days	D = Critical Distance Apart in Kilometres				
	2	5	10	20	40
Cases Category i. All 36 cases—630 pairs					
30	0.140 (1)	0.033 (3)	0.015 (5)	0.6 × 10 ⁻³ (10)	0.004 (15)
60	0.036 (2)	0.048 (4)	0.023 (7)	0.7 × 10 ⁻³ (15)	0.6 × 10 ⁻⁴ (30)
90	0.081 (2)	0.068 (5)	0.036 (9)	0.020 (18)	0.8 × 10 ⁻³ (43)
120	0.027 (3)	0.076 (6)	0.019 (12)	0.004 (25)	0.6 × 10 ⁻⁶ (61)
180	0.065 (3)	0.132 (7)	0.007 (15)	0.002 (35)	0.8 × 10 ⁻⁸ (88)
360	0.274 (3)	0.394 (9)	0.068 (22)	0.002 (61)	0.1 × 10 ⁻⁸ (147)
Cases Category ii. 32 cases from Arua Hospital and Kuluva Hospital only—496 pairs					
30	0.128 (1)	0.029 (3)	0.010 (5)	0.004 (10)	0.017 (13)
60	0.196 (1)	0.087 (3)	0.054 (5)	0.014 (12)	0.009 (20)
90	0.304 (1)	0.249 (3)	0.124 (6)	0.087 (13)	0.031 (30)
120	0.090 (2)	0.216 (4)	0.046 (9)	0.010 (20)	0.8 × 10 ⁻⁸ (45)
180	0.159 (2)	0.250 (5)	0.036 (12)	0.004 (28)	0.1 × 10 ⁻⁴ (67)
360	0.412 (2)	0.444 (7)	0.043 (18)	0.004 (49)	0.9 × 10 ⁻⁴ (118)
Cases Category iii. 26 microscopically proved cases—325 pairs					
30	1.000 (0)	0.265 (1)	0.031 (3)	0.017 (6)	0.011 (8)
60	0.129 (1)	0.079 (2)	0.020 (4)	0.004 (9)	0.6 × 10 ⁻³ (13)
90	0.176 (1)	0.137 (2)	0.056 (4)	0.028 (9)	0.4 × 10 ⁻³ (17)
120	0.283 (1)	0.308 (2)	0.101 (5)	0.001 (14)	0.1 × 10 ⁻⁵ (29)
180	0.370 (1)	0.201 (3)	0.057 (7)	0.2 × 10 ⁻⁸ (19)	0.3 × 10 ⁻⁷ (39)
360	0.641 (1)	0.445 (4)	0.053 (11)	0.3 × 10 ⁻⁸ (34)	0.002 (65)
Cases Category iv. 24 microscopically proved cases from Arua Hospital and Kuluva Hospital only—276 pairs					
30	1.000 (0)	0.278 (1)	0.042 (3)	0.031 (6)	0.021 (8)
60	1.000 (0)	0.346 (1)	0.078 (3)	0.012 (8)	0.007 (11)
90	1.000 (0)	0.444 (1)	0.159 (3)	0.062 (8)	0.010 (14)
120	1.000 (0)	0.624 (1)	0.197 (4)	0.003 (13)	0.2 × 10 ⁻³ (24)
180	1.000 (0)	0.398 (2)	0.105 (6)	0.5 × 10 ⁻³ (18)	0.8 × 10 ⁻⁸ (34)
360	1.000 (0)	0.570 (3)	0.069 (10)	0.2 × 10 ⁻³ (33)	0.001 (60)

* Based on a Poisson approximation (which is very conservative) or on a normal approximation (when the standard deviation of the number of cluster-pairs was less than one-third of its expectation).

TABLE II.—“Significance” Levels* of Observed Time-Space Clustering Obtained with David and Barton's Method. Cases with Known Addresses and Dates of Onset. The Number of Time-only Groups is Given in Parentheses

A = Critical Time Apart in Days	Cases Category†			
	i	ii	iii	iv
10	0.071 (28)	0.179 (25)	0.249 (22)	0.369 (20)
30	0.5 × 10 ⁻³ (20)	0.002 (17)	0.9 × 10 ⁻³ (16)	0.005 (14)
50	0.9 × 10 ⁻⁴ (15) ‡	0.001 (15)	0.2 × 10 ⁻³ (15)	0.005 (14)
56	0.5 × 10 ⁻⁴ (13)	0.008 (14) ‡	0.1 × 10 ⁻³ (14)	0.005 (14)
68	0.1 × 10 ⁻⁴ (11)	0.003 (12)	0.1 × 10 ⁻³ (14) ‡	0.005 (14)
74	0.1 × 10 ⁻⁵ (9)	0.6 × 10 ⁻³ (10)	0.1 × 10 ⁻³ (14)	0.005 (14) ‡
90	0.7 × 10 ⁻⁴ (7)	0.1 × 10 ⁻³ (7)	0.1 × 10 ⁻³ (11)	0.005 (11)
120	0.005 (4)	0.7 × 10 ⁻⁵ (5)	0.053 (5)	0.3 × 10 ⁻⁴ (6)
160	0.001 (3)	0.1 × 10 ⁻⁵ (4)	0.017 (3)	0.8 × 10 ⁻⁴ (4)
200	0.146 (2)	0.066 (2)	0.226 (2)	0.057 (2)

* With the beta function approximation given by David and Barton (1966).

† Cases Category: i = all 36 cases; ii = the 32 cases from Arua Hospital and Kuluva Hospital only; iii = the 26 microscopically proved cases; iv = the 24 microscopically proved cases from Arua Hospital and Kuluva Hospital only.

‡ Selected by David and Barton (1966).

Table I shows that over a wide range of critical distance apart and critical time apart the Knox test also gives very significant results. No *a priori* reasons can be given for choosing any particular values for T and D, and it would appear most sensible to regard this Table mainly as a basis for choosing combinations of T and D to be used with the further data that are now being collected. From Table I it would appear that clusters of cases are most marked within 180 days and 40 kilometres of each other (though longer distances were not tested and might be preferable), and within these limits the chance probability of obtaining 67 (or more) cluster-pairs of category ii cases is 0.00001.

We think it is more than fair to conclude from these Tables that there is strong evidence of epidemic characteristics in

* It is clearly impermissible simply to vary A until a very significant result is obtained (if ever) and then to regard this as the significance level of the test.

Burkitt's tumour cases in the West Nile District of Uganda. If we had been able to include the four Aliba outbreak patients with unsatisfactory onset-date information, the evidence would have been much stronger.

Before accepting this evidence at face value we need to try to exclude explanations of it which suggest that the results are simply an expression of major effective population changes in the area or are due to other similar artifacts. One ingenious explanation offered to us was that the early cases in County 5 did not really live there at all, but simply gave as their addresses the addresses of relatives living close to the hospitals of Arua and Kuluva. Fortunately, we know this to be false at least for five of the early patients, the Aliba outbreak cases, as their homes were in fact visited.

A major relative increase in the actual populations of Counties 2 and 4 has not apparently occurred, though we will need to await the 1969 census to be sure.

Modern medicine is probably accepted to a different extent in different parts of the area, and it may be that between 1961 and 1965 a bigger change-over from traditional medicine was made in the north-eastern counties, so changing the effective population structure of the district. We made some estimate of any differential changes by tabulating the addresses of patients coming to Kuluva Hospital in the two years 1961 and 1965 (Table III). Table III shows that some, possibly all, of the shift in cases to County 4 could be due to an increased effective population there. The shift to County 2 and the shift from County 5 are not explained. These apparently different effective population shifts may, however, themselves be artifacts; it is quite possible that for some reason Kuluva Hospital gained popularity *vis-à-vis* Arua Hospital in County 4 while the reverse occurred in County 2. To find out about this does not seem possible, but it is relevant that the number of patients attending the Government dispensaries in County 4 increased by only about 11% from 1961 to 1965. We are inclined to the view that the effective population structure increased over the period in an approximately proportional manner.

TABLE III.—Children Coming to Kuluva Mission Hospital by County and Year

County	Patients under 12 Years		Ratios of Numbers of Patients under 12 Years 1965/1961
	1961	1965	
1	18	31	1.7
2	15	18	1.2
3	38	76	2.0
4	19	91	4.8
5	166	263	1.6
6	676	893	1.3
7	50	145	2.9
8	25	43	1.7
9	19	58	3.1

This is substantiated to a large extent by the data presented in Fig. 3, which shows the places of onset of the first 11 known patients with onset of Burkitt's tumour in 1966.⁴ We see that patients with Burkitt's tumour are again appearing in the area just north of Arua, and that the disease is now “drifting” back in the south-west direction.

Further Analysis

A purely time and a purely space analysis of these cases is given in Tables IV and V.

Table IV shows that over the five-year period 1961–5 Counties 2, 4, and 5 had the highest rates of Burkitt's lymphoma, while Counties 1 and 8 had the lowest.

The differences are not related to population density, nor to the intensity of malaria in the different areas—though this

* A table giving for each of these patients the same information as for the 1961–5 patients can also be obtained from the M.R.C. Statistical Research Unit.

is known only very roughly.⁵ The low rate in County 8 may possibly be explained by the fact that the local hospital does not inform us so fully of suspected cases, and also sends some biopsies elsewhere than Makerere Medical School, and by the fact that about one-third of the county is at the level of over 5,000 feet (1,524 m.)—a well-established barrier to the disease. We can think of no reason why the rate should be so low in County 1.

TABLE IV.—Burkitt's Tumour by County with Onset 1961–5

County	1959 Population under 16		Density/ Sq. Mile	Burkitt's Tumour Cases		Annual Incidence Rate per 100,000
	No.	%		No.	%	
1	11,444	6.0	38	1	2.5	1.7
2	21,110	11.0	23	7	17.5	6.6
3	24,362	12.7	137	4	10.0	3.3
4	21,282	11.1	48	8	20.0	7.5
5	26,926	14.1	165	9	22.5	6.7
6	13,136	6.9	43	2	5.0	3.0
7	13,124	6.9	18	3	7.5	4.6
8	47,416	24.8	62	4	10.0	1.7
9	12,435	6.5	37	2	5.0	3.2
Total	191,235	100.0		40	100.0	4.2

TABLE V.—Dates of Onset and Presentation by Month and Year

Month	Onset						Presentation					
	1961	62	63	64	65	Total	61	62	63	64	65	Total
Jan.			1	1		2		1		1	2	4
Feb.	1		1	1		3			1			3
March				1	2	3			1	2		3
April	1	1	1			3			2			2
May	2	1	2	1		6		1	2		1	4
June		1	1	1	2	4		1	2	1	1	8
July	1		1	1		4	3			1	2	5
August		1	1	2	2	6	1	1	1	1	1	5
Sept.		2		1	2	5		2	1	3		9
Oct.			2	1		3		1		1		2
Nov.	1			1		2			1	1		2
Dec.	1		1	2	1	5	1			1		2
Total	7*	7†	10	13	9	46	7*	7†	9	13	10	46

* +1 with month unknown.

† +3 with month unknown.

Table V gives the dates of onset and dates first seen by month and year. There is no clear trend over the five-year period. There is a slight excess of cases during the rainy season (which is also the coolest part of the year) from April to October inclusive; it does not approach statistical significance for dates of onset, but is significant at the 5% level for dates of presentation. These findings are difficult to interpret.

Table VI shows the age distribution of the cases from the "low"- and "high"-rate areas. The patients from the low-rate areas are, if anything, younger than those from the high-rate areas, and more of them present with jaw lesions. Why this should be so remains to be elucidated.

TABLE VI.—Age Distribution of Patients by Sex and County. Numbers of Patients (Numbers with Jaw Involvement in Parentheses)

Age in Years	'Low' Incidence Counties 1, 3, 6, 7, 8, 9			'High' Incidence Counties 2, 4, 5		
	Males	Females	Total	Males	Females	Total
2					1 (0)	1 (0)
3						
4	1 (1)		1 (1)	1 (1)	2 (0)	3 (1)
5	2 (2)	1 (1)	3 (3)	4 (1)		4 (1)
6	4 (2)	2 (2)	6 (4)	3 (2)		3 (2)
7		1 (1)	1 (1)	2 (2)		2 (2)
8	2 (1)		2 (1)		3 (1)	3 (1)
9		1 (1)	1 (1)	2 (1)		2 (1)
10					2 (1)	2 (1)
11					2 (1)	2 (1)
12		1 (0)	1 (0)		1 (0)	1 (0)
22		1 (1)	1 (1)			
25					1 (0)	1 (0)
Total	9 (6)	7 (6)	16 (12)	12 (7)	12 (3)	24 (10)

* The recent establishment of a research station in the West Nile District by the East African Virus Research Institute will in time provide the vitally important accurate information on the ecology of this district.

Discussion

A close look has been taken of the microscopically proved and suspected cases of Burkitt's lymphoma in the West Nile District of Uganda. Evidence has been provided which appears to show that Burkitt's lymphoma displays the epidemic characteristic of "drift." This is of sufficient interest to warrant a major effort being made to collect complete data for the area so that this phenomenon may be established beyond doubt.

The Kampala Cancer Registry now makes a sustained attempt to record for all cancer cases the date of first attendance at hospital and length of history at that date and address at time of onset, plus, of course, all the usual information. We hope that by making regular calls on the hospitals in the district the interest of the clinicians will be maintained, and that it will be possible to encourage them to take biopsies whenever ethically justifiable and to have a uniform reporting of non-biopsied cases.

Reo 3, herpes simplex, and herpes-like viruses have been isolated from Burkitt tumour tissue (Woodall and Haddow, 1962; Simons and Ross, 1963; Epstein *et al.*, 1964; Bell *et al.*, 1964), but their importance in the aetiology of the disease is not established. One line of approach to furthering our understanding of these relationships is to do viral antibody studies—to compare areas of "high" incidence to areas of "low" incidence. One might, for example, compare West Nile District to Kigezi District—the area in south-west Uganda where only one case has ever been reported. This study has shown that sampling the population of any one area has to be done with care to avoid local "low" spots, whether these are of short or long duration. It has also shown that valuable information may be gained from intradistrict studies if the quality of the recording of cases in the district is sufficiently uniform to warrant comparisons between small areas. An intradistrict study of the area around Kampala is now in progress.

It is important to draw attention to the fact that the epidemiological evidence brought out here and in previous publications does not necessarily imply the existence of any vector of the disease or, in particular, of a geographically restricted vector. There might equally well be a reservoir of virus with the nature of the reservoir restricting the disease within certain geographical limits. It is relevant to this that Reoviruses have been shown to be antigenically similar to clover wound-tumour virus (Streissle and Maramorosch, 1963), so that if such a reservoir exists it may well be a plant reservoir.

Summary

By studying the distribution in space and in time of all microscopically proved and suspected cases of African malignant lymphoma (Burkitt's tumour) occurring in the West Nile District of Uganda during the five years 1961–5 it has been possible to show that the disease possesses the epidemic characteristic of "drift"—patients whose dates of onset were close together tended to live closer together than could be expected on the basis of chance alone. If this phenomenon can be substantiated by the data from other districts this will provide very strong further evidence for the existence of an infective agent for the disease. Attention is also drawn to the possible existence of "low" and "high" intensity areas within the district.

This study was made possible by the existence of the B.E.C.C.-financed Kampala Cancer Registry and by Mr. D. Burkitt's list of lymphoma cases in Uganda. Special acknowledgement is due to the many pathologists in Professor M. S. R. Hutt's Department, Makerere Medical School, and in particular to Dr. D. H. Wright, for doing the histology of the cases discussed here. We would like to thank Dr. R. Morrow, Dr. D. Bradley, and Mr. A. W. R. McCrae

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Bronchodilator Response Patterns in Patients with Chronic Airways Obstruction: Use of Peak Inspiratory Flow Rate

K. B. SAUNDERS,* M.A., M.D., M.R.C.P.

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In pulmonary disease with airways obstruction the effect of bronchodilator therapy is commonly assessed by simple measurements of ventilatory function, most of which require a maximal expiratory effort by the patient.

During expiration in the normal subject the airways tend to become narrower with increasing transpulmonary pressure: during inspiration they tend to widen (Fry and Hyatt, 1960). In diffuse airways obstruction there may be gross narrowing or collapse of airways on expiration (Dayman, 1951). Macklem *et al.* (1965) point out that in some patients the effect of bronchodilator drugs might not be detected by tests involving maximal expiratory effort, since collapse of large central airways might mask the effect of relief of spasm in small peripheral bronchi.

An attempt is made here to compare response to a bronchodilator drug by means of both peak expiratory flow (P.E.F.R.) and peak inspiratory flow rate (P.I.F.R.), and to correlate changes in these variables with changes in forced expiratory volume in one second (F.E.V.₁) and forced vital capacity (F.V.C.). The response patterns in patients with and without radiological evidence of emphysema are compared.

Subjects

Thirty patients with chronic diffuse airways obstruction were studied. All complained of shortness of breath and 26 had chronic cough with sputum. All had values for F.E.V.₁/F.V.C. of less than 70%; all but two had a P.E.F.R. of less than 300 l./min. All were receiving some form of bronchodilator therapy, which was omitted on the day of lung-function tests.

Methods

Measurement of Peak Flow Rates.—P.E.F.R. and P.I.F.R. were measured with a Wright peak flow meter (Wright and McKerrow, 1959), adapted, as suggested by Nairn and McNeill (1963), by fitting a backpiece with central orifice to take the usual mouthpiece. It was calibrated against steady flows from a glass rotameter (Rotameter Manufacturing Co. Ltd.) over a range of 60–350 l./min. This was done in two ways. (1) By blowing air through the meter (as for recording P.E.F.R.)

(a) with the backpiece on, and (b) with the backpiece removed. There was no significant difference between the calibration curves thus produced (Fig. 1). (2) By sucking air through the meter via a connexion on to the backpiece (as for recording P.I.F.R.). For this calibration the readings obtained on the Wright flow meter were consistently slightly higher for a given rotameter reading than those recorded in the previous two calibrations (Fig. 1). The difference was constant throughout the whole range, and was between 5 and 10 l./min. A value of 5 l./min. was therefore subtracted from all P.I.F.R. measurements. The meter was also checked against the master instrument used for calibration by the manufacturers.

Fig. 1.—Calibration of adapted Wright peak flow meter. ● Air blown through flow meter; back piece on. × Air blown through flow meter; back piece off. ○ Air sucked through flow meter via connexion to backpiece.

Spirometry.—F.E.V.₁ and F.V.C. were measured with a dry spirometer (Collins *et al.*, 1964).

Procedure.—Each patient practised the three manoeuvres until familiar with them. Three readings of F.E.V.₁ and F.V.C. were then made, followed by five readings of P.E.F.R. and five of P.I.F.R. Some patients recorded P.E.F.R. before P.I.F.R. and some in the reverse order, the choice of order being randomized. A period of one minute was allowed between each recording of F.E.V.₁ and F.V.C., and a period of 30 seconds between each recording of P.E.F.R. or P.I.F.R. The means of the two highest readings of F.E.V.₁ and F.V.C. and of the

* Lecturer, Department of Medicine, St. Thomas's Hospital, London S.E.1.