Women younger than 55 in the study group had a 29% higher mortality from breast cancer. This higher mortality among younger women was also observed in the two county study.[7] Although this could be a random phenomenon, negative results of a screening examination may have falsely reassured some patients and caused a deleterious delay in diagnosis. Delayed diagnosis may be more dangerous with rapidly growing tumours than with the more slowly growing tumours.

A proportional hazards analysis of patient survival with breast cancer, stratified for stage and adjusted for age at diagnosis, gave a relative risk of 2·3 (p=0·001) for patients whose cancer was detected in the intervals between screenings compared with patients in the control group. This confirms that carcinomas detected in the intervals between screening were more malignant, stage for stage, than those occurring in the control group. It also confirms preliminary results of this study[16] but is at variance with results from the two county study reported by Holmberg *et al.*[17]

Differences in treatment were also considered as a possible explanation for the differential mortality from breast cancer in the beginning of the programme. A study of the chemotherapy and hormonal and x ray treatment of all patients who died during the first six years of the programme showed only minor differences between the study and control groups. There is no reason to believe that induction of cancer through irradiation would be the explanation.[18]

From a public health perspective mammographic screening remains controversial.[19,20] The different outcomes in results of breast cancer screening programmes show that it is difficult to use the results from one study to calculate the expected benefit in another population. The results of our study cannot be used to advocate introduction of mammographic screening in all ages in an urban population. Although firm conclusions cannot be drawn from analyses of subgroups in this study, our data support previous studies showing that invitation to mammographic screening for breast cancer may lead to reduced mortality from breast cancer, at least in women aged 55 and over.

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The course of untreated epilepsy

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Abstract

As little is known about the course of untreated epilepsy the time intervals between untreated tonic-clonic seizures were examined retrospectively in a series of 183 patients presenting to a neurological department having had two to five seizures. After the first seizure a second attack had occurred within one month in 56 patients, within three months in 93, and within one year in 159. The median interval between the first two seizures was 12 weeks (95% confidence interval 10 to 18 weeks), between the second and third eight weeks (four to 12 weeks), between the third and fourth four weeks (two to 20 weeks), and between the fourth and fifth three weeks (one to four weeks). When patients who had had three, four, or five untreated seizures were considered separately a similar pattern of decreasing intervals was seen. Successive intervals between seizures could be compared in 82 patients. In 48 the interval decreased, in 16 it did not change, and in 18 it increased.

These results suggest that in many patients there is an accelerating disease process in the early stages of epilepsy.

Introduction

The prognosis for controlling seizures in epileptic patients has until recently been thought to be generally unsatisfactory. In a comprehensive review Rodin reported that no more than one third of epileptic patients achieve a remission of two years, and he regarded the disorder as chronic in about 80% of patients.[1] This view was based mostly on studies of patients attending hospital clinics and institutions, where patients with chronic epilepsy tend to accumulate. Recent community and hospital based studies of patients with newly diagnosed epilepsy have shown a much more favourable prognosis. In two retrospective community studies about 70% of all patients were found to achieve a four or five year remission.[2,3] In a

prospective study we followed up 106 patients with newly diagnosed epilepsy; at eight years 92% had achieved a remission of one year and 82% a remission of two years.[4] Similar good rates of response to treatment were reported in studies of patients with newly diagnosed epilepsy followed up for up to two years.[5,6]

A factor missing from all these studies was an understanding of the course of untreated epilepsy. If the response to treatment with anticonvulsants in patients with newly diagnosed epilepsy is so good the question arises, how much better is it than no treatment? For ethical reasons no one has ever conducted a study to examine this, and apart from some observations by Gowers[7] the course of untreated epilepsy has not been studied. In a limited study of the course of tonic-clonic seizures we examined retrospectively the pattern of occurrence of seizures in untreated patients newly referred to a neurological clinic.

Patients and methods

From 1981 all new referrals to the neurology outpatient department at King's College Hospital with previously untreated epilepsy were considered for inclusion into prospective trials of monotherapy.[4,8] Each patient had had at least two tonic-clonic or partial seizures, or both. Those whose seizures were caused by drugs, alcohol, fever, or acute metabolic disturbance and those with a progressive neurological disorder at the time of diagnosis were excluded. At the initial assessment the number and, when possible, the dates of seizures were recorded, as well as demographic and clinical details.

A total of 388 patients were referred. One hundred and seven had experienced partial seizures, petit mal, or myoclonic seizures; as these patients had almost invariably had multiple seizures that could not be accurately dated we excluded them from the analysis. Among the remaining 281 patients with tonic-clonic seizures the intervals between seizures could be accurately ascertained in 183, so these patients formed the basis of this study.

TABLE I—*Characteristics of 281 patients with two or more untreated tonic-clonic seizures: comparison of patients in whom intervals between seizures were known and unknown*

	Intervals known (n=183)	Intervals unknown (n=98)	Total (n=281)
No male	99	46	145
No with symptomatic epilepsy	20	16	36
No with neurological handicap	18	12	30
Median (range) age at first seizure (years)	17 (2-65)	23 (1-82)	19 (1-82)
No of seizures before treatment:			
Two	101	7	108
Three	53	16	69
Four	18	18	36
Five or more	11	35	46
Unknown		22	22
Median (range) interval before treatment (months)	6 (1-132)	9 (1-276)	7·5 (1-276)
95% Confidence interval	5 to 8	6 to 19	6 to 9
Median (range) No of seizures/month before treatment	0·5 (0-3)	0·5 (0-10)	0·5 (0-10)
95% Confidence interval	0·3 to 0·6	0·4 to 0·7	0·4 to 0·6

TABLE II—*Interval between first and second tonic-clonic seizures in 183 untreated patients*

Interval	No of patients
≤1 Month	56
-2 Months	19
-3 Months	18
-12 Months	66
-2 Years	14
-3 Years	4
>3 Years	6

TABLE III—*Median (25th to 75th centiles) intervals between seizures (weeks) in 183 untreated patients*

	No of seizures before treatment				
	All patients	2	3	4	5
From 1st to 2nd	12 (4-28)	12 (4-25)	12 (4-44)	22 (4-36)	24 (4-42)
95% Confidence interval	10 to 18	8 to 6	5 to 24	4 to 36	5 to 52
From 2nd to 3rd	8 (4-16)		8 (4-16)	16 (4-40)	4 (4-12)
95% Confidence interval	4 to 12		4 to 12	4 to 40	2 to 20
From 3rd to 4th	4 (2-23)			6 (2-24)	4 (2-20)
95% Confidence interval	2 to 20			2 to 24	1 to 72
From 4th to 5th	3 (2-4)				3 (2-4)
95% Confidence interval	1 to 4				1 to 4

TABLE IV—*Comparison of successive intervals between seizures. Values are numbers of patients*

	From 1st to 2nd v from 2nd to 3rd	From 2nd to 3rd v from 3rd to 4th	From 3rd to 4th v from 4th to 5th
Decreased	48	17	6
The same	16	5	4
Increased	18	7	1
Total	82	29	11

Table I shows the characteristics of the 281 patients presenting with tonic-clonic seizures. Symptomatic epilepsy was defined as epilepsy associated with clinical or radiological (including computed tomographic) evidence of a cerebral lesion, and neurological handicaps as clinical signs of a cerebral lesion or an intelligence quotient less than 70. The characteristics of the patients for whom intervals between seizures were known were similar to those of the patients for whom the intervals were unknown, except for the distribution of the number of seizures and the interval before treatment.

Results

The intervals between successive seizures were studied in the 183 patients who had had at least two tonic-clonic seizures before treatment. Table II gives an analysis of the interval between the first and second seizures. The median interval between successive seizures seemed to decrease with each seizure that occurred (table III). When patients with three, four, or five seizures were considered separately the results were similar to those obtained in all 183 patients, but the 95% confidence intervals were wider.

Eighty two patients had had at least three untreated seizures; in these patients the interval from the first to the second seizure was on average 18 weeks longer than the interval from the second to the third (95% confidence interval five to 31 weeks). We estimated the confidence intervals for the mean and standard deviation of the distribution and differences between successive intervals between seizures using Student's t test with 81 degrees of freedom. In the 29 patients who had had at least four untreated seizures the mean difference between the second interval (between seizures two and three) and the third interval (seizures three and four) was four weeks (95% confidence interval −9 to 17 weeks).

Most of the patients were treated after the second or third seizure (table I). It was possible, however, to compare the interval between any two seizures with that between the subsequent two in 82 patients (table IV). The interval decreased in 48 patients, remained the same in 16, and increased in 18.

Discussion

In this study we examined the course of untreated epilepsy. Because of the methodological limitations dictated by ethical and other considerations the data were collected retrospectively. For this reason in particular we had to study only tonic-clonic seizures—that is, events of sufficient severity and emotional impact that they can be fairly reliably recalled by patients, who usually seek medical help early. We could not study partial seizures, which are often brief and not recalled and occur more often over a longer time. We included partial seizures that were secondarily generalised (that is, tonic-clonic).

The exclusion of 35% of patients, from whom reliable data were not obtained, may have introduced a selection bias. If the excluded patients had a shorter interval between the first two seizures this would

induce a shortening of subsequent intervals between seizures in the analysed data because of regression to the mean.[9] The data were also influenced by the pattern and timing of referral to our neurological clinic as well as by clinical decisions to give antiepileptic treatment. Goodridge and Shorvon showed in our region that about 80% of epileptic patients in the community are referred to specialised hospital services.[3] They included all types of seizures in their study, and the referral rate for the more dramatic tonic-clonic seizures might be expected to be higher. The timing of the referrals may be influenced by many factors, including the reactions of the patient or the patient's family to the disorder and their attitude to investigation and treatment. Since 1981, however, we have operated a policy of seeing urgently all patients referred to us, whether from general practitioners or casualty officers. In accordance with standard clinical practice all the patients were given treatment with anticonvulsants after careful investigation, except for a few who declined treatment or in whom the interval between the only two seizures was more than one year.

With these limitations the picture that emerged from our study agrees in many respects with the observations and views of Gowers.[7] A second seizure occurred within one month after the first in roughly one third of patients (table II); half of the patients had a second seizure within three months, and 87% within one year. In his study of 160 patients Gowers found that one third had a recurrence within one month and two thirds within one year. After a second seizure the intervals between successive seizures tended to decrease (tables III and IV). Thus in many patients referred to a neurological clinic with tonic-clonic seizures an accelerating disease process may occur at least in the early stages. This is in keeping with the view first proposed by Gowers[7] that seizures may beget seizures, that is, that once a major attack has occurred the brain may more readily undergo a further attack. This is not an invariable phenomenon, nor does it go on for ever. Gowers reported that in 680 patients with confirmed epilepsy, most of whom were untreated, the interval between seizures did not exceed one month in 80%. It is therefore of interest that in those few patients in our study who had had more than three seizures the median interval between them was roughly one month. As well as processes of acceleration of epilepsy the brain may generate processes of remission, as is suspected to occur, for example, in benign rolandic epilepsy of childhood and also in petit mal.

There have been conflicting reports about the prognosis for recurrence of seizures after a single first attack. Recurrence rates as low as 27% at three years[10] or 39% at five years[11] contrast with our own previous finding of 71% at three years.[12] The crucial issue that explains much of the variation in these reports is the interval between the time of the first attack and the time of entry into the study, which usually corresponds to the time of the first referral to a hospital clinic. The results of this study agree with the observation of Gowers that a second seizure follows the first within one month in one third of patients who have a minimum of two seizures. If, as has usually been the case, patients do not enter a study of single seizures until several weeks after the first attack many potential candidates for such a study will have been excluded because they will have had a second attack. Hopkins *et al* reported recently that among adults seen eight weeks after a first seizure 22% developed epilepsy, but among those seen within one week the recurrence rate was 52%.[13] In our previous study all 133 patients who had had a single untreated tonic-clonic seizure were identified within a median of one day after the attack.[12] This almost certainly explains the high recurrence rate (71% at three years), which is also in keeping with both the community based observations of Goodridge and Shorvon, who found that 20% of patients had had a single attack,[3] and the view of Gowers that epilepsy is likely to develop in most patients after a first seizure.[7]

The evidence of an accelerating disease process of epilepsy in many patients presenting to a neurological clinic with untreated tonic-clonic seizures contrasts with the remarkably good results of monotherapy in such patients that we and others have reported.[4-6] We have also reported that the longer such seizures continue after the onset of treatment the less likelihood there is that the epilepsy will remit.[4] The questions therefore arise whether earlier effective treatment will improve longer term prognosis, prevent the evolution of chronic epilepsy, and improve the chances of spontaneous remission.[14,15] The patients in this study have been entered into trials of the comparative efficacy and toxicity of different drugs used as monotherapy, which will be reported later.

Our observations confirm the need for more research into the early course and treatment of epilepsy, which is crucial in determining longer term outcome.[14,15] Our conclusions must be tentative because of the retrospective nature of the study and problems of interpreting the findings. A prospective study is required in which the risk of successive tonic-clonic seizures is estimated from multistate models of recurrence of seizures. If patients presenting with one or more tonic-clonic (or other) seizures were randomly assigned to drug treatment or no treatment data could be obtained on the course of untreated epilepsy as well as on the efficacy and longer term impact of early treatment. Although this would raise considerable practical and ethical issues, which would have to be addressed, such studies are of great importance. We hope that our observations will stimulate their execution.

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Correction

Lyme disease with acute purulent meningitis

An authors' error occurred in this paper by Dr S J Bourke and others (13 August, p 460). In the second paragraph of the case report the antibodies to *Borrelia burgdorferi* were of IgG class at a titre of 1/512 and not of IgM class as published.