TRAUMATIC EPILEPSY AFTER CLOSED HEAD INJURY

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The Problems

During and since the Second World War considerable advances have been made in the understanding and management of cases of head injury. Rich though the rewards of this experience have been—and these may be gauged by the multitude of articles published on special aspects of the subject during the past 10 years—the field for further study is still fertile with many problems, and it is the intention in this thesis to record the results of study of a series of 2,000 case histories of closed head injury at the Head Injury Bureau at Oxford.

Closed head injuries with the dura intact or torn only along fracture lines, as in the basal injuries, are more common in civilian than in military practice, and have received less attention in recent years than the more spectacular group of penetrating brain wounds.

It is particularly in regard to traumatic epilepsy that problems still remain. Many questions may be asked to which there is no answer yet or, at the most, an incomplete and variable opinion, depending on the experience of the authors concerned or the selective nature of the cases studied. Why, for instance, when the incidence of epilepsy after a penetrating injury is so high (about 50%), is it so low in the closed injuries (about 3%)? Why, in fact, does epilepsy occur at all after cerebral concussion without an actual brain wound? When it does occur, is it related to the nature and degree of the injury, to genetic or constitutional factors, to previous head injuries, to complicating factors, such as intracranial haemorrhage, skull fracture, cerebrospinal fluid leakage, or aerocele? What is the gradient of the time-lag between trauma and the first fit? Is the duration of post-traumatic amnesia any guide to the likelihood of later epilepsy? Does a persisting cerebral dysrhythmia indicate that the patient may become an epileptic? What are the relative statistics for focal, general, or combined

seizures? Does one type of fit tend to occur early and the other late after trauma? Has cortical dominance any relation to traumatic epilepsy in unilateral injuries? To most of these questions only a variable and indecisive reply may as yet be given.

The Series

A survey of a large series of head injuries admitted for hospital treatment should be embarked upon in the knowledge that any such series is selective in some degree. Special sampling is made inevitable by the nature of the hospital concerned, the type of population served, the policy of admission and management, speed limits and road safety organization, special industrial concentrations, liquor licensing regulations, peace or war, and a multitude of minor variables. The present series, too, has such limitations, but they are of a special kind. The Military Hospital for Head Injuries, Oxford, resulting from the combined energies of Sir Hugh Cairns and Sir Charles Symonds, was established early during the last war and dealt largely in its early years with closed head injuries in military personnel. This study therefore relates to the effects of head injury of the acceleration-deceleration type in a young, healthy, physically fit, predominantly male population.

Two thousand case records were studied and these fell broadly into three sub-groups: those admitted (1) within three days of injury; (2) within three weeks; and (3) at longer periods following trauma. This hospital drew a large number of admissions in the third group as the result of some special complication developing, such as epilepsy, cerebrospinal fluid leakage, or subdural haematoma.

Delay in admission in this group involved the loss of many fatal cases who died elsewhere. Jefferson (1942) has shown that over half of all deaths occur in the first 24 hours, so that the mortality in this series is exceptionally low.

Detailed information of each case was entered on a card system; such a card is seen in Fig. 1. Data were obtained largely from these cards, but in many

* The paper has been prepared from a rough draft made by the late Gilbert Phillips shortly before his untimely death on September 12, 1952. W. R. R.

FIG. 1.—Photograph of the chart used in the present investigation.

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cases it was necessary to refer to the original hospital notes for confirmation or further detail.

Two main series of cases were studied in detail. The first comprised 500 cases admitted in the acute post-traumatic stage, and in these were recorded such factors as retrograde amnesia, post-traumatic amnesia, focal signs, radiographs, E.E.G. findings, personal and family history, cerebrospinal fluid pressure and its protein or blood content; and complications such as epilepsy, intracranial haemorrhage, cerebrospinal fluid leak, aerocele, infection, mental changes, condition on discharge, and at follow-up after rehabilitation. The second consisted of 190 epileptics, being all the cases of post-traumatic epilepsy found in the series of 2,000 closed injuries.

It is believed that the epilepsy incidence in the "500" series is a reasonably accurate measure of traumatic epilepsy in a young, healthy, male population following relatively severe head injury.

The 190 cases of traumatic epilepsy on the other hand, may not be taken as the incidence in 2,000 cases, as many of the late cases were selected for admission for the investigation and treatment of the late epileptic attacks. These 190 cases, however, *qua* epilepsy alone, form a valuable source of information regarding such internal relations as the relative frequencies of focal and general seizures,

the interval at which the first fit occurred, the effect of extended post-traumatic amnesia, the influence of depressed fracture, and other factors.

Modification of the epileptic series by a number of circumstances has been remembered. Early fits may not be observed at the time of the injury or may be missed on the way to hospital or in hospital at night or when the patient is asleep or stuporose. Early fits may be suppressed by sedatives given for other reasons, such, for instance, as for traumatic delirium. Late fits may fail to be recorded when the patient is lost sight of, or dies from the injury or from some other cause before the fit occurs. Both early and late fits may occasionally be wrongly attributed to the head injury when they are cryptogenic in basis or symptomatic of some other disease. Late fits may be suppressed by the continued exhibition of barbiturates or other sedatives for, say, mild mental symptoms or insomnia. It is probable, therefore, that the observed epileptic incidence frequency is lower than the real value, but the cases missed or suppressed represent an overall loss and do not throw the series out of balance.

In addition to these two main series, two smaller groups were also studied in some detail to bring out special features which, as the work progressed, appeared to be relevant to the general problem of traumatic epilepsy. A group of 38 depressed

fractures was examined to determine the effect of possible local cortical trauma. This seemed desirable, as the number of epileptics who show focal signs after closed head injury is too small to provide more than an impression of the effect of local brain damage on the development of seizures. A second group of 40 cases with a post-traumatic amnesia of over seven days was selected to examine the possibility that the trauma-seizure time-lag might tend to be longer in such a group.

In general it should be noted that a very high standard of documentation is available for study in the card system of the Oxford Head Injury Bureau, which provides a rich and readily accessible source of reliable information and will no doubt supply a fund of material for future workers on problems related to head injury. Some little time is necessary, however, before all the information that the system may offer can be grasped and also in acquiring facility in interpretation. Inevitably, some facts are missing, and the original histories must be consulted. In a few cases interpretation is difficult through omissions and occasional inaccuracies or conflicting notes or opinions. Occasionally one must reject a case entirely for one of these reasons.

The Incidence of Epilepsy

Epilepsy is uncommon after closed head injury. Wagstaffe gave a figure of 2% for its incidence and later authors' reports vary from 1 to 10%. This wide range derives from the special nature of the population and the variables noted above. In no instance yet has the influence of particular circumstances, such as length of post-traumatic amnesia, depressed fracture, or complicating factors, been critically assessed.

In the series of 500 cases (admitted in the acute stage) there were 31 subjects who had a fit following the injury—an incidence of approximately 6%. Of these, 24 were general seizures, five focal, and two mixed. Seven of those with fits had focal signs after injury, and of these five had focal seizures and two general. Of these seven cases, four had depressed fractures of the cranial vault, three with focal seizures. The figures are small, but they suggest some relation between focal seizures on the one hand and focal signs and depressed fracture on the other. All the focal seizures first occurred shortly after injury, within the first six days, whereas the general seizures, although they might be early, more usually did not occur for several months or even years after the trauma.

Complicating factors were rare in this group of 31 epileptics: one case had an extradural haemor-

rhage; one had cerebrospinal fluid rhinorrhoea with aerocele and meningitis.

Four cases had a previous history of convulsive attack before the trauma; three had a family history of epilepsy; and one had both. These relationships do not appear to be significant to the development of epilepsy, as is confirmed later in the larger series.

Only four cases had previously suffered a head injury. A large proportion of the 31 epileptics had suffered severe acceleration-deceleration injuries (18 from motor vehicles, two from plane crashes).

Of the 31 epileptics, 22 had abnormal E.E.G.s, four were normal, and in five cases there was no record.

Delay in Onset of Traumatic Epilepsy

The study of the interval at which the first fit appeared has a special merit in that it contains implications which reflect upon the nature of the cause or causes of this complication. The density of the epileptic effect, apart from total incidence in a series, cannot be gauged from such a study, since it would require a long-term survey of a series of such epileptics, in whom anticonvulsants had not been exhibited, before the degree of the operating cause or causes might be estimated in a traumatic epileptic population. With this restrictive factor in mind we may turn to the time of appearance of first fits in the "190" series of cases of post-traumatic epilepsy, remembering that the observed gradient of time-lag may be somewhat lower than the real value owing to the fact that some fits will be missed as the result of the factors discussed above. The results of such an approach may be seen in Table 1.

TABLE I
190 CASES OF TRAUMATIC EPILEPSY INDICATING
TIME-LAG IN APPEARANCE OF FIRST FIT

Interval after Injury at which Fits Began	No. of Cases
0-3 months	104
3-6 "	27
6-9 "	16
9-12 "	9
12-15 "	4
15-18 "	2
18-24 "	0
2-3 years	15
3-4 "	8
4-11 "	5

The points which merit further consideration are: (1) The large number of cases which occur within three months of injury (104); (2) the rapidly decreasing number of cases after three months; (3) a period of six months in which no fits were seen (from 18 months to two years); (4) the group of late cases after two years.

The large group of early cases (less than three months) represents almost 55% of the total 190 cases. Of these 104 cases, 66 had a fit within one month of the injury and 45 of these occurred in the first two weeks. There would appear to be a number of possible causes of seizure immediately following head injury, apart from the direct effect of trauma on brain cells, and it may be the operation of a number of factors whose influence fades rapidly which determines the high incidence of fits within the first few days or weeks of the injury. The aetiology of these early cases is to be discussed in some detail later.

The steep decline of the incidence curve after three months confirms previous clinical observation and, measured quantitatively here, shows a very rapid fall towards zero at or shortly after 18 months. This fall reflects the decreasing incidence of this early epileptic cause and its evenness makes it unlikely that from three to 18 months more than one cause is operating. On the other hand, as is shown in Table II, the uneven gradient before three months suggests that multiple causes may be operating.

In a recent series of penetrating wounds studied by Russell and Whitty (1952) the time-lag gradient also fell rapidly after an initial high peak, and although the time intervals selected by them were not equal, the general shape of the curve resembled that for the closed head injury cases.

Effect of Severity of Trauma

A most important problem now arises. What is the relation between the degree of trauma and the frequency or the time of appearance of the fits? Are the more severely injured subjects more prone to fits, and, if so, do the fits tend to occur early or late in such cases.

In closed head injuries without complication the trauma is maximal *ab initio* and its effects presumably decrease as consciousness recovers. If trauma is the direct cause of the fit, a seizure should occur at once when the degree of injury surpasses the subject's convulsive threshold. This clearly is not happening in these cases, for the occurrence of a latent interval of varying duration is a very constant feature. This may imply that there is some critical epileptic component related to *recovery* from trauma and that it is not the injured neuron but the cell about to resume function that constitutes the epileptic substrate? This concept would explain the rapid fall in the time-lag gradient after three months, as there would then be a rapidly diminishing *recovering* population from which seizures might originate. This would necessarily mean a later tendency to fits in the reactionary period in the long

post-traumatic amnesia cases and possibly also a higher relative frequency of seizures in the same group. These two points are to be examined in detail later.

It is suggested therefore that the gradient of time-lag shows a large number of fits in a primary phase the duration of which is about three months and which is probably due to several causes; a group of fits rapidly decreasing in number in a reactionary phase from about three months to 18 months, very probably due to one cause only which may be a supernormal excitatory state in the recovering neurons; and a group of secondary fits after two years which may be related in some way to dead neural tissue.

The incidence delay may now be contrasted between general seizures and focal attacks. Of the former 160 cases were recorded; of the latter only 30. In Table II a comparison of these two groups

TABLE II
FURTHER ANALYSIS OF TIME-LAG WITH CASES WITH
GENERAL AND FOCAL FITS SEPARATED

Interval after Injury at which Fits Began	No. of Cases	
	General Convulsions (160 cases)	Focal Convulsions (30 Cases)
Under 24 hours	13	2
1-14 days	22	11
2 wks.-1 month	18	3
1-3 months	32	3
3-6 "	23	4
6-9 "	13	3
9-12 "	9	0
12-15 "	4	0
15-18 "	2	0
18-24 "	0	0
2-3 years	15	0
Over 3 years	9	4

is made by plotting the number of cases against the time of appearance of first fits using shorter initial time periods to demonstrate the behaviour of the focal attacks, almost 50% of which occur in the first few days after injury. The gradient for general seizures follows the same pattern as that seen for the total series in Table I and calls for no further comment. The primary phase of focal attacks, however, appears to be of shorter duration and terminates between two and four weeks, to be followed by a steady low level incidence rate which seems to end at nine months. In a small group of four focal cases epilepsy did not develop until after three years from the injury.

The relation between focal trauma and focal seizure is shown by a group of depressed fractures. The "500" series included 38 cases of depressed fracture of the cranial vault; of these, 26 had fits, of which nine were focal attacks. Not only there-

fore is the general incidence level raised by depressed fracture, but the incidence of focal epilepsy is disproportionately increased. The percentage differences are seen in Table III. Although the depressed

TABLE III

INCIDENCE OF EPILEPSY IN 500 UNSELECTED CASES AND IN 38 CASES OF DEPRESSED FRACTURE EXTRACTED FROM THESE 500

	Unselected Admissions (500 Cases)	Depressed Fractures (38 Cases)
Total incidence	6%	68%
General seizures	5%	44%
Focal attacks	1%	24%

fracture group is a small one the increased incidence of epilepsy over the unselected admissions is remarkable and raises the practical question of the desirability of exhibiting anticonvulsants to all depressed fractures for some months after the injury. There seems little doubt that the chances of a focal attack become very considerably greater after depressed fracture of the vault of the skull. It should, of course, be understood that even a single focal fit leads to the case being segregated into the post-traumatic epilepsy group.

Post-traumatic Amnesia (P.T.A.) and Epilepsy

The duration of post-traumatic amnesia, if not a direct measurement of the degree of trauma, appears at least to indicate to some extent the degree of neuron reaction to trauma. Care must be exercised in using this premise in interpretation since a spatial factor is involved and one may imagine two post-traumatic amnesias of equal duration, in one case due to local disturbance in a specific area and in the other to diffuse concussion operating over the whole cortex. The essence of the problem, in the uncomplicated case, is the fact that amnesia terminates as recovery of brain function takes place, and it is justifiable therefore to regard the length of P.T.A. as a measure of the duration of reintegration.

The two points referred to previously may now be examined. Is the longer recovery period associated with a greater percentage incidence of fits, and do the fits in long P.T.A. cases tend to occur later? Or, in other words, is the epileptogenic factor potentiated by a longer period of recovery, and must further time pass before this may become overt? A comparison of P.T.A. in equal unselected and epileptic series is seen in Table IV.

The difference is clear. The peak incidence of P.T.A. is achieved under one hour in the unselected series and falls rapidly, only about 12% of cases having a P.T.A. of over seven days. In the epileptic

TABLE IV

DURATION OF POST-TRAUMATIC AMNESIA (P.T.A.) IN CASES DEVELOPING TRAUMATIC EPILEPSY COMPARED WITH CONTROL GROUP OF CASES OF HEAD INJURY

Cases of Head Injury	Duration of P.T.A. in Hours (h.) and Days (d.)				
	Nil	1 h.	1-24 h.	1-7 d.	> 7 d.
Unselected (%)	12	38	22	14	12
With post-traumatic epilepsy (%)	8	18	25	24	24

series a peak is not achieved for several hours and thereafter an equal number of cases occur at the P.T.A. intervals selected, approximately double the number of epileptics having a P.T.A. of over seven days than in the unselected series. About 50% of traumatic epileptics had a P.T.A. of over 24 hours.

Determination of the incidence delay in long P.T.A. cases may be approached in several ways. Some selection must occur, since, if it is intended to observe the direct neuron effect which may be associated with long P.T.A., any case containing a complicating factor must be excluded, both because it may be epileptogenic or because it may be related causally to the amnesia. In the "190" series there were 40 uncomplicated cases with P.T.A. of over seven days' duration. In order to make the contrast extreme they are compared in Table V with an equal number of epileptics whose P.T.A. was less

TABLE V

TIME-LAG IN DEVELOPMENT OF POST-TRAUMATIC EPILEPSY IN TWO GROUPS OF 40 CASES WITH SHORT AND LONG P.T.A. RESPECTIVELY

Time-lag in Development of First Fit in Months	Cases with P.T.A. under 1 hr.	Cases with P.T.A. over 7 days
Under 3	31	9
3-6	2	10
6-9	1	4
9-12	2	3
12-15	0	2
15-18	1	2
18-24	0	0
Over 24	3	10

than one hour. The total number of cases is small, but not sufficiently to alter significantly the observation that in 77% of the short P.T.A. cases the first fit occurred within three months of the injury whereas in the long P.T.A. group 77% of first fits appeared after three months. It would be imprudent to seek more than this difference between two small contrasting series; however, the difference is a critical one since, if true, it shows that short P.T.A. epilepsy is predominantly primary, while long P.T.A. epilepsy is for the most part reactionary and secondary. It must be made clear that but little

selection was involved, as the short P.T.A. group represented all the cases of less than one hour in the "190" series, and although four cases of more than seven days' P.T.A. with complicating factors were excluded, the incidence delay in each was over three months.

The group with a time-lag of less than three months contains the largest number of cases, most having a short P.T.A., and includes nearly all the focal seizures. During this phase a number of causal factors in addition to direct cell trauma may be operating to evoke a fit. In the reactionary phase a smaller number of fits is seen, usually in long P.T.A. cases, the number decreasing rapidly as the incidence delay becomes extended. These later cases may be due possibly to an over-excitability state in cells emerging from the effects of trauma. The smallest group of fits occurs in a late secondary stage, after two years, most frequently in long P.T.A. cases, and here the cause may perhaps be foci of unstable cortex surrounding areas of dead neural tissue. The clinical records support this view. The great majority of early fits in the primary phase were single and did not recur, as far as one may judge from the records, although anticonvulsants may not have been exhibited. The focal attacks, as stated above, occurred at this time, and a substantial number of fits, both focal and general, took place while the subject was still unconscious. Fits in the reactionary phase appeared for the most part to respond well to suppression by drugs and usually did not recur after anticonvulsants were discontinued. The epilepsy in the secondary phase appeared to be of a more severe and fixed form. Its onset in several cases was by status epilepticus, and it appeared to be more difficult to control by drugs. The records do not permit a quantitative analysis of these apparent differences, but the overall clinical picture is one of three groups of epileptic subjects differentiated both in time and by P.T.A., the type of seizure, its severity and recurring quality, and the response to drugs. Finally, the relation between P.T.A. and the incidence of epilepsy may be tested by reverting to the "500" series containing 31 cases of epilepsy.* There were 387 cases with a P.T.A. of less than 24 hours; of these 18 had seizures, an incidence of 4.6%. Of the remaining 113 cases with a P.T.A. of over 24 hours 13 had seizures, an incidence of 11.5%. From what has been shown to be the relation between longer P.T.A. and incidence this percentage is probably greater still with post-traumatic amnesias of over seven days.

* Most of these cases were followed up for only two to three years after injury.—Ed.

Constitutional Factors in Aetiology

An overt epileptic would be unlikely to be enlisted in or to remain long in the Services. Of the series of 190 traumatic epileptics only 15 (7.8%) had a previous history of seizure, and in most cases this was a single instance in infancy or immediately succeeding a previous head injury. A control series showed a personal history of seizure in 3% of cases, and the difference therefore is not statistically significant.

Twenty-four (12.6%) cases had a family history of epilepsy, a figure very similar to that given previously for ancestral history in any epileptic group (11%); five cases had a family and personal history of seizure. In the "500" series, however, there were five patients with head injury who had both familial and personal histories of seizures. One of these had frequent fits beginning 10 weeks after the trauma. In the other four cases with P.T.A. of three weeks, five days, four hours, and half an hour, no fit was recorded.

Although this evidence is of a negative kind and relates the incidence of personal and family history in a series of traumatic epileptics, whereas the reverse would be both more positive and more convincing, it may be concluded from the figures quoted that there is no reason to suppose that the subject of cranial trauma is more likely to suffer a fit if he has a personal or a family history of epilepsy or even both.

Evidence of a similar type may be adduced to show that other constitutional factors such as personal or ancestral mental disease or migraine are not causally related to traumatic epilepsy.

Complications

No positive evidence was seen to relate such complications as cerebrospinal fluid rhinorrhoea, aerocele, infection, subdural or extradural haematoma to the development of traumatic epilepsy. However, the series is not suitable for this purpose, and the number of complicated cases too small to justify any definite conclusion.

It is notable that in the 31 cases of fits in the "500" series there were only two with complications. In one there was an extradural haemorrhage, but there was also a depressed fracture of the cranial vault, and the fit was immediately after injury. In the other, there was a combination of anterior basal fracture, cerebrospinal fluid rhinorrhoea, aerocele, and meningitis, and the fit occurred two months later.

In the "500" series, on the other hand, there were 19 cases of cerebrospinal fluid rhinorrhoea without fits, in spite of the customary association of basal

fracture, frontal contusion, and bloody cerebro-spinal fluid in these cases.

Previous Head Injury

The influence of previous head injury on the epileptogenic effect of late cerebral trauma is difficult to assess. It is obvious from what has already been stated here that characteristics of the previous injury, such as P.T.A., focal signs, depressed fracture, etc., must be taken into account.

It is by no means surprising that in the "500" series, predominantly healthy males, there were 44 patients who had received a previous head injury of moderate or severe degree. Only four of these cases, however, suffered a fit, an incidence which is not significantly different from the series as a whole, particularly when the effect of P.T.A. is remembered. Moreover, there were complicating factors in three of these cases in that one had a seizure two hours after injury while still in coma, another had focal signs, and the third was being treated for syphilis. In the "190" "epileptic" series 33 subjects had a previous history of head injury, but 17 cases had a P.T.A. over 24 hours and the degree of the present injury is therefore involved in the relationship.

It is possible that the study of a group of late traumatic epileptics might throw further light on this problem. On the present evidence there is no reason to suppose that a previous head injury from which a full recovery has taken place will permanently lower the subject's convulsive threshold and render him more liable to seizures after succeeding cranial trauma. Whether, on the other hand, an injury followed by incomplete recovery with residual signs of focal damage or epileptiform dysrhythmia may not permanently alter the convulsive threshold is another matter.

Electroencephalography (E.E.G.)

There is little information to be gained in this series of cases from the E.E.G. records. Less impersonal and more sequential studies, such as those of Denis Williams (1941), are necessary before any substantial conclusions may be drawn. Here there is no record of pre-trauma E.E.G. and no overall E.E.G. follow-up, neither of which were possible in a series of this type. The E.E.G. record itself, moreover, is always more enlightening than a report, and successive comparisons appear essential if one is to understand what is happening in the injured brain. In the acute cases studied at Oxford approximately 70% showed some E.E.G. abnormality in the early stages. In the majority of cases this was not fixed and tended to return progressively to normal in two or three months, at which time the

reactionary phase began and some seizures occurred. This point is regarded as important, since it is evident that in this group the epileptogenic component appears as the effect of trauma is passing off and cells are recovering normally integrated function.

Fixed epileptiform dysrhythmias with paroxysmal changes in amplitude or frequency were rare and appeared to be confined mainly to the late cases with an incidence delay of over two years. Focal dysrhythmias in closed head injury appeared to be excessively rare and seemed to be restricted to early cases in the primary phase with focal signs or depressed fracture, particularly when the fit was focal or when a general seizure was preceded by a focal motor or sensory aura. In the "190" series with fits the E.E.G. was quite normal in nearly 30% of the cases in which it was recorded.

Insufficient information was available to determine the percentage of cases developing a fixed dysrhythmia after closed head injury or the number of these patients who subsequently suffered a fit.

Discussion

The trauma-fit relationship is difficult to analyse, as 80–90% of closed head injuries recover and the cellular pathology due to trauma may only be presumed from post-mortem examination in fatal cases, from animal experiment, and possibly also from surgical experiences when complications require exposure of the intracranial contents.

The pathology in fatal cases is, moreover, extremely variable. No macroscopic change may be seen in the brain of a fatal case, or there may be extensive cortical contusion or laceration, free blood in the ventricles and cisterns, and multiple haemorrhages in the mid-brain and pons. In spite of this, the incidence of epilepsy after closed head injury is very low as compared to the incidence in brain wounds, and the relation between epilepsy and P.T.A., which has been shown here to exist for the closed head injuries, does not hold for brain wounds; indeed, many subjects with the latter who develop fits are not rendered unconscious at all by the penetrating injury. These facts would suggest that it is some character of trauma other than the degree of its capacity to cause unconsciousness which contains the critical epileptogenic component. In the search for this it must be remembered that the cortico-spinal tracts are the final common pathway for the expression of an epileptic trend in the brain. That the cells of origin of these tracts lie in a vulnerable area in respect to epilepsy may be gauged from the higher incidence of epilepsy after penetrating injuries when the wound was in the region

of the central sulcus (Russell and Whitty, 1952). The central cortex is rarely injured in closed head injury, and this may be one reason why the incidence of epilepsy is low in these cases. In closed head injuries, too, the damage is general and diffuse, while in brain wounds it is local and concentrated. These associated areal and density factors suggest that it may be a local mass effect of disintegration operating at the central cortex, either on motoneurons or on the fibres converging upon them, which constitutes the substrate of epilepsy after trauma. The differential areal and density relations between brain wounds and acceleration injuries would then explain a high incidence of epilepsy in the former while it was low in the latter.

It appears clear that several factors other than direct neuron trauma may lead to a fit, and it may be in the early period following trauma that several different epileptogenic causes are present. Aetiology may be considered in the groups corresponding to the primary, reactionary and secondary phases defined by the incidence delay trends.

Primary Phase.—Here fits may be classified on the basis of possible causes: (1) Humoral; (2) vascular (venous thrombosis, arterial occlusion (anaemia-anoxia)); (3) mechanical; (4) direct neuronal trauma.

Humoral.—Arterial injection of a minute dose of acetylcholine will cause a fit and the effect is apparently a direct neuronal excitation, as the fit occurs before the onset of bradycardia. Denis Williams (1952) has carried out this experiment on human subjects. Bornstein (1946) has demonstrated that acetylcholine is freely liberated into the cerebrospinal fluid following cranial trauma, and Ward (1950) has seized on this fact in the use of atropine in the treatment of acute head injuries. Recently Eccles (1952), after the study of inhibition hyperpolarization in single motoneurons, has concluded that humoral transmission within the central nervous system is likely. It seems probable, therefore, that in the early primary phase some fits may be due to liberation of an excitatory transmitter by the trauma.

Venous Thrombosis.—This condition is not infrequently seen in the cortical veins at post-mortem examination when death occurs in the early days following trauma. Cerebral thrombophlebitis is a potent cause of epilepsy and may be responsible for focal or general seizures. It is known to have occurred in traumatic patients who have survived, and has been disclosed on numerous occasions at neurosurgical operations. It may therefore not be

excluded as an early cause of fits after acceleration injuries.

Arterial Occlusion.—Pickering (1951) has recently discussed the transient effects of arterial thrombosis in the brain. The relation between thrombosis and trauma is well recognized. Small vessel thrombosis without infarction may occur in the brain and produce focal effects which can resolve completely with time. This type of pathology must therefore be admitted as another possible cause of early epilepsy after cerebral trauma.

Mechanical.—The high incidence of epilepsy, particularly focal epilepsy, with depressed fracture suggests that a local mechanical cause of fits may be operating. It may of course, not be direct, and the excitatory discharge may be secondary to vascular changes produced by the pressure. Cases have been seen by the writer in which focal or adverse attacks persisted until the elevation of a depressed fracture was performed, the fits ceasing immediately after removal of local pressure on the central cortex.

Direct Neuron Trauma.—The experimental evidence available indicates that the excitation threshold of nerve cells is not lowered by concussion. However, the fact that a generalized convulsion may occur immediately after trauma while the subject is unconscious, and that only a single fit may occur, may mean that direct neuron trauma can cause an epileptic attack. Rapid and complete recovery is the rule after molecular concussion alone without complication, and direct neuron trauma must be an unusual cause of seizure, confined perhaps to attacks occurring immediately after the injury.

Reactionary Phase.—As suggested previously, the smooth slope of the incidence delay curve suggests a single cause of seizure from three months to 18 months after trauma. In acceleration injuries the possibilities of humoral, vascular, mechanical, and direct traumatic effects have passed off at three months; the patient may be symptom free, has been discharged from hospital, and appears to have made a good recovery apart perhaps from a mild persisting cerebral dysrhythmia. He then unexpectedly has a fit—usually a generalized attack. The incidence delay of the fit tends to be related to the P.T.A., and the suggestion is that in the reactionary phase the fit occurs at a critical stage towards the end of the period of recovery of cell integration. Damaged cells either recover or die. They undergo chromatolysis and proceed to dissolution and absorption, or the chromatolysis

persists, often for long periods, and the cells then gradually recover normal function, first as individuals, then as integrated groups. This has been well shown by the work of Eccles (1952), who has described the changing pattern of monosynaptic, then polysynaptic, and, finally, monosynaptic reflex integration of anterior horn cells recovering from chromatolysis. It would seem reasonable to infer that similar but probably much more complex integrative processes take place at the cortical level after trauma. The fact that the reflex associative pattern is changing and a cell population undergoing a differential recovery must imply instability. When a critical level of recovery is attained this instability might be expressed in the sudden local excessive epileptic discharge. This might, of course, happen anywhere in the cortex, but where is it likely to be more effective than at the site of maximal associative convergence, of maximal motor integration, at the nodal point of motor control in the region of the central sulcus?

Physiological evidence shows that such instability in recovering neurons may be established in at least two ways: namely, by rebound, and by potentiation.

Rebound, in the sense used by Sherrington, is the sudden excessive synchronous discharge of motoneurons following a period of inhibition. Rebound is responsible for clonus; essentially, it is based on synchrony and fulfils Hughlings Jackson's concept of sudden, local and excessive activity. In closed head injury we may imagine during the recovery of cortical neurons that there is a period during which inhibition is prepotent. This may follow simply from reduction of trans-cortical excitatory processes by trauma while inhibition from deeply placed centres is relatively unaffected, or it may be due to transient polysynaptic inhibition at the cortical level while motoneurons are recovering from chromatolysis. Clinically, such inhibition is reflected in drowsiness, lack of interest, and reduction of affect and motor display. Rebound then becomes likely as the recovering cell population is reintegrated as a functional entity. One fit only may occur or a number may be seen over a period. The epileptogenic phase is, however, transient; it is not a fixed state, and it passes away, *pari passu*, as full recovery is reached. By definition, such fits, in acceleration injuries, would be generalized seizures for the most part, except for the rare case of focal damage, and these seizures should be expected to respond well to the anticonvulsant drugs. Clinical observation confirms both these facts. A similar result might follow if impulses were circuited around a damaged area to bombard adjacent cells. Potenti-

ation might then occur and the degree of overactive instability reach an epileptic value. It is probable, however, that this mechanism is more likely in late cases where unstable cortex round a central scar may initiate the fit.

Secondary Phase.—About 15% of the cases in the "190" series suffered a first fit more than two years after injury. It is felt that this group contains the severe post-traumatic epileptics. Here the epileptic state may be fixed and is not simply a reaction to transient pathology or to a stage of recovering integration. The seizures were mainly generalized, with onset in status in several cases. A few have been known to persist for years and require heavy sedation for their control. The great majority have an epileptiform dysrhythmia. Are these, then, not the cerebral scars with perimeters of unstable epileptogenic cortex? They are indeed a most interesting group and require more detailed survey than was possible in the present study.

Concluding Remarks

This study began with the general attitude that after acceleration injuries a small number of cases might suffer a fit; that a number of these might be delayed for longer or shorter periods; and that the fits were for the most part directly due to neuron injury. The conclusions which have been drawn, however, are that the incidence of fits rises quite rapidly as the P.T.A. becomes longer, and at the same time the fits tend to appear later. Incidence delay curves suggest three phases in reaction to trauma by convulsion. In the first phase fits may occur as the result of some supernormal excitatory state through which injured neurons must pass to attain integrated recovery, while in the third phase a fixed tendency towards convulsions is determined, probably by instability of neurons at the perimeters of dead cells. Finally, the much higher incidence of epilepsy in penetrating injuries may be related to a mass effect of neural disintegration, particularly when the wound is adjacent to the final motor pathway from the cortex.

Summary

Two thousand cases of closed head injury were studied from the war-time records of the Military Hospital for Head Injuries, Oxford.

Five hundred of these were a relatively unselected group and the incidence of post-traumatic epilepsy was 6%.

One hundred and ninety cases of traumatic epilepsy were considered in some detail.

Focal seizures developed earlier than did general seizures.

Cases with a long post-traumatic amnesia (P.T.A.) had a higher incidence of epilepsy, and the fits developed after a longer time-lag than occurred in cases with a short P.T.A.

Constitutional factors appeared to be relatively unimportant.

The possible significance of the varying interval at which fits develop is discussed from the point of view of the aetiological factors concerned in traumatic epilepsy.

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