1944

Epilepsy : its etiology and its relation to heredity

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"EPILEPSY"

ITS ETIOLOGY AND ITS RELATION TO HEREDITY

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Presented to

The University of Nebraska,
College of Medicine, Omaha,
September, 1944

INTRODUCTION

This review of the recent literature on epilepsy was undertaken with two main objectives in mind; first, to present to those who may be interested in the subject, a concise and easily accessible reference by which they can obtain a general knowledge of the more recent theories concerning the particular phases of the disease to be discussed; secondly, to give to the writer an opportunity to furnish himself with at least a reading knowledge of a subject, which, although known for centuries, still presents many problems which remain unanswered, or, if answered, the answer is hypothetical in many cases.

This paper is not intended to be an exhaustive study of the subject, but is intended to cover only the salient features of two particular phases of the disease, which, in the writer's opinion, are the most important, the most controversial, and offer the most practical and the most recent advances in the field and study of epilepsy.

The two phases to be discussed are:

1). The etiology of epilepsy.

2). The relationship of epilepsy to heredity.

Near the close of the paper, the writer will state some of the conclusions that he has reached from this work, but it should be remembered that these are only one man's interpretations, and do not neces-

sarily constitute, nor were they intended to do so, the last word on the subject.

By way of introduction, it might be well to mention a few general facts, which though probably known by many, are on the other hand, probably only realized by a few. These might serve further to give a hasty and rather sketcy general background to the subject, and also to bring to life the vast scope and importance of the condition known as epilepsy.

Epilepsy is older than man himself, but to man this disease has been a recurring curse since he first stood erect. The trephined skulls of the early Neolithic period bear mute testimony that even then man was attempting to liberate from the cranial cavity the demons responsible for epilepsy and headache. Thus, we see that we are not dealing with something "new", but are concerned with the subject that has been challenging man for centuries, and continues to do so.

Epilepsy is a much larger and more costly problem, and also a more hopeful one, than most people realize. Epilepsy affects about five to ten per cent of the population of the United States, or approximately six hundred thousand cases (26); as many as the victims of active tuberculosis, of diabetes, or of infantile paralysis. Of this number, only about one-

fourth have any known defect, or irreversible pathological change, disease, or condition, which might act as an exciting cause (61).

The tenth part of these patients who are hospitalized at public expense, occupy as one-tenth as many hospital beds as all medical, surgical and obstetrical patients combined. Furthermore, epileptics, no matter how able-bodied or clear minded, are denied service in our Armed Forces and in our industries (34).

For many years, the patient who suffered with convulsions, was branded as an epileptic and was abandoned to a life of ostracism and despair. Today, however, we have a different view. It is now generally accepted that epilepsy cannot be considered as a unitary disease entity, but is, on the contrary, a symptom complex accompanying a variety of conditions which directly or indirectly impair the integrated function of the Central Nervous System (28). Today we look upon convulsions in much the same way as we look upon fever, pain, nausea, etc.-- simply as a clinical symptom (24).

In regard to this, Lyerly (43) says that to make a diagnosis of epilepsy when a patient has a convulsion without a complete neurological study, is as unjustifiable as it is to say he merely has a headache when there is a brain tumor present. Epilepsy should be

regarded as synonymous with convulsions and it means nothing more than a symptom of some underlying disease of the brain.

The definitions of epilepsy are many and varied, ranging all the way from the absurd to those bordering on the supernatural. For the purpose of this paper, a definition will be given that is a combination of several definitions which, after careful sifting and sorting, seemed to the writer to be the most logical.

The essence of the definition of epilepsy is contained in the Greek word "epilepsia", which means "a taking hold of, a something seizing the subject as though that 'something' were outside himself."

In the light of the above, I shall define epilepsy as: "A tendency to periodic, involuntary, neuronal explosions (48), resulting in recurring epileptic seizures characterized by a sudden, brief or prolonged, loss of consciousness, and is usually accompanied by a convulsion" (65).

With these few facts in mind we shall now proceed with the thesis proper.

CLASSIFICATION

Here again we encounter a situation complicated by many and varied types of classifications. Penfield (50) makes use of three main classifications. He classifies epilepsies according to 1) an anatomical basis, 2) on a chronological (according to age of onset) basis, and 3) on an etiological basis. Because we are concerned primarily with etiology of the disease, it is that classification which we will set forth in detail and later enlarge upon. However, certain phases of the other types of classifications present some interesting facts and deserve mention.

Chief among these, is the classification based on age of onset; however, such a classification is only tentative, and should never be more than hypothetical (50).

According to Penfield (50), seizures in infancy suggest early brain injury caused by a birth injury, cerebral degeneration, or by a congenital lesion. Onset of seizures around puberty without an antecedent history of head injury suggest idiopathic epilepsy. In this regard, it might be mentioned in passing, that the term "idiopathic epilepsy" has lost favor in many clinics within recent years. Because we are unable to find the cause for many of these convulsive disorders it does not follow that they arise spontaneously (27). Lennox (24), agrees with this statement, and suggests

the term "genetic" as a substitute for "idiopathic". It should be remembered that the diagnosis of idiopathic epilepsy automatically condemns the patient to a lifetime of convulsions and, in many cases, progressive mental deterioration (53). The definition of idiopathic epilepsy made by the late Dr. M. Smith in a facetious mood -- "Idio-I don't know; Pathic-a damn thing about it (27)", probably sums up the situation regarding idiopathic epilepsy as well as anything.

However, to get back to our classification, both authors are of the opinion that attacks after twenty years of age suggest the possibility of brain tumor, brain scar, or a cerebral vascular disease.

Another interesting theory and classification is that proposed by Graff (24), who is of the opinion that every convulsion indicates either a pathologically irritable brain or else a pathologically irritated brain. The etiologic factors contributing to either of these states are numerous and diverse. Among them the author lists such factors as biochemical mechanisms, inflammatory and post-inflammatory processes, traumatic sequele, etc.

However, as stated previously, for the purpose of this paper, I am going to use a classification which is a composite of several, and which seems to me to be the

simplest, yet the most comprehensive, and most suited for this paper. Again it should be remembered that this classification is based solely on possible etiological factors. I shall present it below in outline form and enlarge upon it in the subsequent section.

EPILEPSIES DUE TO OR ASSOCIATED WITH:

1) Expanding lesions.
2) Trauma.
3) Infections.
4) Birth injuries.
5) Congenital malformations and maldevelopment.
6) Miscellaneous

ETIOLOGY

As an introductory premise to the subject of the etiology of epilepsy permit me to say that every convulsion originates from an irritable focus or pathological process in the gray matter of the brain; and, according to Lyerly (43), this irritable focus or pathological process may be a scar from an old brain trauma, brain tumor, abscess, cerebral vascular disease, and many other things. The pathological process sets up a state of irritation with abnormal discharges in the neighboring nerve tissues. Thus there may be established an "epiliptegenic" zone from which the impulses causing the convulsive seizures arise.

We will now discuss the individual entries presented earlier, in the order of their appearance in the classification.

I. Expanding Lesions

a) Neoplasms

According to Dandy (41, 12), tumors represent one of the most common causes of epilepsy at all ages, but especially between the ages of fifteen and sixty. Penfield (50), on the other hand, states that before the age of fifteen, tumor as a cause of epilepsy is rare. From birth to the twenty-fifth year, tumors become progressively more frequent, and about one-third to

one-half of all epilepsies beginning after the twenty-fifth year are due to tumor. Lyerly (43), is of the opinion that whenever an adult has a convulsion for the first time, brain tumor is a strong possibility.

Himler (28), examined one thousand non-institutionalized epileptic patients, in every case of which a diagnosis of Grand or Petit mal epilepsy has been made. The groups studied involved 577 males and 843 females, of which 842 had typical Grand mal attacks and the remaining 158 had Petit mal attacks without accompanying major seizures. Although the group included patients of all ages, the majority were children and young adults. These patients had all had the routine neurological examination, skull roentgenograms, spinal fluid examination, and ten per cent had encephalograms. In this entire series he only found twenty-one definite cerebral neoplasms; nineteen of which were accompanied by Grand mal seizures and two by Petit mal seizures

Sachs and Parker, quoted by Lyerly (43), found that incidence of convulsions with brain tumor is around 20.7 and 21.6 per cent. Pilcher (53), although he did not state the number of cases studied, reports that thirty per cent of his patients with brain tumors had, or have had, convulsions. Pigott's (52), findings tend to support those of Himler (28). He

reviewed one thousand cases of convulsions in childhood, of these, 553 have been classified etiologically, and out of this number intracranial tumor was diagnosed as the causative factor in only four cases.

Kerrmann (27), reviewed twenty-two consecutive cases of repeated convulsive seizures in children between the ages of one and eighteen, and the duration of the attacks was from one month to eighteen years, the majority being less than five years. In this series, he was able to demonstrate a cerebral neoplasm in only one case, thus further emphasizing the rarity of tumors as a cause of convulsive seizures before the age of fifteen.

According to Penfield (50), whether an intracranial tumor produces recurring epileptic seizures or not, depends upon a number of elements, among which, the most important are the tumor location, its nature, and its chronicity. The susceptibility of the individual to seizures may also be an element, although the very high incidence of seizures among cases of certain slowly growing neoplasms suggest that special individual resistance to seizures, if it exists, is comparative and not absolute.

Convulsive attacks may develope with the local expansion of a brain tumor, cease after tumor

removal, and later recur without a recurrance of the neoplasm (44).

Clinically, the epileptic reactions associated with brain tumor do not differ from those seen in the so called "idiopathic" type -- evidently there exists in these different pathological states some factor common to all which is capable of producing cortical irritation of sufficient intensity to establish ultimately an epileptegenic zone and an epileptic reaction. According to Ney (44), this common factor seems to be an increase of local cortical tension, which develops in the area surrounding an expanding cortical tumor.

In regard to the first factor presented earlier in this section, namely, tumor location, we find the following information: According to Lennox (33), there may be certain patients who have a tumor of the frontal or parietal lobe, in whom the pathology is the sole cause of the seizure, but such cases constitute only an insignificant fraction of the total number of patients who are subject to seizures. In distinction to this we have the opinion of Lyerly (43), who (quoting Parker), showed that fifty per cent of the patients with frontal or parietal lobe tumors have convulsions. Penfield (48), is also in accord with Lyerly, and finds that fifty-three per cent of tumors

in the frontal lobe and sixty-eight per cent of the tumors in the parietal lobes were associated with seizures. Papex (47), also agrees with the latter author.

Erickson (17), on the other hand, considers tumors associated with convulsions are a little more frequent in the temporal lobes, but thinks that in general the difference of incidence is not marked in the various lobes of the hemispheres. His studies showed that seizures occurred in sixty-eight per cent of the cases of tumors of the parietal lobe, in forty-eight per cent of the temporal lobe, in fifty-three per cent of the frontal region, in seventy-one per cent in the fronto-parietal region, and in eighty per cent in the fronto-temporal region. The lowest incidence of seizures occurred with tumors of the occipital lobe--thirty-two per cent. It is apparent that the incidence increases as the site of the tumor approaches the Rolandic fissure (Central Sulcus).

In regard to tumors of the pituitary gland-- in forty-nine cases of Penfield's (50), only four patients had seizures, and in these four cases the tumors had escaped from the sella and pressed upon the brain. Erickson (17), is also in accord with this, and states that intra-sellar neoplasms do not

produce seizures unless they escape from the sella turcica, but that supra-sellar tumors may do so when they are large enough to embarrass the basal regions of the brain.

All of the authors (17, 50), et al. are in quite general agreement that tumors of the cerebellum do not produce seizures.

Erickson (17), in an analysis of 703 cases of intracranial tumors found that supratentorial tumors constituted 79 per cent of the total number, seizures occuring in 45 per cent of the cases. Intracerebral tumors occurred almost twice as frequently as extracerebral ones, and intracerebral tumors were associated with epileptiform seizures in 51 per cent of the cases as against 47 per cent of the extracerebral group. He also found that deep seated neoplasms do not have a higher incidence of seizures than superficial ones. This was explained by Penfield (50), on the basis that the incidence of convulsions falls as the distance from the sensorimotor cortex increases in any direction.

Tumors of the remaining regions of the brain such as the third ventricle, thalamus, etc., are occasionally associated with convulsions, but the incidence is so low that they will not be discussed here.

From the preceding, I think that we can

agree with the conclusions of Ney (44), who states that an expanding lesion may or may not produce sufficient cortical disturbance to induce convulsive phenomena, but, when their occurrence precedes the incidence of attacks, they are usually considered causative, particularly so when the attacks exhibit focal symptoms. However, it should be remembered that the absence of focal attacks is not sufficient to eliminate even a well - localized lesion (41), for many brain tumors do not instigate attacks with Jacksonian features, and this also often true of attacks following local cerebral lesions. Lyerly (43), goes one step further, and is of the opinion that whenever an adult has a convulsion for the first time, brain tumor should be considered as a strong probability.

We can briefly sum up the situation in the words of Dandy (12), who says that recurring convulsions have only one significance; they unequivocally mean a lesion of some type in the cerebral hemispheres and not in the cerebellum or in the brain stem. And, according to Dandy (12), there is no exception to this.

We now must consider the second most important factor, namely the nature of the lesion. However, I think that this can best be understood if it be discussed along with the discussions of the indivi-

dual lesions, rather than to set forth a lenghty dis-dissertation at this time.

In regards to the third factor, namely, chronicity of the lesion, this can be summed up by simply stating that most of the authors (37, 14, et al.) are in accord that the more slowly growing neoplasms have a higher incidence of secondary epilepsy than do the more rapidly growing tumors, and Erikson (17), thinks that this can probably be best explained because of the fact that death terminates the history sooner in cases of the latter type.

In regard to the nature of some of the lesions studied: in a group of 230 cases of gliomas reviewed by Penfield (50), the most malignant of the group, i.e., the glioblastomas have the lowest incidence of seizures. Of the 103 cases, only 38 patients (37 per cent) complained of seizures. This is also in accordance with the findings of Erickson (17). On the other hand, of the more benign astrocytomas, there were 64 cases, and only 70 per cent were associated with epileptic seizures. The forms of glioma are too few in number to be considered from a statistical point of view, and I was unable to find any literature evaluating them.

So much for neoplasms of the brain.

b) Abscesses

In the formation of brain abscess there are several different stages, and convulsions may be produced either at the acute stage of the infection, or in the end state of repair, i.e., when the abscess has been replaced by scar tissue. In the acute stages seizures are perhaps less common than later, and probably rarely begin until a year or two after the acute stage, though occassionally there is no free interval. The incidence of epilepsy from healed abscesses is higher than from tumors, and, although an exact percentage is hard to estimate, it is thought that about 60 to 70 per cent is not too high (41). In a series of 54 patients studied by Penfield (50), 27 had epileptic seizures at some period. Of the 27 cases, 17 had their attacks begin within one month of the onset of the preliminary trouble.

In general, therefore, abscesses are apt to be associated with focal epileptic seizures during an early stage, but recurring seizures, if they appear at all, do so months or years after the initial infection, and are the result of cicatricial changes.

According to Pilcher (53), one-third of all patients with brain abscesses have convulsions,

and since the abscess of the brain may develop as a blood born infection from a distant, and sometime undiscovered, focus, the diagnosis may easily be overlooked.

c) Meningiomas

Here again statistical evidence is conspiciously lacking, but according to Graff (24), epilepsy as a symptom of meningioma is more frequent than is generally supposed, occurring in about 30 per cent of the cases. In 71 cases of meningeal tumors reviewed by Penfield (50), 48 of them (68 per cent) were associated with seizures. Papez and Rundles (47), reported a case of epilepsy caused by a meningioma of the right optic nerve situated at the optic foramen.

II. Trauma

Because, as stated earlier, the definition of epilepsy varies considerably among writers, it is difficult, on the basis of available statistical data, to say anything definite about the frequency of epileptic attacks among patients with brain injuries. However, in spite of the lack of information, it can be safely said that epileptic attacks are frequent in cases of penetrating skull wounds, so frequent indeed, that one must be prepared for their appearance in every case.

According to Goldstein (23), when one includes all forms of epileptic attacks, approximately every second patient must be considered as a potential epileptic. In a review of 244 cases of epilepsy by Riddoch (57), there was a history of head injury prior to the fits in 16% of the cases. Of 533 cases of convulsions in childhood, which had been classified etiologically by Pigott, et al. (52), trauma, and its resulting damage to the brain, was followed by epilepsy in 188 cases. The types of injuries were many and varied.

Dandy (12), agrees with Goldstein (23), when he says that any severe head injury with accompanying brain trauma is a potential source of convulsions. Rosenbleuth and Cannon (59), however, are of the opinion that for a head injury to be followed by epilepsy, there must be a certain type of brain, and that unless the brain is of this type, no amount of trauma will result in convulsions. They failed, however, to ellucidate further on this, so I am unable to offer any explanation as to what they meant by "a certain type of brain".

It should be kept in mind that it is necessary to distinguish between early and late epilepsy, as there is a very definite and important time relationship between the accident and the time of

onset of convulsions. Moreover, this time relationship has an important bearing as to the prognosis of the patient with regard to the duration, severity, and number of convulsions. The first fit may occur within a few hours after injury, or may be delayed as long as twenty years. According to Goldstein (23), by far the greatest number of epileptic attacks occur in the first two years after injury. Ascroff's (3), investigations show that fits which occur in the first two weeks after injury do not predispose the onset of epilepsy at a later date.

Along these same lines Ascroff (3), showed that the subsidence of epilepsy occurred most often in the cases in which the convulsions began within two years, and never when the first fit occurred more than two years after injury. Goldstein (23), thinks partly along these same lines, when he says that the convulsions rarely occur more than 18 to 24 months after the injury, and if an individual with a brain injury has his first epileptic attack more than four years after the injury, the possibility of the attack being caused by some other disease must and should be considered. The same author reports two cases of epilepsy who had their first attacks eight years after brain injury, and no othercause than the brain injury could be found.

Whether or not an individual will develop epilepsy following a head injury depends upon a number of factors such as the location of the trauma, duration of unconsciousness, etc., outstanding of which is the type of injury.

As to the degree of unconsciousness, we find a variance of opinion. Ascroff (3), is of the opinion that the presence or absence of concussion (immediate unconsciousness), does not influence the subsequent liability of epilepsy. In contradistinction to this, Dandy (12), says that if an individual is unconscious from five to six hours or longer, there is a 75 per cent chance of epilepsy developing later on.

The site of injury to the brain appears to have less influence upon the development of epilepsy than might have been expected, for, though it is more common after wounds of the sensorimotor cortex, it may follow injury of any part of the brain, excluding the cerebellum (20). Goldstein (23), is of the opinion that epilepsy is especially frequent as a result of injuries located in the parietal regions, and the general opinion of various writers seems to be in accord with his opinion.

Probably the most important single factor in determining whether or not epilepsy will develop following an injury to the brain, is the type of injury

and whether or not sepsis is present. Ascroff (3), in his series of cases, found that in cases in which the dura had been penetrated, fits were twice as frequent (45%), as in the scalp and skull wounds in which the dura was intact (23%). In this same series, he found further, that scalp wounds due to missils are more likely to be followed by epilepsy than are scalp wounds due to blunt injury. This writer gave me the opinion, that it made little or no difference whether or not sepsis was present. Riddoch(58), however, is just as firm in his convictions when he states that epilepsy is twice as common after there has been sepsis, whether the dura was penetrated or not. Cairns (8), is in accord with Riddoch (58), and says that he thinks that in gunshot wounds there is a great tendency towards sepsis, and this fact is responsible for the high incidence of epilepsy in such cases.

In 34 cases of gunshot wounds of the head operated on by Cushing during 1917, the incidence of epilepsy was 25% in the cases of non-penetrating injuries and 36% in cases of penetrating injuries.

Of the penetrating type, by far the most frequent single causative factor is gunshot wounds of the head. And since I will probably personally come in contact with many such cases in the near future, I am

taking the liberty to discuss this particular phase of the subject quite exhaustively, and hope that the reader will find it interesting.

Figures of the incidence of epilepsy following gunshot wounds of the head are available from last war. In 1920, the records of the Ministry of Pensions showed that out of 18,000 cases of such wounds, 4.5% had developed epilepsy. In France, Renague (Quoted by Feiling '20'), found epilepsy in 12.1% of 2523 cases--these figures, however, make no distinction as to whether or not the dura was penetrated. Some other available statistics are as follows: (All of these writers are quoted by Lancet (20).) Rawlings reported a series of 452 cases and an incidence of epilepsy in 25%; Stinthal and Nola found an incidence of 28.9% in a total of 639 cases; Credner gives an incidence of 38.2% in a total of 1990 cases; Ascroff reported a series of 317 cases in which 34% developed epilepsy.

From the above data, one can readily see the close relationship between gunshot wounds of the head and the subsequent development of epilepsy, and one cannot help but realize the vast importance of this relationship in view of the present world conflict.

When discussing head injruies and their

relationship to epilepsy, one cannot help but wonder just to what extent scar tissue formation resulting from the trauma might influence the condition.

As an introduction to this particular aspect of head injuries, it might be well to quote Palmer and Hughes (46), who say: "No distinctly characteristic epileptic neuropathology has ever been demonstrated, although there are certain cases in which organic injuries to the brain or it's enveloping membranes have resulted in scar formation with the result that contraction and irritation have given rise to local or generalized seizures".

The cicatrix is the result of the brain wound, and is frequently attached to the overlying dura and skull, thereby causing a pulling and stretching of the brain. In this manner a zone of irritability is set up about the scar eventually leading to convulsions and epilepsy. It may take one or more years for the irritation to break down the stability and integration of the normal cortex and for the convulsions to occur.

Dandy (12), explains the situation as follows: He believes that epilepsy is merely an explosion of electrical function in the brain, very much like an arc lite, and as long as the carbons are in opposition there will be no spark and no lite. But

separate the carbons a little and the electric lite comes on; this is due to the current crossing the gap. So it is in the brain. Any scar tissue in the brain may be regarded as a defect in the nerve fibers of the brain, and it takes a normal brain to be proof against convulsions. Therefore, he concludes from this, that any kind of scar defect on the cerebral hemispheres is a potential source of convulsions.

Another side to the picture is that one brought out by Pilcher (53). He believes that certain traumatic or inflammatory lesions of the brain may cause complete, or almost complete, obliteration of the Basilar Cisternae, which in themselves serve as the only connecting pathway in the circulation and absorption of the cerebrospinal fluid, thru adhesions. These adhesions will result in a damming back of the fluid (At intervals, at least, in the event that the Basilar obstruction is not complete), with the result that convulsions may occur. Ney (44), on the other hand, says that convulsions are not dependent upon, or characteristic of, an increase in intraspinal pressure.

In distinction to Pilcher's (53), viewpoint we have the opinions of Dandy (41), who thinks that the relationship between cortical adhesions and epilepsy is greatly overrated and much absurd. He goes on further and says that adhesions are not un-

common findings of trauma and even occur without trauma, but that they are not the cause of convulsions is assured by the fact that after every cranial operation adhesions practically cover the brain which has been exposed, and convulsions do not develop from post-operative adhesions.

Another condition often closely associated with epilepsy is the hematomata developing from trauma, or as the result of a vascular accident. Although the literature in this respect is rather sparse, we have a series of seventy-one cases of subdural hematomata above the tentorium reported by Erickson (17). Of this entire number, only 18% showed evidence of seizures, and this led him to the conclusion the subdural hematomas have a low incidence of seizures and the attacks, even then, seem to be due to the cerebral injury that may have resulted from the trauma rather than to the hematoma itself. Pilcher (53), says that such hematomas are very likely to become encapsulated and produce irritative symptoms long after the original episode.

A depressed skull fracture is one of the more common causes of epilepsy. The convulsions frequently begin immediately or soon after the injury and continue. Usually these convulsions will disappear

when the depression is removed, but this is far from being always true as, in the last analysis, the ultimate result doubtless depends upon how much actual damage has been done to the underlying brain tissue (41). Feilding (20), collected 3906 cases of fractured skulls, and out of these epilepsy developed in nine (about 0.5 %). In another series of 7625 cases of skull fracture collected by the same gentleman, epilepsy developed in 24 cases (about 0.125%). From this it seems fairly evident that the chances of the development of post-traumatic epilepsy is increased by the presence of an accompanying skull fracture.

III. Infections (Including The Granulomas).

This sub-title involves a host of conditions, as just about every type of infection has, at one time or another, been reported as being the causative agent of a subsequent epilepsy. However, many of them are so rare as to not deserve even a passing mention, hence just the more important and the more frequently mentioned ones will be presented and discussed in any great detail.

I am going to head the list with a discussion of a topic which, although comparatively new and unknown in this country at the present time, will, I

feel sure, assume paramount importance as soon as our soldiers begin returning from the Tropics, India, etc. This particular topic is concerned with infestation of the brain with gysticercus cellulosae, larva of Taenia solium, with resulting epilepsy.

Infestation of the human brain with Cysticercus cellulosae is a medical curiosity in this country, for the condition occurs principally in sections of the world in which poor sanitation exists. This condition is now, however, being recognized as less uncommon and more important than was formerly supposed. And it seems likely that infestation with tapeworm will be frequent among our armed forces in the Near and Middle East.

Man may harbor not only the adult intestinal worm, but also the larvae which reach the digestive tract in polluted water or food, and then spread by way of the blood stream to the various tissues of the body. The larvae have a predilection for the muscles and the central nervous system, but may invade almost any part of the body (54).

In the central nervous system, the larvae are found in the meninges, the ventricles, the parenchyma of the brain, and occasionally in the parenchyma of the cord (5). In fatal cases, sometimes as many as

300 or 400 cysts have been found in a single brain (67).

According to Dickson and Willis (67), when the parasite is still alive, it becomes surrounded and shut off by a zone or capsule of thickened and proliferated glia and a varying amount of fibrous tissue; and, unless the cysticercus is in some specially vital position in the brain, a species of symbiotic harmony between parasite and host is established, which may last for several or perhaps many years. Thus, serious pathological disturbances result in many instances, only on or after the death of the parasite. As soon as the larvae die and degenerate, they tend to swell from imbibition of fluid, and irritative phenomena supervenes in and around them which is responsible for the cerebral symptoms (67).

Convulsions are the most common of all symptoms, and may be the first noteworthy manifestation of the disease (54). Convulsions, or other nervous manifestations, have been known to occur within a few weeks after infestation with Taenia solium, while, in other cases, it is assumed that a number of years have intervened before the onset of symptoms attributable to involvement of the central nervous system.

Almost all of the cases(the number was not reported), recorded in England, have been in soldiers

or in soldiers' families (67), and, according to Bronson and Ray (54), the average interval between infestation and involvement on the central nervous system is probably five years.

From this rather hasty sketch, we can readily see the importance of the situation, and emphasis should be placed on the necessity of regarding every case of epilepsy occurring in a previously healthy adult who has no evidence of familial or personal epileptic trait, neoplasm, syphilis, or after effects of a head injury, and who has lived for a period in the Tropics, as a probable case of Cysticercosis until it has been proven otherwise (5).

Next in order of importance, in my mind at least, we have the Granulomatous diseases, notable among which are Syphilis and Tuberculosis.

Syphilis, both congenital and acquired, is responsible for many cases of infantile epilepsy, and can create in adults as well as children all forms of epilepsy. In a review of seventeen cases by Himler (28), 14 cases of epilepsy were caused directly by syphilis. Of 553 additional cases reviewed by Himler (28), congenital syphilis was responsible for eleven cases and acquired syphilis was responsible for eighteen cases of epilepsy.

That parental syphilis may give rise to various congenital cerebral defects in children, and is the cause of infantile and juvenile syphilis of the brain, all of which may be accompanied by convulsions, is, of course, well known; but, according to Wechsler (65), it is a debatable question whether the epileptic state "per se" is the direct result of congenital lues. Wechsler further states that the fact that less than 2% of epileptic children show a positive Wassermann reaction does not militate against syphilis as a cause, because it is well known that negative serology is extremely common in congenital syphilitics.

Dandy (41), believes that the incidence of epilepsy with the gummata is about the same as for tumors; Fourier (Quoted by Babolion '4'), thinks that whenever a case is labeled a so called "idiopathic" epilepsy, eight times out of ten it is a luetic epilepsy.

Syphilitic epilepsy has no clinical character which belongs only to it, and therefore specific diagnosis remains quite difficult. Syphilis can also be the cause of epileptiform troubles such as the compressive troubles due to cerebral gumma or to osteoperiostitis of the inner table of the skull (4).

As to the relationship between Tubercu-

losis and epilepsy, specific data is very much in absence, and most authors are content to mention that there is a definite relationship but go no further than that. Dandy (41), however, includes tubercles in the same category as gummata, and says that the incidence between tubercles and epilepsy is about the same as that for tumors and epilepsy. Aside from this short paragraph, the writer is unable to furnish any additional information on this particular subject, with the exception of that presented under the sub-title of "Allergy" on page 50.

We now come to the topic of epilepsy in relation to various infective and febrile states such as meningitis, encephalitis, etc., as causative agents.

Acute infectious diseases as a cause of convulsive seizures are peculiar to early childhood, provided one eliminates from consideration those infectious agents which directly invade the cental nervous system to provoke an encephalitis or menigitis.

The importance of acute infections in this regard is emphasized in this series of one thousand cases of convulsive disorders in children by Peterman (51). In 34 per cent of these cases, respiratory infections and infectious diseases, excluding encephalitis, menigitis, and gastrointestinal diseases, were responsible for the convulsions occuring with fever.

Although convulsive attacks accompany many acute infectious diseases of childhood, inflammatory changes of the nervous system can be demonstrated by the pathologist in only a small proportion. According to Penfield (50), several factors may be of importance such as the severity of the infection and the undeveloped immunological responses of children. The immature condition of the brain is another factor which may account for the difference in susceptibility of the child and the adult to the same infectious disease.

Lack of myelin, difference in cellular permeability, difference in water content, and difference in the electrical activity of the infant as compared to the adult brain are possible factors which might account for the greater susceptibility of the child to convulsions under these conditions (50).

Another possible explanation as to why convulsions frequently occur in children is that given by Wortis (69); according to him, the brain tissue of younger animals has a greater oxygen consumption than that of adults. This factor may be another condition accounting for the especial susceptibility of individuals to convulsions during early childhood when toxic and other factors more easily impair brain oxidation. Zimmerman (71), also favors this mechanism.

So much for generalizations; let us now discuss a few of the more important specific clinical entities.

Epidemic encephalitis rarely causes epileptic seizures, perhaps because the pathological process does not affect the cortex to any great extent (50). Dought (16), reports the case of a boy, aged five, who developed encephalitis during the fifth week of an attack of the whooping cough and who developed epilepsy and mental retardation five years later. However, he is of the opinion the epilipsy is a rare sequel of such encephalitis, and hence is in accord with Penfield (48).

Meningitis of various types is a more common cause. Pigott (52) found 29 cases that could be attributed to a meningitis in a review of 1000 cases of convulsions in childhood. Meningicoccus meningitis in young children frequently begins with convulsions, and may also occur some years later as a result of a healed meningitis (50). On the other hand, attacks are rare in the course of acute purulent meningitis of hematogenous origin, but may occur in benign lymphocytic meningitis.

There are certain infectious diseases such as measles, mumps, vaccinia, varicella, variola, pertussis, and scarletina, which may produce organic lesions in the brain. The actual involvement of the brain may

vary from a slight toxic effect with no demonstrable histological change, to gross cerebral damage. Convulsions, as well as mental deficiency and a variety of neurological disorders, may occur during the acute stage of the disease and continue after recovery (50).

Pertussis frequently effects the nervous system with special severity, so that encephalitis is usually responsible for the convulsions. Hemorraghes and cerebral asphyxia (69), from the paroxysms of coughing, as well as tetany, amy, however, be the cause of convulsions in some cases.

Scarletina is also most important as a cause of seizures in children. Peterman (51), in his review of 1000 cases of convulsions showed that, up to one month of age, acute infection was infrequent cause (8 of 79 cases), in the age group of one month to three years, it was a common cause (24 of 580 cases), from three years to ten years it was fairly common (61 of 251 cases).

IV. Birth Injuries.

It is a well known and appreciated fact that lesions that may be acquired in birth and infancy may serve as causative factors in the production of seizures later in life. In the examination of epileptic patients, the history often records a single, early con-

vulsion, a transient paralysis, a difficult labor followed by a few weeks of unsatisfactory or difficult feeding, etc. Many of these patients have, in fact, received a cerebral injury at that time, which resulted in habitual seizures only years later. This may be unsuspected because moulding of the skull and brain during the first years of rapid head growth, and the ability of the brain to substitute one part for another, may erase the ordinary signs of the injury (50).

Penfield (50), presents an interesting discussion concerning the relationship between head growth in infancy and the subsequent development of epilepsy at a later date. He says that if one of the large cerebral arteries is occluded, the part of that hemisphere which depends on it for nourishment is suddenly destroyed and disappears quickly, with the result that the underlying ventricle evaginates to fill up the dead space. This will eventually result in that particular half of the cranium being smaller than its fellow, with the result that the hemisphere, or hemispheres, depending on the size of the artery occluded, are compressed or lacking. These exist as possible epileptic lesions for some later date.

Therefore, the size of the head and the time of the closure of the anterior fontanel not infrequently give a clue to congenital lesions. Although macrocephaly

and microcephaly may exist, the latter is by far the more common, and premature closure of the anterior fontanel will frequently be the first indication of a microcephalic brain of congenital origin.

Following severe cerebral trauma at birth there is destruction of the cortex, but far more, the subcortex (48). There are also hemorrhages of varying size which must be absorbed. The end-products of this resolution are of two types: 1). Atrophy of the brain and, 2). Scar tissue formation. The final result in either case is a cerebral defect which is just as potent as a "locus minor resistentiae" for the production of epilepsy as any of the lesions already discussed.

Trauma at birth is always regarded by the laity as the source of epilepsy, and is therefore tremendously overrated as a factor (48). On the other hand, it has long been recognized as a fact that convulsions might be the result of birth injury resulting in cerebral compression due to intercranial bleeding (Crathers, quoted by Wechsler '65'). Crathers also showed that fourteen out of every hundred "normal" babies had blood in the spinal fluid. I question the value of this last statement however, as the blood might easily have been due to trauma to the tissues while doing the puncture, etc.

In a group of 553 etiologically classified

cases studied by Pigott (52), 99 cases were definitely attributed to birth injuries, and the age of onset varied from six to forty nine years of age. Ford (Quoted by Keith and Penfield '30'), concluded that in about one third of all children with spastic paralysis due to birth injury, focal or generalized convulsions develop. He also states that epilepsy in approximately 2-3% of all cases is related to birth injuries, but Keith (30), says that this per centage should be considerable higher.

This question of the relationship between birth injuries and epilepsy assumes tremendous importance for us as physicians if we digress for a moment, and look upon it from the medico-legal point of view. Although there are some occasions when this relationship is difficult or impossible to evaluate correctly, the determination can usually be made. Dandy (41), gives us a nice working hypothisis to go on: He says that trauma at birth can usually be eliminated as a cause of epilepsy when the fontanel was known not to have been full and tight, when the child was not blue, when respirations were induced promptly and continued easily and regularly, and when the baby took its feedings at the breast. Conversely, birth trauma must be considered as a <u>possible</u> cause when the anterior fontanel was full and tight, when the baby was blue and respirations had to be induced by stimulation,

and were shallow and irregular afterwards, and when it was necessary to feed the baby with a medicine dropper for several days or weeks.

V. Congenital Malformations and Maldevelopment.

Dandy (12), considers malformations and maldevelopment as the most important cause of epilepsy, and believes that they account for an overwhelming percentage of convulsions occur before the age of twenty-five. He also states that in about ten per cent of his private patients, mental changes also were present in addition to the convulsions-he considers these mental changes inevitably indicative of congenital malformation of the brain.

In a series of 1000 cases reviewed by Pigott, et al. (52), congenital defect was the second largest group of causative factors, and consisted of 110 individuals. This series consisted of patients suffering from microcephaly, macrocephaly, and hemiplegia or monoplegia present at birth with no evidence of definite disease in the mother or birth injury.

The number of cerebral deviations is legion. Macrogyria and microgyria are usually present. At times a large part of a hemisphere may be entirely devoid of convolutions, or there may be marked asymmetry in the size and shape of the hemispheres. Not un-

commonly there are large localized defects in the hemispheres and many cases of partial hemiplegia of congenital origin are due to the gross contraction of part or all of the hemispheres (31).

In a high percentage of epilepsies of congenital origin, mental stigmata of some kind are present, and, therefore, offer diagnostic evidence that the lesions are of congenital type. In perhaps 85-90% of the inmates of most epileptic colonies, the higher grades of mental stigmata are present. In nine cases of convulsions presented by Cosomajor (11), all of them had cerebral hemiatrophy and homolateral hypertrophy of the skull and sinuses. All of these cases were children under fifteen years of age, and in most cases the convulsions were principally on the side of the body controlled by the atrophic or hyperplastic brain.

Another matter frequently discussed in the role that anoxemia in the newborn plays in producing convulsions at later periods of life. In regards to this matter of anoxemia during difficult birth, Penfield (50), believes that if both hemispheres are subjected to anoxemia which is sufficient in degree and duration, the ganglion cells are irreversibly damaged, although the interstitial cells are unharmed. If the respiratory centers are included the child dies of course, but if these

vital centers survive, the child may live although neither hemisphere will grow very much. Here again we encounter the small brain and the damaged hemispheres already discussed on page 39.

Two rather new congenital malformations have recently appeared in the literature, namely, "Tuberous Sclerosis" (70), and "Arachnoidal Fistula" (44), and because they are so consistently associated with epilepsy, I am going to discuss them at some length with the hope that the reader finds them instructive and interesting.

In regards to the first condition, Tuberous Sclerosis: In the way of a definition, it will be sufficient to say that Tuberous Sclerosis is a congenital lesion consisting of whitish or yellowish, hard, nodules (tubera), which may be seen almost anywhere in the cerebral hemispheres and brain stem, but which are distinctly more common in the cortex of the medial wall of the hemispheres (gyrus cinguli), hippocampus, and in the walls of the lateral and third ventricle along the sulcus terminalis (striothalamicus), and the rostral portion of the hypothalamus where they may accumulate and appear like corale gutterings.

In the typical case of Tuberous Sclerosis, the highly characteristic abnormalities of the skin, viz., sebaceous adenoma of the face, 'shagrien' patches in the

sacrolumbar region, tumors of the nail beds, etc., associated with epilepsy and congenital mental defects, permit one to recognize this condition during life at a glance.

The epilepsy, with or without mental deficiency, may be the only clinical manifestation of this congenital abnormality of the central nervous system. Such clinically incomplete or abortive cases of Tuberous Sclerosis are more frequent than is generally believed, the condition being often disclosed unexpectedly at autopsy in cases of chronic, unexplained epilepsy.

It is well known that an outstanding feature of the reflex integration in the fetal nervous system is its extreme unstability; reflex regulation of the steady state of the internal medium by the automatic nervous system is a later, in many respects, a post-natal acquisition. In the light of these facts, it is east to conceive that an impediment in the process of morphologic differentiation of the central nervous system must disturb the time relation between the successive phases of the development of the nervous integration from the loosely connected elementary reflex patterns of the fetus, to the intimately, coalescent, simultaneous and successive combinations of the complex reflex patterns of the mature organism.

There is, as a result, a congenital fragility of reflex action persisting into post-natal life. The epileptic seizure may be regarded as a pertinent example of such congenital fragility of the nervous integration in certain persons.

Indeed, the epileptic seizure reveals two fundamental traits of the nervous system reminescent of the fetal state: first, the deficiency of neurovegatative regulation of the steady state of the internal medium, with a readily resulting state of vegetative vasomotor instability, and second, the paroxysmal dissolution of the cerebrospinal functions into the lower, more elementary, reflex paterns, i.e., loss of consciousness, coma, convulsions, etc.

Applying the general functional implications of developmental defects of the central nervous system given above specifically to the neoplastic malformation of the brain in Tuberous Sclerosis, one is led to assume that the malformation along the zone of cleavage and differentiation of the telencephalic and diencephalic reflex mechanism is responsible for the disassociation in the rhythm and rate of the respective activities of these two levels.

The psychic abnormalities, the peculiar "epileptoid" personality traits, the paroxysmal cerebral

"dysrhythmia" in the form of a petit mal attack, etc., may all be explained on the basis of congenital malformation in the critical zone of differentiation of the reflex mechanisms at the higher levels of nervous integration.

In the case of Tuberous Sclerosis, such an interpretation of the relation between the nature and localization of the cerebral malformation and the epilepsy, as the foremost clinical symptom of the condition, is supported by morphologic evidence. How much of such evidence could be disclosed in cases of so called genuine epilepsy is an open question, nevertheless, the possibility that the basis of idiopathic epilepsy is a congenital, functional, and therefore structural, malformation of the specific reflex mechanism in the brain has occurred to many.

So much for Tuberous Sclerosis. Let us now discuss, somewhat briefly, "Arachnoidal Fistulas" and their relationship to epilepsy.

Arachnoidal fistulas are defects in the arachnoid through which fluid leaks into the subdural space; the brain, losing support, then gravitates to dependent portions of the skull, traction is exerted on the corticodural attachments at the extreme vertex of the brain where the cortical motor centers are located. In time, this traction produces a fairly well localized area of cortical hyperirritability, or epileptogenous zone,

which characterizes lesions responsible for epilepsy. These fistulas are usually located at the extreme vertex of the brain adjacent to the angle of a cortical vein as it turns parallel to the sagittal sinus (44).

At this time, I think it would lead to a far more clearer understanding of this entire picture if we digress for a moment, and discuss this matter of "postural stability of the brain". Two main factors are responsible for maintenance of the brain in a situation of postural stability within the skull: 1), The adhesive action of the normal thin film of subdural fluid which maintains arachnoidodural contact, and 2), A subdural negative pressure, which, when film adhesion is disturbed, maintains the brain in a certain degree of postural stability.

Now, in the presence of Arachnoidal Fistulas, there results an excess of subdural fluid, which disturbs the fluid film adhesions between arachnoid and dura, and cerebral support is then maintained solely by subdural negative pressure. This negative pressure syphons additional amount of cerebrospinal fluid into the subdural space with an increasing degree of cerebral postural displacement. This traction stress results in corticodural attachments and fixations, especially around the large cortical veins at the vertex. These corticodural

attachments are usually surrounded by a hyperirritable zone which reacts to stimulation with convulsions; these corticodural irritations eventually results in an epileptigenous zone.

Ney (44, believes that this condition should be considered as a definite causative factor in the chronic convulsive states, and found this type of lesion in 225 out of 272 cases of epilepsy at surgery.

VI Miscellaneous.

This group is composed of a host of entities with causative factors varying all the way from such conditions as pregnancy and food allergy to hydremia and Vitamin B defficiency. Obviously, all these conditions could not be discussed as time and space would not permit it. Aside from this, a great number of these conditions occur with such rarity that they have little or no practical clinical value. In view of this, I have taken the liberty to list and discuss those possible etiological factors which are the more common and the most controversial, and eliminating entirely those which do not qualify for the above.

1). Allergy.

Spratling (Quoted by Dewar '14'), in 1904, was the first to draw attention to the possible associa-

tion of epilepsy with food sensitization when he noted that patients who acquired Tuberculosis showed a lessening or a complete disappearance of fits. Along this same line, Crockett (Quoted by Dewar '14'), in 1921, treated 23 tuberculous epileptic patients with tuberculin, and noted that 11 of these were free from attacks for more than three months, and one patient, who had 300 attacks in the month preceeding treatment, was free for 19 months.

In the spring of 1935, Lazell (32), made a clinical study of the occurrence of convulsions in relation to certain articles of food, and found that certain of these patients had convulsions in definite relation to the ingestion of certain foods such as pork, eggs, etc. Food diaries of these patients showed that the number of these convulsions occurring in a group of 36 epileptics was increased and decreased in definitely recurring cycles.

Next, he established the connection between the convulsions as recorded in the food diary and sensitization of the individual patient to the corresponding food by the scratch and intracutaneous tests. The results proved, at least to him, that the epileptic is heavily sensitized to certain foods, and the cause and effect relationship between the ingestion of a food to which the patient was sensitized and the occurrence of the convul-

sion was definitely established.

Two years later, Clein (51(, reported the successful treatment of six cases of epilepsy, 3 of Grand mal, and 3 of Petit mal. They were all entirely or greatly relieved by treatment on the basis of an allergic etiology.

In the same year, Bray (quoted by Dewar '15'), however, was unable to obtain a single positive reaction to the skin test in 30 epileptic children. He has never been able to substantiate the view that many unexplained epilepsies are, or might be, a sensitization disease.

Among the most recent investigations along these lines, was that done by Dewar (14), in 1941. A careful analysis was made of a group of 24 adult epileptics in whom there was no history of birth or subsequent trauma, and to whose disability no cause could be attributed. It was found that the presence of allergic phenomena was a marked feature of this group. Sixty per cent gave either a positive personal or a positive family history of allergy, while in twenty per cent of the cases positive findings occurred in both instances. This group was then treated for protein sensitiveness, and 14 were positive.

Of this group, 12 were available for treat-

ment: they were given a course of elimination and desensitization for one year. Nine of the twelve showed definite improvement-in one instance, there had only been a single seizure in the past year, whereas, prior to the treatment, the monthly average had been eight.

From this, it would appear that epileptics exhibit an allergic phenomena common to them as a group (14). Nevertheless, it still remains doubtful whether convulsions arise from the presence of this hypersensitivity, or whether there is a primary factor which predisposes the brain center, so that the allergic reactions act merely as a secondary stimulus. Again, it may be that the circulating protein picks out for choice the weakest structure of the individual's economy, which, in the potential epileptic, will be the central nervous system, and, by irritating it, initiates convulsions.

Ward (Quoted by Dewar '15'), maintains that the relation between food sensitization and epilepsy is clear, and says that if an effort was made in every case of infantile convulsions to find the offending protein, many cases of future epilepsy would be aborted. He believes that the periodicity of attacks is due to accumulation of protein poison within the organism, and that the precipitation of fits varies according to the sensitivity of the nerve center, and the amount of foreign

protein gaining entrance to the circulation.

2). Vitamin B Deficiency

Here again the literature is quite deficient, and what few results have been recorded, have been attained chiefly along the lines of animal experimentation.

Recent studies in the laboratory for experimental psychology at the University of Pittsburgh, have demonstrated clearly that the vitamin B complex deficiencies and enanition both induce sensitivity to epileptoid seizures (31). Along these same lines Chick, et al. (9), observed fits of an epileptiform nature in a series of 20 rats for long periods-4 to 5 months or over-on diets lacking in vitamin B. These fits were prevented and cured by daily administration of vitamin B. As to just how much all this means in relation to the etiology, and perhaps even to the treatment, of epilepsy, we will have to wait until more work has been done.

3). Biochemical Factors:

Attention has turned in recent years to an explanation of the cause, or the causes, of epilepsy in terms of biochemical and physiologic dysfunction. And certain facts have been accumulated which clearly demonstrate the rise and fall of irritative susceptibility of the nervous system in relation to certain biochemical shifts. (46).

Twenty years ago an osteopathic practicioner observed that prolonged starvation had a restraining effect on convulsions. The suggestion was early made that this autocannabalistic diet might be replaced by one which simulated starvation, a diet containing a plethora of fat and a minimal amount carbohydrates and protein. This ketogenic diet proved as effective as fasting and more practical. Early investigators assumed that the diet was beneficial because of the sedative action of ketone bodies (34). However, acidosis induced by other means such as the administration of large quantities of Hydrochloric acid or of acid forming salts was found to inhibit seizures; this was later explained on the basis that acidosis or ketosis will decrease the irritability of the cortical cells (46).

Conversely, alkalosis, induced by over-ventilation or by ingestion of large quantities of alkali, tend to precipitate seizures. Thus for many years, workers have attempted to show that voluntary hyperpnea can produce seizures in a patient with epilepsy.

In 1940, Lennox, Gibbs, and Gibbs (36), reported that when over-ventilation resulted in a seizure, the latter was almost invariably a Petit mal seizure, but that they had never observed Grand mal type of seizure to be so produced in several hundred trials. In a recent

series of 146 epileptic patients studied by Robinson (57), only 14 had a seizure during or following a 6 minute period of hyperventilation. The seizures were Petit mal in 2 cases and occurred in 11 on hyperventilation, and in one after hyperventilation.

Numerous theories were advanced to explain this phenomena. Study demonstrated no abnormality in the acid-base balance of the epileptics, but only that an acute upset of the patient's balance would alter the frequency of his attacks (34). Palmer and Hughes (46), explained the mechanism on the basis that alkalinity, and more specifically alkalosis, increases the irritability of the cortex of the brain, and, in predisposed persons, hastens the development of convulsive seizures.

Lennox (quoted by Simpson '61'), on the other hand, suggested that due to the alkalosis, the blood gives up oxygen less readily, thereby causing oxygen lack in the tissues, with resulting convulsions. On the basis of this premise, it should be possible to predict the occurrence of seizures as the result of voluntary hyperpnea. A review of the literature shows a great lack of agreement as to the incidence and mechanism of seizures produced by either hyperventilation or anoxia. And Simpson (61), is of the opinion that anoxia per se does not seem to be a factor in the production of epileptic

seizures.

Continued investigation disclosed also that disturbance of the acid-base balance is only one of various factors which may alter the frequence of seizures (34). In patients subject to Petit mal attacks, these seizures could be induced by mild degrees of anoxemia, and could be inhibited by increasing the oxygen tension in the patient's tissues (46).

McQuarrie (Quoted by Lennox '34'), studying along different lines, was able to induce seizures in epileptic patients by a large fluid intake combined with injections of pitressin. This then led to the theory that hydremia and increased blood volume might be classified as a causative agent of epilepsy. Against this work however, we have the later studies of Stone, et al. (62), who, in a series of 31 patients, 2000 cc. of water was drunk by each patient in 15-30 minutes and pitressen was given hyperdermically before and after the water drinking, he was unable to produce convulsions in a single instance. He also brings out the fact that convulsions are not described as a part of the clinical picture in a frank case of nephrosis marked by considerable and prolonged edema, hypoproteinism, and increased blood hydration.

The facts that fasting and a high fat and a low carbohydrate diet are known to benefit patients

with epilepsy, and that the procedure brings about a change in the concentration of blood lipids (1), have led to the investigation of the vital lipids as an etiological agent.

Of all these various lipids, cholesterol has especially been studied, and men such as Targawla, Berman, etc., reported hypercholestremia in patients with epilepsy. They concluded however, that the rise in cholesterol is secondary to disintegration of brain tissue rather than to any specific pathologic state.

In summing up the biochemical etiological aspect of epilepsy, it might be said that such biochemical phenomena such as anoxia, anemia, hydration, increased blood lecithin (Barnstein, quoted by Guchot '1'), increased blood guanidine (46), increased cholesterol, and all the rest, are, in themselves, not primary causes of epilepsy, but should be regarded as only precipitating factors. The secret of epilepsy lies in the chemistry of the discharging neurons of the brain.

4). Vascular Accidents:

Other causes of epilepsy are embolic and thrombotic disturbances in the blood vessels, and, in later life, arteriosclerosis closes the vessels and the resulting defect is the source of subsequent convulsions, so called "senile epilepsy" (19). Aneurysms of the brain are another

common cause. In 333 cases of convulsions reviewed by Himler (28), 36 were attributed to one of the above mentioned etiological factors.

Thrombosis and embolism may occur at any time during life, and result in extensive and permanent loss of brain tissue. The resulting cerebral defect is subsequently the cause of epilepsy in many cases (41). Following a severe drop in blood pressure, as in shock from trauma or surgical operations, cerebral thrombosis and subsequent epilepsy is not uncommon.

In later life, arteriosclerosis may occlude vessels of any size in the brain, leading to precisely the same effect as thrombosis or embolism. The end result of arteriosclerosis is one of the two principle sources of epilepsy in adults, brain tumor being the other (41). The so-called "senile epilepsy" of advanced years is due to atrophy of the brain from arteriosclerosis. However, according to Wechsler (65), atrophy of the brain in the aged and cerebral arteriosclerosis are rare causes of epilepsy.

According to Dandy (41), arterial aneurysms of the brain only occasionally cause convulsions, and usually only when the aneurysm is in the interior of the brain and is of large size. Most of the arterial aneurysms arealong the great arterial highways at the base of

the brain, and in any of these positions, lesions rarely cause epilepsy (41).

On the other hand, arteriovenous aneurysms nearly always cause epilepsy. Perhaps it would be safer to say that, with few exceptions, arteriovenous aneurysms anterior to the tentorium have been discovered through epilepsy as the outstanding symptom. Most of the convulsions were Jacksonian or, at least unilateral. Transient paralysis after attacks is frequent with this lesion, and also with the cavernous angioma, which, in many ways, the arteriovenous aneurysms resemble.

5). Cerebral Blood Flow:

According to Watterson (64), decreased cerebral blood flow thru vasoconstriction, has often been thought to play an important role in causing or precipitating epileptic convulsions. Along this same line, Kalinowsky and Kennedy (29), presented the observation that a symptom frequently occuring immediately before the onset of electrically produced convulsions was constriction of the retinal vessels, which vessels are an index for the state of the cerebral vessels. These findings were anticipated because they correspond to the initial vasoconstriction in the cerebral vessels, first described by Kennedy working on the brain exposed at operation.

Among recent observations in this connect-

ion, is one which might be thought to support the contention that cerebral anoxemia produced by circulatory disturbance, is an important causative factor in convulsive states. This is supported by the observation that certain induced convulsions are inhibited by the administration of vasodilator drugs (64).

Penfield (29), however, believes that proof of constriction of cerebral vessels at the onset of an ordinary seizure is quite lacking. He goes on further to say that in cases of convulsions induced by electrical stimulation, as was done by Kalinowsky and Kennedy (29), one might well expect that the vessels themselves might constrict at time of stimulation, but in ordinary seizures, there is no good evidence of preliminary construction. As far as his experiments went, he was unable to find any decrease in the blood flow at the time of the seizure or just preceding it. In fact, in his experiements (60), in all cases of electrically produced convulsions, it was found that during the seizure there is an <u>increase</u> in circulation within the circumscribed area of the cortex which is involved in the discharge that produces the fit.

Against this, we have the evidence that during an epileptic seizure in man, the most frequently observed objective change in the brain is the cessation of visible pulsations of the pial arteries-this however,

is not due to decreased blood flow (60).

Santha (60), sums the situation up by saying that evidence, at present, indicates that vasospasm plays no role during a seizure, nor is the evidence of widespread anemia following it of any consequence. Vascular spasms may be concerned in the pathological background of epilepsy, but they play no role in the actual mechanism during a seizure.

6). Epilepsy and Heart Disease:

That heart disease may be of importance in the production of convulsive seizures has been known since the studies of Littre (21). However, no great importance was attached to this relationship until during the last decade, when a number of cases began to be reported in the French literature under the term of "Cardiac Epilepsy". The patients, ranging in age from 5 to 60 years, developed convulsive seizures which in many instances resembled idiopathic epilepsy (7). On physical examination there was present, in the majority of cases, chronic, rheumatic, cardiovalvular heart disease.

The epileptic seizures had made their first appearance from 3 weeks to 11 years after recovery from Rheumatic fever. Prior to the first attack of acute articular rheumatism, none of the patients had had a single convulsion. Other possible factors which might have

caused the seizures were not present, and there was no familial history of epilepsy.

The question was then raised whether the chronic rheumatic valvular lesion could be linked with the epileptic seizure. In an attempt to determine whether rheumatic heart disease is of etiological significance in the production of seizures. Foster (21), reviewed 2,153 patients with rheumatic heart disease. Of these, 29 had an associated diagnosis of a convulsive disorder-in all of these cases, all other epileptogenic factors had been ruled out. Since a goodly number of these patients were in the early stages of the heart disease, this figure is probably too low; 18 of the 29 patients had the onset of the seizures after the age of 30, and many of them had not reached the age of 30.

In recent years, several theories have been advanced as to the possible mechanism of the convulsions, but it is now generally believed that the epileptic convulsions in these patients are the result of an obliterating rheumatic arteritis of the cerebral vessels (Affecting particularly the small meningeal-cortical vessels.), with their dependent gross and microscopic areas of cortical infarction (7). The possibility of this complication appears to be ever present in individuals with rheumatic valvular disease, although, wide-

spread and clinically manifest obliterating arteritis, seems to occur only in a smaller number of such patients (7).

Foster (21), on the other hand, offers a somewhat more extensive view on the possible etiological mechanism. Since he was unable to find any single, constant, feature in the series of patients studied by him, he interpreted this to mean that there are several mechanisms associated with the rheumatic state capable of producing seizures in the predisposed person. Among these he mentions such conditions as paroxysmal cardiac arrythmia, passive congestion of the cerebrum, delayed auriculo-ventricular conduction time, cerebral infarction, etc. The possibility of an old rheumatic encephalitic scar, however, should not be discarded in patients who develop epileptic convulsions following chorea, or in the wake of Rheumatic fever, particularly if there were delirious episodes during the febrile period (7).

The fact that the majority of cases of Rheumatic fever show no convulsions, can be explained by the findings of Foster (21), who showed that the familial incidence of convulsive seizures appears in the case of Rheumatic heart disease with seizures 6 times as frequently as in cases of Rheumatic heart disease without seizures.

7). Endocrine Disturbances:

In both men and women, especially in the latter, in a review of the literature on epilepsy in which basal metabolic rates were estimated, there is a preponderance of low readings. These statistics are significant in emphasizing the frequency of an associated hypothyroidism in cases of epilepsy. Confirmatory also, is the increased cholesterol content of the blood (9).

In the above authors three cases of a mother and her two daughters who suffered from migraine and epileptic attacks, and who also showed a hypothyroidism, all were free from attacks of either as long as they stayed on the daily use of thyroid, and showed remissions only when they failed to do this. The above two paragraphs were all the literature that I was able to find on the possible relationship between epilepsy and thyroid disturbance as a possible etiological factor.

Hypoglycemia has been thought to be a possible cause of epilepsy; this view was based on the observation that epileptics who have diabetes seem to have fewer seizures when their diabetic condition is the worst (33). After many studies, the conclusion has been reached that, although epileptic persons might show labile blood sugar levels, hypoglycemia per se is only rarely a cause of seizures (26).

At Marson State Hosp., Palmer, Mass., only two cases have been seen to date which could be diagnosed as hypoglycemic epilepsy. A significant factor in the recognition of hypoglycemic epilepsy is the time relationship of symptoms to the ingestion of dood; convulsions occur predominantely during the fasting state. Symptoms tend to occur several hours after the meal, especially if the body carbohydrate stores are depleted by exercise. For the same reasons, convulsions are apt to appear at night when the patient is asleep.

From these observations, Hadley (26), is of the opinion that, although rare, hypoglycemic epilepsy does occur, and should always be kept in mind as a possible etiological factor. Dandy (41), in marked contrast, is just as firm in his convictions, and believes that epilepsy cannot be accounted for in any way whatsoever on the basis of a glandular dysfunction, no matter what the type or how serious the disturbance. Here again the reader must decide for himself what course he is to follow.

8). Pregnancy and Eclampsia:

In both these respects the literature is quite lacking and very inadequate; however, we have a report of 6 cases studied by Pigott, et al., (52). In only one of these cases did epilepsy follow a still-birth,

and in the remainder of cases occurred during the pregnancy with the onset occurring in one individual six days after having given birth to a baby.

Hadley (26), reports a case following eclampsia which developed into a permanent convulsive state. In both epilepsy and eclampsia with water retention and possibly an increased permeability of the nerve cell membranes, edema is produced. According to Lennox (Quoted by the same author.), the physiological changes which tend to precipitates seizures of epilepsy are poor oxygen supply, alkalosis, and increased intercranial pressure. All these changes are found in both eclampsia and epilepsy, thus we have a possible explanation of the mechanism of the relationship between pregnancy, eclampsia, and epilepsy.

9). Reflex Epilepsy:

I thought it fitting to bring to a close this discussion of the miscellaneous etiological factors of epilepsy, and also of the general subject of epileptic etiology, with a presentation of a resume of an interesting piece of work done by Allen (2), on the subject of Reflex Epilepsy, a clinical entity, the existence of which is completely denied by many authors notable among which is Wechsler (65). To me, Reflex Epilepsy, and the possible mechanisms of its production, is the

most interesting and most intriguing of all the epilepsies, and offers the most opportunities for new studies and investigations.

According to Allen (2), Reflex Epilepsy may be defined as the condition in which an individual sensory stimulus precipitates an epileptic attack. The following results and conclusions are based on the study of 12 cases of Reflex epilepsy.

Attacks occurred in response to touch, to pin-prick, to light, and to sound. In over two thirds of the cases, surprise was undoubtedly an essential factor. Knowledge that the stimulus was about to be applied prevented the appearance of attacks after the stimulus had been applied. Further, after the production of an attack or of a series of attacks, the application of the usual stimulus failed to produce an attack during a period which varied in duration with the individual patient.

In a few cases, stimulation by cotton, wool, or pin-prick anywhere initiated an attack: there was no special areas from which the above attacks could be produced. In one case, attacks followed the application of these stimuli to any part of the surface of the body, but they occurred much more easily when one particular area (limited area of face, forearm and hand on one side, etc.) was stimulated. The author has record of only three

cases in which visual stimulation was affected. In one case, unexpected shining of a bright light on the eyes precipitated an attack. In the second case, the sight of a piece of paper turning over without noise caused an attack. In the third patient, a moving object in the right half of the visual field was the active stimulus. In Granberg's (2) own case of unilateral visual phenomena to the right following thrombosis to the left cerebral artery, closing of the eyes or the placing of an opaque lens over the right half of the visual field caused then to disappear.

In one third of the cases, sudden, unexpected noise, which need not be loud, was followed by an attack. In one case there was a scarring of the posterior end of the left second temporal convolution, and stimulation of the edge of the area resulted in an attack identical with that which followed unexpected noise.

In the majority of the patients studied, there was no structural lesion of the brain, and the sensory stimulus was effective only when applied in a particular area, which was sometimes very limited in extent and always constant for the individual patient. In many of these cases, the motor attack began in the neighborhood of the part where the application of the stimulus was most effective. This was so even when there were other

areas from which the attack could be initiated. This is clear evidence that the association between the stimulus and the motor discharge was at the cortical level and not lower. In the small group of cases in which there was a structural lesion of the cerebral cortex or of the cerebral hemispheres, the area of the skin to which the stimulus was applied and was effective, was related physiologically to the area of the cerebral cortex in which the lesion was found.

In the group of patients in whom individual attacks were preceeded by an awareness of fear, none of them had any control over the frequency and severity of the attacks by treatment over a long period of time. Investigation of the personal background of each patient showed that in each case, an association of fear with other factors which had become related to the attacks was fully exposed. The full exposure of the association was followed by complete control of the attacks in the usual way. It was evident, that the original emotional tone (fear), which had formed part of the association, had been able to aggravate the expression of the epileptic tendency in the form of attacks only when the original association and the emotion were not appearing fully in consciousness.

According to the author, these facts indicate the numberof factors involved in the appearance of

the individual epileptic attack and gives a glimpse of the conflict between excitation and inhibition at the level of the cerebral cortex, and show how abnormal increase of excitation or arousing of a forgotten emotional factor will throw the balance to the side of excitation.

From the above, the author concludes that in the patient in whom the epileptic tendency is present, a condition of unstable balance may exist between the inhibitory effect of the higher cerebral cortex level and the excitability of the sensorimotor level of the cerebral cortex. Whether the inhibition or the excitability produces a disturbance of the normal function depends upon the readiness of the inhibition and upon the rapidity with which the excitability is rising.

Thus we have covered quite exhaustively the literature since 1937 on the possible etiological factors of epilepsy. Personally I have a much more secure knowledge and foundation of this vast subject than I had before undertaking this work, and hope that anyone reading this might pick up at least a few illuminating and helpful "nuggets".

We will now proceed to the second half of this paper, namely, the relationship between epilepsy and heredity and race.

EPILEPSY AND HEREDITY

Ever since Hippocrates expressed the opinion that epilepsy is a familial disease, the inheritance of epilepsy has been a subject for a great deal of debate and discussion (37). As a result, many publications have appeared in the literature concerning this particular problem, but it is difficult, if not impossible, to draw any conclusions in regard to the inheritance of epilepsy from most of the early literature because of the lack of a unified plan of collection of data, and because of too great a reliance upon institutionalized cases. For example, Staber (Quoted by Penfield '50'), says that inheritance in ten or twenty per cent of epileptic patients found in institutions may be quite different from that in the larger number of patients seen in ordinary hospital or private practice.

By way of introduction, it might be well to refer again to a statement appearing earlier in this work (Page 8): In the light of new knowledge of epilepsy gained thru the use of the electroencephalograph, the term "genetic" is sugged as a substitute for "essential", "idiopathic", or "cryptogenic" epilepsy, and the term "acquired" for "symptomatic" epilepsy (33). This terminology has the advantage of placing epilepsy on the same footing as other metabolic diseases, while the words "idiopathic" or "cryptogenic", on the other hand, imply an origin which

is mysterious and unknowable, a sort of spontaneous combustion of devastating symptoms. The term "genetic" however, implies predisposition, or more specifically, genes and chromosomes and their chemical substances which, even if they cannot be seen, can at least be visualized. "Acquired"is entirely distinct from "genetic", and yet the processes are complementary.

Modern geneticists emphasize what glinicians have postulated for centures, namely, that heredity and environment are complementary factors whose joint action produce many of the ills which beset body and brain. Diabetes, hypertension, tuberculosis, obesity and cancer are but few examples of scores of disease conditions which are both transmitted and acquired.

Although in the great majority of patients, both factors are at work, their relative importance varies from patient to patient. The case is rare in which only heredity or only an acquired cause is responsible for seizures. In fact, according to Lennox (35), in three fourths of patients, the genetic forces seem to prevail and in one fourth, one or more of the environmental factors.

Nevertheless, these two categories are clinically useful, if, when we speak of either genetic or acquired epilepsy, we recognize the probability that acquired or

genetic factors respectively are also partially responsible. This point must always be kept in mind, because a comprehensive and effective program of treatment must be based on a recognition of multiple causes in the individual patient.

In studying heredity in nervous and mental diseases, it has proved useful to study not only the incidence of identical clinical entities in other members of the family, but also to observe the occurrence of other personality or physical trends which appear to be related in some way to the disease under study (63). Such characteristics may be found in many members of the family who may, nevertheless, not manifest clinical evidence of the disease itself. In studies of heredity, it is obviously important to study not only the direct line of descent with regard to the factors under analysis, but also the total family, including siblings, where the latent element may possibly occur.

Though the opinion that heredity is an important influence in epilepsy is widespread, modern authorities (72, 36, 50, etc.,), are, for the most part, in agreement that epilepsy as such is not hereditarily transmitted, but it is usually stated that a special predisposition to epilepsy is inherited.

Like an underground stream, the predisposition to

seizures can flow unrevealed and unsuspected thru numerous generations, and then suddenly, assisted perhaps by some injury to the brain, appear in certain individuals as epilepsy. This predisposition carried as it is in abnormal genes, has never been demonstrated in the clinical laboratory (36).

There are reasons for believing that a study of cortical electrical activity might clarify the problem of inheritance in epilepsy (36). This cortical rhythm, as recorded by the electroencephalograph, is a fundemental constitutional characteristic. Evidence of this is the individuality of each persons electroencephalogram and, what is more convincing, the similarity of the electroencephalograms of similar twins (Described more fully in the following pages.). This similarity is observed both in twins with normal and in those with abnormal records.

Now, since epilepsy is a paroxysmal cerebral dysrhythmia (see preceding section), it should, if it is a constitutional characteristic, be demonstrable in persons who have no epilepsy but only the predisposition (36). Furthermore, although the frequency of the electrical waves of the brain vary with changing activity of the brain, an inherited disorder, which was present in the parent before the conception of the child, should persist throughout life.

The development of electroencephalography has revealed that abnormal electroencephalograms can be found in epileptics, not only during seizures, but also in many cases between seizures (63). Considering the findings in the electroencephalograms as possible evidence of either the manifest or the latent existence of an epileptic tendency, it seemed important to study to what extent electroencephalographic abnormalities are present in the relatives of known epileptics.

On the basis of these premises, electroencephalographic studies have been made by numerous investigators in the field on both the epileptics and their non-epileptic relatives, and it is with these findings that we shall next concern ourselves.

Robinson (56), conducted electroencephalographic studies on fifteen known epileptics and thirty of their non-epileptic relatives, consisting of twenty five parents, fifteen siblings, and one maternal aunt. In all cases tracings were recorded during a period of quite rest, and during a six minute period of hyperventilation. None of the patients or their relatives had a seizure during the recording.

Of the fifteen epileptic patients, the electroencephalograms of twelve (80%) were abnormal and that of one was doubtful. Of the thirty six relatives of the

epileptic patients, the electroencephalograms of thirteen (36 %) were abnormal, and those of ten (27 %) were questionable. Thus, judged by broad criteria for normality, an appreciable number of this small group of relatives showed aberrant electroencephalograms.

Strauss et al (63), conducted similar studies upon ninety three parents and siblings of patients diagnosed as idiopathic epilepsy. In general, the records revealed two family groupings. One family group consisted of those cases in which several persons with abnormal records were found. The other group consisted of those in which the relatives did not show any evidence of electroencephalographic abnormalities. Thus it is clear that the abnormal records were not equally distributed throughout the various families.

The number of relatives studied varied from one to seven in the various families. Of the 93 relatives examined, 30 were parents of the epileptic patients, and of these, 7, or 23 %, of such parents showed abnormal records. Of the 63 siblings of the epileptic patients, 18, constituting 28.6 %, gave abnormal records. Of the 31 epileptics whose families were examined, at least one person with an abnormal record was found in 14 cases, or 45 %. Definite abnormality of at least one parent was present in 8 cases, or 34.8% of the 23 cases in which one or both parents were

examined. Abnormal records in at least 1 sibling in 11 were found or 46 % of the 23 cases in which the siblings were examined.

As a result of these studies, it is evident that many subjects with abnormalities of the electroencephalogram can be found in the families of some epileptics, and also that similar abnormalities are not found in the families of other epileptics. On the basis of these two groups of findings, it seems possible that in time, on the basis of the electroencephalogram, at least two forms of epilepsy may be established; one with abnormal brain potentials in the family, and one without abnormal brain potentials in the family (63).

Further studies are being made by this same group of men to determine whether these two groups of patients, as determined by the incidence of abnormal electroencephalographic findings in their families, correspond to the two groups, which, on careful clinical examination, might be separated out into the idiopathic and the symptomatic convulsive disorders. These results should prove interesting, but as yet have not appeared in the literature.

Lennox, Gibbs, and Gibbs, (36), ran a similar series of cases and obtained results quite closely approximating those of Strauss, et al (63). They recorded electroencephalographic tracings in 138 parents, children, or siblings of patients with epilepsy, and obtained de-

finitely abnormal records in 54 % of the relatives, against 6 % in a control group who were unrelated to epileptic persons. In 46 % of the families, records were made of both parents, and in 94 %, at least one patient had abnormal records. One fact was especially interesting and that was that the degree of abnormality varied considerably, and that occasionally a normal parent had a worse looking record than his epileptic child.

In another series of cases conducted by these same workers (37), 183 relatives of 94 known epileptics were examined. Sixty per cent had definite dysrhythmia, and 8 % had records which were classed as questionable. Therefore, on 32 % of these near relatives had electroencephalographic records which were unmistakably normal.

This same problem was approached with a somewhat slightly different viewpoint by Lennox (38), when he investigated a number of cases on the basis of the relationship between seizures and mental defects. He is of the opinion that seizures and mental defects are related genetically, and hence, both seizures and mental impairment should be present in an unusual number of blood relatives of epileptics. Furthermore, the number of affected relatives should be greater of the patient's seizures were "essential", that is, if they began early in life (As this is indicative of hereditary influence),

and if impatient of the patient's mentality was congenital.

According to Lennox (38), in the so-called "essential epilepsy", the seizure tendency is inherent; it is hereditary. In "symptomatic epilepsy", the factor of hereditary, as judged by the number of relatives affected, is less than one half as great as in the essential group. If seizures and mental defect have a genetic linkage, persons who have essential epilepsy should have more relatives with mental impairment than patients who suffer from symptomatic epilepsy.

In 10,902 relatives of 1845 epileptic patients analyzed with this in mind, it was found that the number who are mentally defective is greater if the patient's epilepsy is essential.

On the understanding that an early onset of seizures indicates increased heredity, further evidence is obtained by breaking down the data on the basis of the age of patients at the time of the first seizure. In both groups of patients, those who are mentally defective, and those who are normal at birth, an early onset of epilepsy is associated with a high incidence of epilepsy among the relatives. Along this same line, we have the opinion of Penfield (50), who has found that the age of onset is earlier among deteriorated patients found in institutions than in the collected groups seen in practice or in the

hospital clinics.

Of 387 relatives of epileptics (the number of epileptics was not given), studied by Lennox (38), 8.8 % of the relatives had epilepsy if the patient's attacks began before the age of 5 against 3. 9 % if seizures began after the age of ten. In patients mentally normal at birth, the corresponding percentages are 4.3% and 1.9 %. Patients deficient at birth who became epileptic before the age of 5 had nearly 9 times as many relatives with epilepsy as patients who were normal at birth and became epileptic after the age of 30.

And so I could go on listing numerous other authors and their statistical and experimental data, but I fear this would only serve to bore the reader. I think it will suffice to say that the majority of authors and workers in the field are of the opinion that there is sufficient evidence to substantiate a close relationship between epilepsy and heredity. In fact, I was able to find only one investigator who is not of this opinion (72). He goes on to say that the basis for the hypothesis that a special predisposition to epilepsy is inherited has three premises: In the first place, epilepsy is said to be so infrequent an occurrence in brain lesions, e, g., head injuries, as to be less readily explained on an acquired basis than by hereditary predisposition. Moreover,

there is no constant brain lesion which causes epilepsy. Secondly, the incidence of epilepsy is reported as being greater among the relatives of epileptics than among the relatives of "normal" controls. Finally, recent statistical studies of epilepsy in twins favor an hereditary predisposition. The evidence for each of three premises as presented by the author (72) will now be considered separately.

In regard to the first premise, namely the relation of cerebral lesions to spilepsy; The old dictum that epilepsy complicates brain lesions only rarely has been shown to be inaccurate in the face of modern statistics. This author adds nothing materially new to this paper with this statement, but merely substantiates the work of various other men (37, 50, etc.,), quoted in the section on etiology, and says that, to the contrary, convulsions are a frequent manifestation in cases of brain injury and tumors, and particularly so if the lesions are in the anterior portions of the cerebral hemispheres. These facts do away with the necessity of assuming a hereditary predisposition to explain why certain lesions of the brain are associated with convulsions and others are not (72).

In regards to the familial incidence of seizures, Ziskin (72) states that statistics on the family trees

of epileptics purporting to show an increased incidence has been presented as evidence of an hereditary factor. According to him the evidence should be evaluated from two standpoints: First, is there actually a familial preponderance, i. e., are the statistical data adequate? Secondly, does an increased familial incidence necessarily indicate an hereditary influence? Furthermore, the statistical reports on the frequency of epilepsy in families show no uniformity, hence the necessity for controls. In addition, the number of children similarly affected in families of epileptics is reported by different investigators as high as 50 % and again by others as los as 0.29 %. Where the results vary so greatly, one is at loss to know how to evaluate the figures and profound skepticism is justifiable (72).

In regards to the second query, familial predominance of an illness is by no means proof of it's hereditary character. Many acquired causative factors may be latent within the family group. For example, the family incidence of Tuberculosis is well known, but this is not accepted as evidence of the hereditary character of this disease. In regards to this point, Lennox (Quoted in the same article), says that the data on Tuberculosis is very apt, but everyone knows that there is an hereditary factor as well as a genetic factor in the etiology of Tuberculosis.

As for the evidence gained from the study of twins, Ziskin (72), states that although studies in epilepsy show a greater degree on involvement of both members of monozygotic twins than in dizygotic twins, this concordant predominance in the identical twins can well be due to acquired factors as well as to a genetic influence, and hence is not proof for an hereditary etiologic factor.

I personally, do not place much worth on this author's work. In the first place, I think that the evidence yielded by each of these three group studies (cerebral lesions, familial studies, and twin studies), is in itself, of course, inconclusive, but that the evidence taken as a whole, however, points so consistently to the existence of an hereditary factor, that it seems to offer a definite preponderance for, rather than against, heredity in the etiology.

Out of all this maze of statistics and figures, there is one problem which presents itself which, in the writer's opinion is the entire basis for the work already done and still to be done in the field of epilepsy and heredity. That is the question of marriage and epilepsy.

The doctor is often asked no more insistent or difficult question than this: "Should I, an epileptic, or the relative of an epileptic, marry and have children?

Certain stock answers built from statistical data can be given to the inquiring patients such as that epileptics occur in about 2.8 % of the near relatives of non-institutional patients, or five times more frequent than in the general population, et cetera (39).

However, the chances of having epileptic offsprings are lessened by other numerous and various circumstances; if the patient has no family history or epilepsy or migraine, if he was mentally normal at birth, if his seizures began late in life, if a history of brain injury ante-dated the first seizure, and above all, if he marries a person who carries no predisposition to seizures. These criteria are at best of presumptive value, but to those who are most interested and want an individual and not a general answer, of what help is the electroencephalogram?

Obviously, to the insistent question about heredity, the pulsations of the brain can give no answer if these pulsations are the result of environmental conditions. And this fact must be constantly kept in mind in order to correctly interpret any electroencephalographic tracings (37).

A series of twenty twins (twelve identical), who gave a history of convulsions, were studied by Lennox (39). In each of these twelve twins the brain wave records of the epileptic twin and of his non-epileptic

co-twin were alike with respect to being normal or abnormal and with respect to the underlying dominant rhythm. However, if the epileptic member had suffered brain injury or if his seizures had been present for many years, his brain wave record presented abnormalities not found in the record of his normal twin (39).

As a result of these observations of twins affected by epilepsy, the authors (39) are of the opinion that essential epilepsy develops on the basis of a pre-existing cerebral dysrhythmia. Each of the identical twins had a predisposition as evidenced by the dysrhythmia, but the brain of the epileptic twin received some injury or underwent some physiologic upset which caused the dysrhythmia to be expressed in overt seizures.

This latter statement causes us to digress for a moment and wonder about the possibility whether relatives of epileptics, clinically non-epileptic, showing abnormal electrical patterns may develop overt seizures at some other time. This would seem to be especially important in those young siblings of epileptics, in which the abnormal electroencephalographic findings are present even though overt seizures have not yet occurred. According to Strauss et al (63), it seems highly probable that only a small per cent of relatives with abnormal electroencephalographic findings ever develop overt clinical seizures.

But to get back to our study of twins (39). These investigations were then extended by making electrical records of other members of the immediate family of the epileptic patients. Of the 312 relatives examined, brain wave records were judged to be abnormal in 52 % of the cases. Both parents were examined and in 27 % of these families both parents had abnormal records, and in only 8 % were the records of both clearly normal.

Epilepsy has long been recognized as a recessive mendelian trait, but the studies of Lennox et al (36), suggests the possibility that cortical dysrhythmia, the essential manifestation of epilepsy, may be a dominant trait.

Since epileptic persons form about 0.5% of the population (36), those predisposed to epilepsy or a kindred disorder would number about 10 %. Thus, a mating of two predisposed persons by the laws of chance would occur only once in a hundred matings. Yet, in a series of studies conducted by Lennox (36) definite cortical dysrhythmia occurred in 28 % of the families. In view of these findings, the authors recommend that if an epileptic marries, he should choose a person with normal brain waves. Marriage is safer by far for such a pair than for two persons whose personal and family history are free of seizures, but who both have cortical dysrhythmia.

Leaving the sea of brain waves and statistics, what can we conclude about the heredity of epilepsy? Lennox (39), says that epilepsy per se is not inherited, but a "predisposition" or "tendency" may be inherited. This predisposition (heredity) lies dormant until activated by injury or some serious disturbance of the brain (environment).

Evidence collected suggests that an abnormal brain wave pattern which is constitutional and not acquired may indicate a predisposition to epilepsy or some other disorder associated with cerebral dysrhythmia (63). If this suggestion is confirmed, we may be able to advise epileptics, patients and their relatives about children on the basis, not of general statistics, but of actual observations of the brain wave patterns of those who marry or propose marriage.

In arriving at a conclusion several points deserve emphasis: first, the need for taking into consideration other inheritable and valuable traits which may outweigh the presumably undesirable trait of cerebral dysrhythmis; second the importance of securing a record of the supposedly normal partner (Also suggested by Lennox ' 36 '), and, third, the need for determining the significance of the degree of abnormality or of the specific pattern of a given brain record (39).

Both in the population which is closely related to the epileptic and in the general population, persons with dysrhythmia outnumber those who are subject to seizures twenty times or more (39). Therefore, it is easy to see that questions of marriage and children apply not only to persons with seizures but also to the very much larger group who may be capable of transmitting the dysrhythmia and the predisposition.

The word "heredity" connotes the inevitable, but Eugenics is given a new weapon, the opportunity to deal not simply with the few fictims of a certain disorder, but the twenty times more numerous "carriers" of the disorder.

As a means of bringing this work to a conclusion, permit me to say that hereditary dysrhythmia can be prevented only by means of Eugenics, either by forbidding progeny to all persons with transmitted and serious brain wave disorders, an imposing task, or perhaps by dilution of the trait through marriage with persons possessed of normal brain waves (35).

On the other hand, even if a disordered pattern of brain waves has been inherited, epilepsy itself may possibly be prevented if environmental conditions which act as precipitants of seizures, such as head trauma, certain infections, et cetera, can be avoided. Prevention of these

precipitating conditions lies partly with the public and its elected representatives, and partly with the individual (35).

Thus, individual prophylaxis has a new meaning, for possibly the enemy's invasion bases can be destroyed, and possibly disordered brain waves can be corrected before symptoms have an opportunity to appear.

These observations should be of practical value in the prophylaxis and eugenics of epilepsy, and should assist the physician in tracing the descent of epilepsy and in advising patients and their relatives about marriage.

SUMMARY

1. It is now generally accepted that epilepsy cannot be regarded as a unitary disease entity, but is, on the contrary, a symptom complex accompanying a variety of conditions which directly or indirectly impair the integrated function of the Central Nervous System.

2. Brain tumors represent one of the most common causes of epilepsy at all ages, but especially between the ages of 15 and 60; and, whenever an adult has a convulsion for the first time, brain tumor should be considered as a strong possibility.

3. The incidence of epilepsy increases as the site of the tumor approaches the Rolandic fissure (Central Sulcus).

4. Brain abscesses are apt to be associated with focal epileptic seizures, during an early stage, but recurring seizures, if they appear at all, do so months or years after the initial infection as the result cicatrical changes.

5. Whether or not an individual will develop epilepsy following a head injury depends upon a number of factors such as the location of the trauma, the duration of unconsciousness, the type of injury, etc.

6. Penetrating injuries that pierce the dura are much more likely to cause the subsequent development of epilepsy than if the dura was intact.

7. Every case of epilepsy occurring in a previously healthy adult who has lived for a period in the tropics should be considered as a case of Cysticercosis until proven otherwise.

8. Syphilis and Tuberculosis are responsible for many cases of infantile and adult epilepsy.

9. Acute infectious diseases as a cause of convulsive seizures are peculiar to early childhood, provided one eliminates from consideration those infectious agents which directly invade the Central Nervous System to provoke an encephalitis or a meningitis.

10. Severe cerebral trauma at birth may cause destruction of the cortex and the sub-cortex, and the resultant damage may act as a potent "locus minor resistentiae" for the production of epilepsy at a later date.

11. Congenital malformations and maldevelopment account for an overwhelmingly percent of convulsions occurring before the age of twenty-five.

12. It is undecided whether the convulsions of an epileptic nature which are frequently associated with an allergic phenomena, arise from the presence of this hypersensitivity, or whether they act merely as a secondary stimulus.

13. Biochemical phenomena such as anoxia, anemia, hydration, etc., are in themselves not primarily causes of epilepsy,

and should be regarded as only precipitating factors.

14. Vascular spasms may be concerned in the pathological background of epilepsy, but they play no role in the actual mechanism during a seizure.

15. The possibility of an old rheumatic encephalitic scar as a possible causative factor should be considered in patients who develop epileptic convulsions following chorea, or in the wake of Rheumatic Fever, particularly if there were delirious episodes during the febrile period.

16. Although heredity is an important influence in epilepsy, it is generally recognized that epilepsy per se is not hereditarily transmitted, but rather, a special predisposition to epilepsy is inherited.

17. Although the frequency of the electrical waves of the brain vary with changing activity of the brain, an inherited disorder, which was found in the parent before the conception of the child, should persist throughout life.

18. Essential epilepsy develops on the basis of a pre-existing cerebral dysrhythmia.

19. Hereditary dysrhythmia, which may prove to be a dominant rather than a recessive Mendelian trait, can be prevented only by means of Eugenics.

20. If an epileptic marries, he should marry a person with normal brain waves, as marriage is safer for such a pair than for two persons whose personal and family history

are free of seizures, but who both have cortical dysrhythmia.

CONCLUSION

In the light of our present day knowledge of epilepsy, the tremendous variability of possible etiological factors, and the disagreement among various authors and workers in the field, I do not think it possible at this time to draw any dogmatic and all-inclusive conclusion or conclusions regarding the etiology of epilepsy.

I do think however, that from the facts presented, we can conclude with a relative degree of impunity that in all cases of convulsions developing before the age of 15, we should think first of some type of congenital malformation or maldevelopment as an etiological agent. Conversely, in cases of convulsions developing between the ages of 15 and 60, brain reaplasms or brain trauma should be given primary consideration,. Convulsions developing at the age of 60 or after most likely will have their etiology on an arteriosclerotic basis.

As regards to the inheritance of epilepsy, I think it is quite well established that although epilepsy "per se" is not inherited, a tendency or predisposition towards epilepsy may well be inherited. This tendency or predisposition is evidenced by a cerebral dysrhythmia.

On the other hand, I do not think that every cerebral dysrhythmia, as recorded by the electroencephalograph, should be enterpreted as a possible "epleptic dysrhythmia",

but the conclusion seems enescapble that the cerebral dysrhythmia associated with epilepsy is inheritable, and the parent of an epileptic patient who shows such cortical dysrhythmia is a carrier of the disorder.

The question of whether this transmitted dysrhythmia is a dominant or a recessive, and whether disordered brain waves could be "bred out" by crossing with ordered brain waves, must await the collection of more data and the decision of the geneticists.

Moreover, given a person whose electroencephalogram is abnormal, we must know that this dysrhythmia is transmitted and not acquired, and we must learn the genetic significance of various degrees and types of abnormality before any definite and stable advice concerning marriage, the children's chances of developing epilepsy, etc., can be given with any degree of surety.

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