Etiology of idiopathic epilepsy

William J. Resnick
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ETIOLOGY OF IDIOPATHIC EPILEPSY

William J. Resnick

SENIOR THESIS PRESENTED TO
THE UNIVERSITY OF NEBRASKA
COLLEGE OF MEDICINE
OMAHA, 1937.
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Introduction

Epilepsy is a symptom, not a disease. The literal meaning of this Greek word is "to seize upon" or "seizure". Clinically, epilepsy is characterized by the sudden and repeated appearance of seizures, in which disturbances of consciousness, or convulsive movements, or both, are the principle elements. There is no constant pathological condition associated with the convulsive state, though there is a large number of pathological changes in the brain and outside the brain, which are capable of producing convulsions. There is no constant physiological or chemical pathology found in the body of the epileptic, though many functional disturbances may cause convulsions.

The term "seizure" has been used in describing a wide variety of clinical manifestations. Among these manifestations of the convulsive state are included the following: 1. Grand mal:—a syndrome consisting of repeated seizures of sudden onset, often preceded by a warning, the "aura," and characterized by sudden loss of consciousness, tonic spasm followed by clonic spasm, and ending in a period of stupor of a variable time duration. 2. Petit mal:—a syndrome consisting of very transitory losses of consciousness, usually unaccompanied by muscular twitchings. These minor spells lead,
often enough, to major epileptic seizures. 3. Jacksonian epilepsy:--in which there is localized clonic movements beginning in a single muscle, or group of muscles, and spreading thence to the muscles whose cortical areas of representation adjoin that of the muscle first involved. The spread of the clonic movements is frequently characteristic. If the face is involved first, the arm follows, and then the leg. If the hand is attacked first, the convulsions spread up the arm, then to the face, and last to the leg. In the severer cases, where the whole side of the body is involved, consciousness is lost, and then the convulsions may become bilateral and generalized. 4. Pyknolepsy:--a condition, occurring in childhood, spontaneously terminating at puberty, and characterized by frequent transient losses of consciousness of short duration, and usually unaccompanied by clonic movements of the muscles. 5. Dreamy states, especially those with an aura of taste or smell, which are called "uncinate fits", and usually signify organic disease around the uncinate gyrus of the temporal lobe of the brain. 6. Narcolepsy:--in which there are periodic attacks of somnolence, the desire to sleep occurring suddenly, and the sleep lasting from a few minutes to an hour, the symptom complex of repeated attacks of sleepiness being often combined
with cataplexy. 7. Cataplexy:--in which the patient falls to the ground helplessly, and without power of voluntary motion, though without unconsciousness, these attacks being usually precipitated by strong emotion, such as laughing. 8. The borderland states of epilepsy, which includes such diverse phenomena as vaso-vagal attacks, migraine, furor states, automatisms, and many others. The above clinical syndromes may be produced by either organic or functional causes.

For purposes of convenience, epilepsy has been divided into two great groups, the symptomatic, and the idiopathic. The symptomatic epileptic is one in whom some definite known organic change is precipitating the convulsive seizures. Examples of symptomatic epilepsy are the convulsions occurring in the course of neurosyphilis, brain tumor, or rickets. The idiopathic epileptic is one in whom thorough clinical investigation has revealed no cause for the periodically recurring convulsions.

My study leads me to say that all individuals are potentially epileptic, though the degree of potentiality varies greatly from individual to individual, and from time to time in any given individual. The tendency toward convulsions decreases with age. According to their susceptibility to convulsions, I would classify all indi-
viduals into three groups. The first group comprises the idiopathic epileptic whose susceptibility to seizures is very great, so that minor physico-chemical or emotional strain can precipitate a convulsion. The second group is more stable and is less susceptible to convulsions than the idiopathic epileptic. In this group a brain tumor, a cerebral scar, an acute infection, or a lowering of the blood calcium may cause a convulsion, so it can be seen that this second group corresponds to the clinical concept of symptomatic epilepsy. The third group of individuals are those individuals whose central nervous system is so highly stabilized that extreme measures are necessary to produce convulsions in them. Large doses of poisons, including cocaine, strychnine, picrotoxin, and so forth will cause convulsions even in this last well integrated group of persons.

There are thus two factors involved in the production of epilepsy. They are 1. "the seed", and 2. "the soil". The "soil" is the so-called constitution of the patient, a specific tendency in the patient to seizures. The "seed" is the extrinsic stresses and strains which happen to exert their influence on the patient. The seed in one patient may be a brain tumor, in others syphilis, in still others hypoglycemia. If the soil is unfertile, the seed will be wasted. Thus only 35% of tumors of the frontal
lobe of the brain cause convulsions, (54) and only 4½% of patients who have received head traumas in the World War later developed convulsions. (69)

Those readers of this paper who are agriculturalists, will exclaim that there is a third factor which we shall call the "cultivation" of the soil. This third factor does exist, and in the case of convulsions, we shall call it "factors which modify convulsions". One of the factors which modify convulsions is the acid-base balance, another is the oxygen supply of the brain, and a third is the fluid balance of the body. Many other physicochemical changes also exert an influence in determining the frequency of the convulsions and their severity.

The scope of any paper must be limited, and this paper will limit itself to generalized convulsions of unknown origin, idiopathic epilepsy. It will only concern itself with etiological factors in idiopathic epilepsy.

I wish to acknowledge my debt to Lennox and Cobb, and to Temple Fay, from whose writings I have obtained the background necessary in writing a paper of this type, and from whom I have quoted freely and at length in this paper.
History of Epilepsy

Affliction with epilepsy is an ancient and widespread condition. It is only natural that anything as spectacular as a generalized convulsive seizure should have aroused the curiosity and amazement of even the most primitive man, from the very beginnings of time.

Human skulls recovered by the archaeologists bear silent witness to the fact that trephining was practiced among prehistoric people in the eastern as well as the western hemispheres. Neolithic medicine men trephined for epilepsy with a perforating outfit that consisted of a flake of obsidian or a shark’s tooth. Thus, prehistoric man picked at the brain pan in the firm conviction that epilepsy and convulsions in general were intracranial affairs. (48)(75)

The Babylonian priests regarded epilepsy as special marks of possession or of divine condemnation. It was their belief that epilepsy was contagious, and this belief was carried on into the middle ages, when epileptics were not allowed to sell food or drink, and isolation hospitals existed in Alcase as late as the fifteenth century. (7)

Among the early greeks, convulsions were regarded as soul-racking visitations of a divinity (Cybele, Poseidon, Hecate, Apollo), and epilepsy was referred to as
"the Sacred Disease". It was also referred to as "the Disease of Hercules", some historians believing that Hercules had epilepsy, and others believing it was so referred to because of the strength and violence of the seizures. (39)

In primitive countries today, epilepsy is still attributed to demonic possession, or to temporary loss of the soul from the body. At Amoy in China, when some mischievous spirit has produced a fit by drawing the soul out of the body, definite means are taken to recover the lost soul. If the patient is a child, the mother rushes to the rooftop, and waves about in the air a bamboo pole to which the child's garments have been attached. While she is doing this, she several times calls the child by name and begs it "to come back, to return home". Another inmate of the house simultaneously bangs a gong to attract the attention of the lost soul to the familiar garment. In Northern India, today, epilepsy is still believed to be due to demonic possession. Magic and religious rites are employed to drive out the unwanted spirit. Soundly thrashing the patient with a sacred iron chain is supposed to immediately and invariably expel the demon. (78)

It was the mystical and divine conception of the disease that Hippocrates (460--377 B.C.) sought to smash with one blow. In a satirical vein, he wrote "On the
Sacred Disease. Its opening argument is dynamic, "To ascribe to divine maladiction an affection which is purely human is chittering folly". He continues, "Epilepsy is a curable disease"...."it arises thru hereditary and attacks phlegmatics only, never choleric"...."the cause of the disease is phlegm in the brain." (35) His explanation of the etiology of the disease is very well done when we stop to consider the paucity of scientific facts which were available. Phlegmatic embryos, he said, are insufficiently purified of the phlegm which later causes epilepsy. If the phlegm can be eliminated from the body in post natal life by such mechanisms as ulcers with slimy discharges, lung troubles with productive cough, and so forth, then the predisposed epileptic may be saved from his fate. If however, the phlegm is diverted to the brain, "the patient becomes dumb, he suffocates, foam flows from his mouth, the teeth are clenched, the hands cramp, the eyes twisted, and the patient loses consciousness, while many lose excrements." (35)

Hippocrates writings on "Aphorisms" contains many references to convulsions, and clearly indicates that this master clinician clearly understood the differences between idiopathic and symptomatic epilepsy, and could in many cases prognose the outcome of the seizures.
"Spasm supervening on a wound is fatal"....Such persons
as are seized with tetanus die within four days, or if they pass then these recover"...."A convulsion supervening on a copious loss of blood is bad—from taking hellebore is of a fatal nature"...."Better a fever supervenence on a convulsion, than a convulsion on a fever"...."Those cases of epilepsy which come on before puberty may undergo a change, but those which come on after the age of twenty-five are for the most part fatal". (2)

Serapion (280 B.C.) was more concerned with the treatment than with the etiology or prognosis of the convulsive states. Among his remedies are included the brain of the camel, the heart of the hare, rennet from a seal, and the blood of the tortoise. (52)

Celsus (30 B.C.—50 A.D.) in common with other Roman writers styled epilepsy as "morbus comitialis", because if any member of the Senate convulsed, it was regarded as a bad omen, and the Senate would adjourn for the day. Celsus was little concerned with etiology or pathology. Therapy was his high argument, "Purge the patient with alum or black veratrum, anoint his head with old oil or acetum, fast him, keep him out of the sun, from baths, from wine, from venery, from dizzy heights, avoiding vomitus, undue fatigue, and all business cares of whatever nature". "Some seek to cure themselves by drinking the warm blood of fallen gladiators....a miser-
able remedy, serving merely to make more miserable those who suffer from an intolerable disease." (75)(39)

In the ministry of Jesus, there were brought to him "all sick people that were taken with divers diseases and torments, and those which were possessed with devils, and those which were lunatick, and those which had palsy, and he healed them." (Matt. 4:24). Other holy men were also available to "cast out devils", and thereby cure the convulsive states. (St. John the Baptist, St. Michael, St. Vitus, St. Cornelius, St. Valentine, St. Gilles, St. Hubert.) (75)

Frequent references are made in the Jewish Talmud to epilepsy, "he that hath intercourse during blood letting, that child shall develop epilepsy". (39).

In the ninth chapter of Mark, we read a passable clinical description of epilepsy, "Master, I have brought thee my son for he is lunatick, and sore vexed, and hath a dumb spirit. And wheresoever he taketh them, he teareth him, and bruising him hardly departeth from him. And he foameth, and gnasheth with his teeth, and pineth away." And they brought him unto him, and when he saw him, straitway the spirit tore him, and he fell to the ground, and wallowed, foaming. And he asked him, "Father, how long is it ago since this came unto him?" And he said, "Of a child, and oftimes it has cast him into the fire, and into the
water to destroy him." He rebuked the foul spirit, saying unto him, "Thou deaf and dumb spirit, I charge thee come out of him and enter no more unto him". And the spirit cried and rent him sore, and he was as one dead, in so much as many said "he is dead".

Archigenes of Apamea (54-117 A.D.) is said to have been the first to describe the aura of epilepsy, and to demonstrate that hemiplegia affects the side of the body which is opposite the cerebral lesion. (53)

Arateus, the Cappadocean, (117-158 A.D.) is said to have written a classical thesis on epilepsy. The clinical manifestations of the disease were minutely described, and the tendency to physical and mental deterioration were noted for the first time. In describing the deterioration he says, "If the epilepsy passes into the chronic stage, the sufferer is no longer able to rehabilitate himself in the interval between crises. He is heavy, morose, bruised in spirit, cruel, intractable, nor will age or feebleness succeed in mollifying him. He sleeps little, has monstrous bad dreams, no appetite, digestion deranged, his complexion pale, leaden. Incapable of attention because of the dual obfuscation of mind and sensory faculties, he is hard of hearing, has ringing in the ears and noises in the head. Speech is embarrassed, halting. Either this is characteristic of the disease or results
from accidental wounding of the tongue during an access. Often the reason finally becomes so involved that the unhappy creature sinks into a state of imbecility. (48)

Galen of Rome, (131—201 A.D.) wrote extensively on epilepsy. He is credited with the description of the facial aspect of the chronic epileptic. For therapy, he recommends the avoidance of physical and mental strain, light diet, purging as needed (especially in the spring), and exercise. In the way of drugs, he used vinegar of squill, rue, and pepper. The disease he attributed to an obstruction of the ventricles of the brain by phlegm so that the animal spirit is prevented from flowing freely into the nerves of sense and motion. Galen is said to have noted that epilepsy occasionally disappeared after an attack of quartan malaria. (7)(36)

Coelius Aurelianus, (440 A.D.) first mentions the occurrence of epileptiform convulsions as a manifestation of hysteria, and was the first to describe recurrent attacks of "absence" without muscular spasm. (Petit mal). (7)

Alexander of Tralles (525—605 A.D.) wrote of convulsions of childhood. He was opposed to bleeding and trephining in epilepsy, using the trephine only in the treatment of depressed fractures. Baths, diet, and exercise were his treatment for epilepsy. (80)
With the waning of Greek medicine, Roman medicine degenerated into sorcery, priest rule, and insignificance, and no addition of knowledge of convulsions occurred until the rise of the Arab School in the eighth century. At this time, Avicenna, in whose text the word epilepsy was used for the first time, experimented extensively with convulsant posons. (7)

With the revival of learning and advent of the alchemists, it is interesting to note that Paracelsus, (1493–1541 A.D.) attributed epilepsy to hyperacidity of the body. Today the production of acidosis by the ketogenic diet is one of the more popular methods of treatment in epilepsy. Paracelsus recommended a little angular bone found in the skull of executed criminals, which when dried and administered as a powder would cure epilepsy.

Sennert of Wittenburg (1537–1633) reverted to the demoniac origin of the disease, but he also established epilepsy as a disease common to the whole animal kingdom, and made extensive observations on convulsions, in sheep, goats, dogs, and cats. Hippocrates had noted epilepsy in goats, two thousand years earlier than Sennert, for he said, "Observe the goat, for that animal is most prone to the disease....open his head, you will find the brain wet, bathed in a hydroptic fluid of evil odor....there you will find evidence that it is not the divinity, but disease,
that thus alters the body." (35)

Frederick Hoffmann (1700) introduced the theory of spasm of the blood vessels of the brain as the essential cause of convulsions. (7). In 1710, came Boerhaave's magnificent classification of the causes, descriptions of the signs, and exposition on the treatment of epilepsy. At this time, there was reported in the literature a case of pituitary tumor with convulsions, terminating in blindness and death. (39)

In 1853, Lacock reported a case of epilepsy to the Royal Medico-Chirigico Society in London, who by taking potassium bromide, completely freed himself from convulsive attacks. Bromides were used universally for epilepsy from that date until Hauptmann in Germany in 1910, and Grinker in this country in 1912, began using phenobarbital as the drug therapy for idiopathic epilepsy.

Sir Astley Cooper was one of the first to experimentally produce convulsions in animals. In 1836, he tied the carotids in rabbits, then compressed the vertebrae digitally, causing convulsions to appear. On releasing the vertebrae, the convulsions would disappear, only to reappear when the vertebrae were again compressed. (12)

In 1854, Radcliffe wrote a monograph on convulsive seizures. He expounds at the length on the differential
diagnosis of convulsions. For therapy, he recommends bromides, and also the high fat diet, though it is obvious that the rationale of the high fat diet was not understood at that time. (65)

In 1863, Hughling Jackson first described the convulsions which bear his name. These he attributes to "coarse disease" of the contralateral cerebral hemisphere, which irritating the brain causes discharge of motor impulses to the muscles. Jackson mentions the dreamy state and hallucinations of taste and smell which he found to be associated with lesions of the temporal lobe. Jackson was an ardent advocate of the use of the ophthalmoscope (invented ten years earlier by Helmholtz) in all cases of suspected intracranial disease, and describes constriction of the retinal arteries at the onset of the fit. (37)(38)

In 1870, Fritsche and Hitzig discovered the electrical irritability of the brain, and showed that the irritability spread centrifugally from the site of stimulation. By their discovery, the beginning of the study of cerebral localization was inaugurated, and the various areas of the brain mapped out from the functional standpoint.

We will close our historical survey with the name of W.R. Gowers, who in his monograph on epilepsy published
in 1885, first discussed epilepsy in the modern manner. His studies were all carried out on institutional epileptics, and is responsible for much of the misinformation still seen in textbooks concerning epilepsy. This is true since only from five to ten per cent of all epileptics are in institutions, the other ninety to ninety-five per cent of patients being extra-mural.

While epilepsy is a social handicap to the individual, and usually is found in persons with lower intelligence quotients than normal, still the roster or epileptics throughout the ages has shown many distinguished personages in its midst. Among those known to have been epileptics are Moses, Mohammed, Julius Caesar, Napoleon, Peter the Great, St. Paul, Lord Byron, Mendelssohn, Mozart, and Paginini. Edgar Allen Poe was an epileptic, and the writings of Dostoyeffsky on epileptics are vivid since he, too, had the disease. In "the brothers Karamazov," Dostoyeffsky speaks of the feeling of bliss that comes to every epileptic when he is about to have his fit, the exquisitely lovely joy of the aura, which was a blessing which he would not trade for all the other happiness in life.
Conditions which may cause seizures

Since convulsive seizures show little difference, irrespective of the cause, it is necessary and illuminating to first enumerate all the pathological states which may cause fits, and as far as possible to classify them. (78) (10)

I Causes within the Nervous System

1. In which there is structural change

   1. Congenital defects—cerebral aplasia, cerebro-macular degeneration, congenital idiocy, tuberous sclerosis, porencephalic cyst

   2. Acquired defects

      1. Traumatic—(birth injuries and post-natal) hemorrhage, gliosis, arachnoidal adhesions, scars

      2. Inflammatory—meningitis (tubercular, syphilitic, epidemic, pyogenic) encephalitis (epidemic, tubercular, syphilitic) brain abscess, chronic arachnoiditis, venous sinus thrombosis

      3. Degenerative—multiple sclerosis, senile degeneration, arteriosclerosis, cerebral hemorrhage, thrombosis, and embolism

      4. Neoplastic—glioma, meningioma, metastatic, anzioma, aneurysm, and so forth
2. In which there is functional change

1. Cerebral vascular spasm

2. Brain edema—alcoholism, uremia, eclampsia, water intoxication, pituitrin intoxication, head trauma

II Causes outside the Nervous System

1. Vascular—arteriosclerosis, hypertension, Raynaud's disease, angioneurotic edema, acute and subacute bacterial endocarditis, Stokes-Adam's syndrome, paroxysmal tachycardia, cariac decompensation, and disease of the carotid sinus

2. Metabolic—protein sensitization (exogenic or endogenous) heat stroke, uremia, toxemias of pregnancy, acute yellow atrophy of the liver, acute febrile disease, hypoglycemia, tetany

3. Respiratory—pleural epilepsy, hyperventilation, asphyxia from any cause

4. Renal—uremia

5. Endocrine—Hypothyroidism, hypoglycemic shock, hyperadrenalism, thymus (?), hypoparathyroidism, hypo- and hyper-pituitary states, gonads (?)

6. Hematological—Pernicious anemia, hemorrhage

7. Intoxications—botulism, tetanus, rabies

III Causes outside the body—(exogenous)

Water intoxication, insulin, acute fever, whooping
cough, alcoholism, cocaine, camphor, lead, arsphenamine, picrotoxin, magnesium sulphate, strychnine, caffeine, ergot, nicotine, adrenalin, electrocution, oxygen intoxication, alkalosis from any cause

IV Psychogenic—hysteria, emotional shock

From the bewilderingly long list of possible causes of convulsions, we can generalize that almost any pathological condition of the nervous system, and many that merely effect the nervous system secondarily can produce convulsions.

Though the pathological states are both numerous and diverse in nature, it is easy to hypothesize (though much harder to prove) a few simple physiological mechanisms which can cause convulsive seizures. Cobb (46) classifies the predominant physiological causes as 1. nervous tissue destruction, 2. Direct irritation of the brain, 3. Increased intracranial pressure, 4. Brain edema, 5. Cerebral vasoconstriction, and 6. Anoxemia. These will be discussed later in more detail.
Incidence of Epilepsy

Affection with seizures is an ancient and widespread condition. Spratling (76) in 1904 estimated that there were 150,000 epileptics in the United States, an incidence of one epileptic per 700 population. These figures were probably too low. Thus, if we accept for the entire population, the incidence among men drafted during the World War in the United States, there were 500,000 epileptics in this country, an incidence of one epileptic per 200 population. Anderson in 1936 found the following incidence in Michigan. (1)

<table>
<thead>
<tr>
<th>Rate per 100,000</th>
<th>Incidence ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>In general population</td>
<td>210</td>
</tr>
<tr>
<td>In penal institutions</td>
<td>254</td>
</tr>
<tr>
<td>In county infirmaries</td>
<td>829</td>
</tr>
<tr>
<td>In home for high-grade subnormals</td>
<td>853</td>
</tr>
<tr>
<td>In all hospitals for mental disorders</td>
<td>1754</td>
</tr>
<tr>
<td>In hospitals for criminally insane</td>
<td>3079</td>
</tr>
<tr>
<td>In home for low-grade mental defectives</td>
<td>8931</td>
</tr>
</tbody>
</table>

Anderson believes his figures for the incidence of epilepsy in the general population may be too low, due to the tendency of the patient and his relatives to hide his disease.
It has been estimated that from five to eight per cent of all epileptics are in institutions. Since the rest of the patients are extra-mural statistical data of any value to the practicing physician must be gathered from the non-institutional patient. (45)(46)

According to the Department of Commerce, Bureau of Census, in Washington, first admissions of epileptics to state, city, and private institutions for the year 1935 included 2,498 patients. Of these 2,498 patients, 1,603 or 64% were mentally defective as well. There are at present approximately 20,000 epileptics in institutions for mental defectives and epileptics in the United States at this time.

The incidence of epilepsy does not bear any relationship to race or religion, epilepsy being of about equal frequency in all races. (16)

In Gower's series (32) of 1450 institutional cases there were more men than women with epilepsy in the ratio of thirteen to twelve. Spratling (76) found epilepsy more frequent in males than in females in the ratio of five to four, while Davenport (14) found epilepsy more frequent in males (52%), Lennox and Cobb (45) found 58 males to 42 males in a series embracing 8,114 cases both institutional from the Craig colony, and non-institutional. Sixty per cent of the first admissions to institutions for epileptics
in 1935 were males, according to the United States Census of that year. Anderson (1) in his survey of epilepsy in Michigan in 1936, found that 53.9% of the epileptics were males. The slightly greater incidence of epilepsy in males may be due to the greater opportunities of the male to incur head trauma, and perhaps, to the larger size of the male head in the fetus with a larger incidence of birth injury for that reason.
Relation to Age

It is generally agreed at the present time that epilepsy can develop at any age. Convulsions are, however more common in the young. In two-thirds of the cases of idiopathic epilepsy, the age of onset is before the age of twenty.

In Gower's series (32) of institutional epileptics more than one-quarter began under the age of 10, one-half between the ages of 10 and 20, one-sixth between the ages of 20 and 30, one-seventh between 30 and 40, 2½ % between 40 and 50, and ½ % thereafter. Spratling's statistics (76) are quite similar to those of Gower's. Lennox and Cobb (45) recently reported the age of onset of seizures in 7350 cases of the Craig colony, and of 844 non-institutional cases. The age of onset, tabulated below, shows a striking difference between the two groups.

<table>
<thead>
<tr>
<th>Age of Onset</th>
<th>Craig colony</th>
<th>Non-institutional cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 4 years</td>
<td>30 %</td>
<td>14 %</td>
</tr>
<tr>
<td>.. 9 ..</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>.. 14 ..</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>.. 19 ..</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>.. 24 ..</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>.. 29 ..</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>.. 34 ..</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>.. 50 ..</td>
<td>6</td>
<td>16</td>
</tr>
</tbody>
</table>
The earlier age of onset of generalized convulsive seizures in institutional epileptics is due to the fact that a large proportion of convulsions in the institutional cases is caused by cerebral birth injuries, or congenital brain defects. These are the patients who are most apt to suffer from mental deficiency as well, and are therefore institutionalized. From the above statistics, we can conclude that the earlier in life convulsions appear the poorer is the prognosis, excluding infantile convulsions caused by spasmodophilia, and acute infection.

In all branches of medicine, the age of the patient is of great diagnostic value. Carcinoma of the stomach would never be thought of in an infant who is vomiting, nor would diphtheria be considered in an old man complaining of sore throat. There is in epilepsy, just as in heart disease, distinct epochs according to the age of the patient.

Since the law of probabilities is of such great importance in directing the line of investigation of any presenting symptom, the following table of chief causes of convulsions at the various age levels is presented. (51)(61)(79)

Birth to one month

1. Cerebral birth injury or congenital defect 54.7

2. Acute infection 12.3
3. Idiopathic Epilepsy 9.0%
4. Tetany 6.0
5. Hydrocephalus 6.0
6. Congenital lues 3.0
7. Miscellaneous & unknown 9.0

One month to six months:
1. Acute infection 29.4%
2. Cerebral birth injury or congenital brain defect 23.5%
3. Spasmophilia 16.1
4. Idiopathic epilepsy 7.4
5. Gastro-enteritis 4.5
6. Miscellaneous & unknown 19.1

Six months to three years:
1. Acute infection 39.3%
2. Spasmophilia 22.4
3. Epilepsy 19.1
4. Cerebral birth injury or congenital brain defect 13.4
5. Meningitis 5.0
6. Miscellaneous & unknown 11.5

Three years to ten years:
1. Idiopathic epilepsy 59.0%
2. Acute infection 13.0
3. Cerebral birth injury or congenital brain defect 11.5
<table>
<thead>
<tr>
<th>Disease</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Tetanus</td>
<td>3.0 %</td>
</tr>
<tr>
<td>5. Brain tumor</td>
<td>1.5 %</td>
</tr>
<tr>
<td>6. Miscellaneous and unknown</td>
<td>12.0 %</td>
</tr>
</tbody>
</table>

**Ten years to fifteen years**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Epilepsy</td>
<td>81.3 %</td>
</tr>
<tr>
<td>2. Cerebral birth injury or congenital brain defect</td>
<td>9.4 %</td>
</tr>
<tr>
<td>3. Tetanus</td>
<td>6.3 %</td>
</tr>
<tr>
<td>4. Encephalitis residue</td>
<td>3.1 %</td>
</tr>
<tr>
<td>5. Miscellaneous and unknown</td>
<td>1.0 %</td>
</tr>
</tbody>
</table>

**Fifteen years to thirty years**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Idiopathic epilepsy</td>
<td>63.0 %</td>
</tr>
<tr>
<td>2. Brain tumor</td>
<td>13.0 %</td>
</tr>
<tr>
<td>3. Neurosyphilis</td>
<td>12.0 %</td>
</tr>
<tr>
<td>4. Post-traumatic</td>
<td>9.0 %</td>
</tr>
<tr>
<td>5. Miscellaneous</td>
<td>5.0 %</td>
</tr>
</tbody>
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**Thirty years to forty years**

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>1. Idiopathic epilepsy</td>
<td>51.0 %</td>
</tr>
<tr>
<td>2. Brain tumor</td>
<td>15.0 %</td>
</tr>
<tr>
<td>3. Neurosyphilis</td>
<td>15.0 %</td>
</tr>
<tr>
<td>4. Hypertension &amp; arteriosclerosis</td>
<td>3.0 %</td>
</tr>
<tr>
<td>5. Miscellaneous</td>
<td>16.0 %</td>
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**Forty years to fifty years**

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<tr>
<th>Disease</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>1. Idiopathic epilepsy</td>
<td>36.0 %</td>
</tr>
<tr>
<td>2. Brain tumor</td>
<td>20.0 %</td>
</tr>
</tbody>
</table>
3. Neurosyphilis 20.0
4. Hypertension and arteriosclerosis 13.0
5. Post-traumatic 4.0
6. Miscellaneous 8.0

Fifty years and older
1. Hypertension and arteriosclerosis 30.0
2. Brain tumor 12.0
3. Neurosyphilis 6.0
4. Miscellaneous 3.0

Summarizing the causes of convulsions in five hundred cases below the age of fifteen years, one-third are caused by idiopathic epilepsy, one-fourth by acute infection, one-sixth by birth injury or congenital cerebral defect, and one-seventh by spasmophilia. In one-tenth of the cases some miscellaneous disease entity was the cause, and in six per cent, no diagnosis could be arrived at.

Summarizing the causes of convulsions beginning in adult life, we can say that one-half are due to idiopathic epilepsy, one-sixth to brain tumor, one-sixth to neurosyphilis, one-seventh to hypertension and arteriosclerosis, four per cent to trauma to the head, and four per cent of miscellaneous and unknown cause.
Influence of Heredity

The older studies on epilepsy all indicated a strong hereditary tendency to the disease. Gowers (32) for example, reported that 66% of his patients gave a family history of epilepsy. The older studies, however, were made on institutional cases, and in the institutional case epilepsy is often an incidental finding to some graver mental defect. We do not deny the influence of heredity in idiocy, we merely assert that for the great bulk of epileptics (who are extra-mural), the influence of heredity seems to have been greatly over-rated.

That mental deficiency is a common accompaniment to epilepsy in the institutional patient cannot be denied. In the Craig colony (45) only 14% of the patients are mentally normal. Of the patients admitted to state institutions for epileptics in 1935 (United States Census), 64.3% are classified as mentally defective.

Because of the great practical importance of the hereditary influence in epilepsy from the eugenic standpoint, studies applicable to the non-institutional epileptic only, can be given serious attention. Lennox and Cobb (45) estimate that in only 6% of epileptics is heredity important, and that this 6% being mostly institutional cases will have little opportunity for procreation. The problem of epilepsy could not be solved by sterilization
because of all the silent carriers of the disease. Thus according to Lennox and Cobb (46) epilepsy is more common in the children of migrainous parents than of epileptic parents.

The hereditary tendency toward epilepsy, though slight does exist. Thus Paskind and Brown (55) found that of the 342 children of 162 extra-mural patients, .29% developed epilepsy, while the incidence in the general population, they estimate to be .25%. Cobb (10) found that in a group of non-institutional epileptics, 21.4% of their relatives were epileptic, as compared to a series of normal controls in which the incidence in the relatives was only .26%. In the relatives of symptomatic epileptics (post-traumatic), he found only 1.47% of their relatives had epilepsy. From these studies, Cobb postulates a slight hereditary tendency to seizures even in the normal persons, a slightly greater tendency to seizures in those patients who convulse after trauma, tumor, and so forth, and a still greater hereditary tendency in the idiopathic epileptics.

Spratling (76) expresses the current opinion as follows, "Epilepsy, etiologically considered, is a symptom complex based on two variables--either a maximum of inherited influence with a minimum of exciting cause, or a minimum of inherited influence with a maximum of ex-
citing cause."

Acceptance of this constitutional factor, common to all persons who develop seizures, enables us to understand why only 4½% of patients after severe head trauma (69) and only 35% of patients with frontal lobe tumors (54) develop generalized convulsions. According to this viewpoint, the convulsions developing during acute infections in children are not as innocent as some textbooks of today still insist they are. We would believe that the child who developed convulsions under the stress of infection, would have a lower convulsion threshold than the child who did not.

Paskind's (56) studies on the hereditary factor in epilepsy causes him to speak of a neuropathic constitution rather than an epileptic constitution. He found that migraine and epilepsy were more common in the relatives of epileptics than in the relatives of normal controls, but he also found epilepsy to be more common in the relatives of psychopaths in general. In Manic-depressives, schizophrenics, and psychasthenics, the familial incidence of epilepsy was as great as in the families of epileptics. Thus, he speaks of a psychopathic constitution or inheritance, which in one case may manifest itself as epilepsy, in another as migraine, and in still another as schizophrenia, or hysteria.
Influence of Birth Trauma

Children who have suffered gross brain injury during birth often develop convulsions in later life. Peterman (61) states that 54.7% of the convulsions developing in the first month of life are due either to brain injury or congenital brain defect. Spratling (76) states, "We are reasonably safe in stating that fully 40% of all hemiplegias of infancy become epileptic."

Birth injuries according to the review of Young (87) may be of three types, all of which are more common in pre-matures. The first type is hemorrhage, which is venous in origin, which may be gross, (due to laceration of the dural folds or venous sinuses, or rupture or laceration of the cerebral veins), or petechial, into the brain tissue itself. The second type of birth injury, is due to stasis and thrombosis of the cerebral veins or dural venous sinuses, due to the difference in pressure on the fetal head as compared to the fetal body after the amniotic sac has ruptured. The third type of brain injury is due to edema of the nerve cells without any gross hemorrhage associated. The main neurologic residues are spastic hemiplegia, diplegias, the epilepsies, idiocy and feeblemindedness, the choreas, athetoses, and hydrocephalus.

The difficulty in deciding what the relationship of birth injury to epilepsy is, is that we are concerned in this paper to idiopathic epilepsy. Obviously, if ep-
ilepsy develops in a child who has suffered definite birth injury, we must call the condition symptomatic, and not idiopathic epilepsy. A further difficulty arises when we stop to consider that a spastic hemiplegia or paraplegia in an infant may be due to either a birth injury of the pyramidal tracts, or a failure of these pathways to develop (agenesis).

Furthermore, idiopathic epilepsy is not very common, the highest estimates of its incidence being 1 per 200 population. Birth injury on the other hand is exceedingly common, if we accept as its incidence, the incidence of bloody spinal fluids found in the newborn. For example, Smith (72) did cisternal punctures on 190 consecutively born babies, and found grossly bloody spinal fluid in 16.9%, whereas microscopically bloody spinal fluid was found in 73.5%.

Lennox and Cobb (45) state that a large percentage of idiopathic epileptics give a history of difficult or instrumental delivery. It is interesting to note that the percentages of babies with bloody spinal fluid rise in direct proportion to the difficulty of the labor. Thus, Smith (71) found grossly bloody spinal fluid in none of the Caesarian section babies, in 10% of the spontaneous labors, in 24% of the low-forceps babies, and in 40% of the breech extractions. Statistical data on the incidence of idiopathic epilepsy in hysterotomy babies,
though not available, would do a great deal toward solv­ing the relationship of birth trauma to idiopathic epilepsy.

Further evidence suggestive of a relationship of birth trauma to idiopathic epilepsy is the finding that epilepsy is relatively more frequent in the first-born than in later-born children. (45) (1) The greater incidence of idiopathic epilepsy in the male is suggestive, since the birth of the male with his larger, firmer head and greater birth weight, is more difficult than that of the female.

Clinically diagnosable birth injury, followed in post-natal life by convulsive seizures, must be classified as symptomatic epilepsy, since the precipitating cause is known. Several workers have suggested that sub-clinical birth injuries may be the fundamental pathological substratum of the convulsive state, as far as idiopathic epilepsy is concerned. Olkon (53) believes idiopathic epilepsy has as its etiological substratum, the capillary hemorrhages produced during birth. Olkon also describes changes in the capillary system of epileptics and in the experimental animal. He studied the capillary changes in the pia-arachnoid of anaesthetized dogs in whom convulsions were produced by drugs. With the aid of the skin microscope, he noted kinking, spasm, and distortion
of the capillary bed during the convulsions, while the larger capillaries were found to be atonic and to show constricted areas.

That blood is an irritant to both the pia-arachnoid and the nervous tissue has been proven. Thus, Bagley (5) injected fresh blood into the subarachnoid space of puppies, and later necropsy showed definite thickening of the pia-arachnoid with adhesions. Many of the dogs who were not killed later developed convulsions.

The fact that convulsions in the idiopathic epileptic do not develop for months and even years after birth cannot be used as an argument against the fact that birth injury may be the fundamental pathological cause of idiopathic epilepsy. This latency is common to other epilepsies. Thus convulsions following head trauma may develop immediately as an accompaniment of the brain edema which follows, or may show a latent period of five months to fourteen years. (23)

In conclusion, it may be stated that the relationship of birth injury to idiopathic epilepsy is at present unknown.
Mechanism of the Fit

As our knowledge of neurology, of physiology, of biochemistry, and of psychiatry broadened and deepened, numerous theories as to the mechanism of origin of the convulsion were expounded. At present, there are three main theories of origin of the fit from the neurological standpoint. These theories are one, the "irritation theory", which postulates an area of over-excitation in the cerebral cortex, due to some localized irritation, two, the "release" theory, which maintains that fits are due to release of the lower motor centers from cortical control, and three, the "short-circuiting" theory, which believes fits result when destruction of association fibers has been sufficient in amount, to cause a decrease in the resistance which the incoming sensory impulse meets before it is transposed into motor action. A fourth theory attempts to explain the occurrence of epileptic convulsions in psychological terms. According to this theory epilepsy is a functional psychosis, comparable to schizophrenia, and manic-depressive states. The fifth theory, the "explosive" theory, looks upon the neurological pathways involved as being merely incidental. It postulates that the fit arises as the result of some wide-spread sudden change in the brain tissue.
Neurological theories

The first theory, which is based to a large extent on the observations of Hughlings Jackson, (37)(38) is called the "irritative" theory. It postulates an area of overexcitation in the cerebral cortex, this area of overexcitation being the result of irritation of "coarse disease". If this area of overexcitation is in the sensory areas of the brain, an aura is produced, which aura will be visual if the pathologic epileptogenous area is in the occipital lobes, gustatory or olfactory if in the temporal lobe, localized paraesthesias if in the posterior central gyrus of the parietal lobe, and localized muscular twitching if in the anterior central gyrus of the parietal lobe. If the epileptogenous zone is in a "silent" area of the brain, there will be no "aura". The wave of excitation spreads centrifugally in all directions through the brain, and down the brain stem. When the motor cortex is reached in the precentral gyrus, the convolution, at first tonic, begins. Consciousness is lost due to overstimulation of the "center" of consciousness.

It was by this spread of a wave of cerebral excitation that Jackson accounted for the definite "march" of the convulsive movements which he had so frequently observed in the focal epilepsy which bears his name.
Jackson observed that organic disease in various parts of the brain would set up convulsive seizures. By noting the localization of the muscles in which the movements began he could predict what part of the brain the "epileptogenous" area was. He believed the aura also demonstrated the site of origin of the epileptogenous impulses, and described "uncinate" fits.

The discovery of the electrical excitability of the brain by Fritsch and Hitzig in 1880 did much to apparently put this theory on a firmer basis, and, indeed, to cause an expansion of the original conception as the physiology of the brain became more fully understood. Thus, the conic elements of the fits were attributed to excitation of the motor cortex, the tonic elements to the excitation of the basal ganglia, and other subcortical regions. Vasomotor changes were ascribed to irritation the bulbar and diencephalic center, turning of the head and eyes to irritation of the frontal adversive field, and so forth.

Electrical stimulation of various parts of the brain will result in either localized or generalized convulsions. The traction of scar tissue (23), the irritation of neoplasms, and so forth likewise cause periodic convulsions. Pollock's(63) experimental work indicated that epileptogenous qualities are possessed by the ganglion
cells of both the brain and brain stem, and that convulsive movements could be evoked by stimulation of such cells at any level, the symptoms produced being dependent on the level so stimulated. The threshold for convulsions varies in different parts of the brain however. Pike and Elsberg (63) found that clonic movements could be produced only by exciting the cerebral motor cortex in intact animals. However if the cerebral hemispheres of animals had been removed, after a time interval of variable duration, clonic convulsions could be obtained by stimulating the subcortical centers.

Jackson's "irritative" theory certainly explains the localized clonic movements of "Jacksonian" epilepsy, for it is true that this type of convulsion is always dependent on some localized brain pathology which would set up a hyperirritable focus in the brain. Brain tumor, trauma, focal encephalitis, localized syphilitic processes, and so forth are the localized "coarse disease" in these cases. It cannot explain idiopathic epilepsy, since in the idiopathic epileptic no localized pathologic processes are found.
The second theory is the "release" theory. This theory was suggested as the result of the observations on decerebrate rigidity in animals, this rigidity being produced by sectioning the brain stem above the entry of the eighth cranial nerve. This theory maintains that convulsions come, not from overexcitation, but rather from temporary suspension of function of the higher centers, allowing the lower centers to discharge nervous impulses in an exaggerated, uncontrolled manner. In the major seizure, then, the sequence of events can be interpreted as a sudden cutting off of the higher levels. With release of the cerebral cortex, there occurs unconsciousness, and the discharge of the lower levels produce the tonic stage of the fit. The tonic stage is interpreted as an abrupt rigidity of the decerebrate type. The clonic convulsions which follow are interpreted as the result of the gradual resumption of function of the cortex, which is incapable at first of producing orderly volitional action. Stupor, which follows the fit, lasts for that duration of time which the cerebral cortex takes to rehabilitate itself from a functional standpoint. (40)(46)(67)
The third theory is the "short-circuiting" theory advanced by Southard in 1908. (46) This theory is that any lesion of the brain, irrespective of its nature, must of necessity destroy many axons, and thereby will interrupt many of the complex association pathways connecting the various parts of the brain. Normally, these association pathways cause a delay in the interval between sensation and motor discharge, because it is the purpose of the association pathway to diverge the incoming sensation to all parts of the brain, to be again reassociated and find expression as a motor impulse. The delay due to dissociation over the association pathways is comparable to the delay which a resistance wire offers to the electrical current. With less resistance, due to the destruction of association pathways, the sensory impulses take a shorter abnormal route through the brain instead of spreading widely thru the association pathways. This leads to a "short-circuit", an explosive motor discharge, which finds its muscular expression in the convolution.

This theory helps to explain why such a wide variety of pathological states are associated with convulsive seizures. Thus a tumor, a scar, a cyst, or an area of softening due to vascular change, all, according to this theory, produce convulsions merely because in their evolution they have destroyed some of the association pathways
of the brain.

Interruption of certain of the nervous pathways seems to be more effective in "short-circuiting" than interruption of others. Gibbs and Gibbs (29) performed the following experiment on 348 cats:—the skull was trephined under anaesthesia, and a stimulating needle was thrust into various parts of the cat's brain. The cat was allowed to regain consciousness, and with the stimulating current the convulsion threshold was determined. Since the needles were stuck into different parts of each cat's brain, the "Convulsion threshold" for various parts of the brain were determined, the cats were killed, and then the brains were dissected to determine the exact site of the needle. From this experiment, the conclusion was reached by plotting the areas of lowest thresholds in the cat's brain, that the essential structures implicated are a system of short fibers connecting the thalamus, the frontal cortex, and the basal ganglia. Experiments performed on man by Nature give us information about the convulsion threshold of various parts of man's brain. Thus in Parker's (54) series of 313 brain tumors, those involving the frontal, temporal, or parietal lobes showed generalized convulsions as a symptom in over 50% of the cases, whereas none of the subtentorial or occipital lobe tumors of this series caused convulsions. The fact that
none of the posterior fossa tumors produced convulsions in his series of cases is a strong argument against the theory of increased intracranial pressure as a cause of convulsions. List (49) reviews 300 cases of glioma of the cerebral hemispheres and found an incidence of generalized convulsions quite similar to that of Parker's. He also lists other types of epileptic attacks associated with brain tumors in various locations as Petit mal, uncinate fits, certain types of auditory and visual hallucinations, and dreamy states. Both he and Parker state that a convulsion may be the first symptom of brain tumor. They also note that removal of the tumor does not necessarily prevent the convulsive seizures from taking place, which is further evidence favoring Southard's short-circuiting theory.

The involvement of the frontal lobe by either atrophy, aplasia, or other pathologic change has been observed in the convulsive state at operation, at necropsy, and by encephalography. Bateman, (8) found gross agenesis, either bilateral or unilateral in the frontal lobes in 68 of 146 necropsies reported on institutional epileptics. Bateman interprets the frontal lobe changes as agenesis, and not as atrophy due to increased intracranial pressure as does Fay.(20). He believes that atrophy would be generalized if it were the result of increased intracranial
pressure, and would not selectively implicate the frontal lobe. The commonness of implication of the frontal, as compared to the other lobes of the brain, he interprets as being due to the fact that phylogenetically it is the youngest of the lobes of the brain, and embryologically it is the latest to develop. Dandy (14) in his surgical experience with epilepsy, found pools of subarachnoid fluid over the brains of epileptics, these pools being the most marked over the frontal lobes. This excess fluid is merely space-compensating, because of the decreased size of the frontal lobes in the epileptic, according to Dandy. Pendergrass (58) reports that encephalograms show some amount of cerebral atrophy in all of the convulsive states, irrespective of the cause, this atrophy being most marked in the frontal region of the brain, and being revealed by some dilatation of the ventricles, increase in space between the skull and the brain, and increased thickness of the subcortical air-markings, as well as some dilatation of the cisternae. Both he and Dandy agree that encephalography is indicated (in the absence of choked disc) in all cases in which a diagnosis of the pathological cause of the convulsions cannot be made with the routine clinical and neurological examination. Furthermore, encephalography occasionally causes marked clinical improvement of the patient, in some cases, decreas-
ing the number and severity of the fits. Encephalography appears to be especially beneficial in the case of arachnoiditis.
Psychobiological concept of Epilepsy

Clark (9) describes what he calls the "epileptic personality". The personality consists of a mixture of psychic components which are mutually antagonistic. Thus, obstinacy combined with superficial docility, mendacity with ethical perversions combined with piety and pleasing speech, openness with distrust, misanthropy and childlike cheerfullness, are often seen. With the above variegated phenomena, there is a general tendency to severe ethical deterioration. The epileptic is unsocial, quarrelsome, inclined to lying and violence. During the development of the epileptic character, the intellectual faculties may remain intact, but later there is intellectual failure. There is narrowing of the mental horizon, piety with emphasis of trifles, lack of judgment, egotism, sensitiveness, fits of irritability.

Epilepsy, according to this hypothesis, is a purely functional aberration of the psyche, with somatic manifestations. Clark maintains the epileptic personality is present in all cases of idiopathic epilepsy before the appearance of the seizures, and is not the result of the seizures themselves, as most other neurologists believe. Indeed, in the absence of the pre-existing epileptic personality, Clark would be inclined to believe the epilepsy was symptomatic in nature. As in schizophrenia, hysteria
and other functional psychoses of the nervous system, there is a defective functioning of the whole organism, a peculiar inferior adaptive mechanism. According to his theory, fits are an adaptive mechanism, a regression to the fetal stage, a flight from reality, which enables the epileptic to compensate temporarily for his psycho-biologic inferiority, and as the power of adaptation becomes more and more damaged by the inability of the epileptic to meet the stress of every-day situations, there is a progressively great introversion, and tendency to dementia, just as there is in the schizophrenic.

Clark's theory has not been kindly received by the neurologists, but on the contrary was derisively ridiculed by his fellow members of the Association for Research in Nervous Mental Disease.

Bridge (8) while not denying that personality changes do accompany idiopathic epilepsy, states, "In all probability, the so-called epileptic personality is not an entity which bears any specific causal relationship to the disease, but represents in large part the response of such patients to the problems and situations which the very nature of their disease creates. In addition to the tremendous influence of environment on the personality epileptic patients, the underlying process has an undoubted
effect on the mental state. The interference with normal cerebral function caused by whatever scarring may be present in the brain, the general restlessness, irritability, and loss of memory of a temporarily functional nature observed during the active and progressive stages of the disease, and finally, the damaging effects of the convulsions themselves on the nervous system are all of unquestionable importance in producing the clinical picture of the epileptic personality, psychoses, and dementia.

The last theory of the origin of the fits looks upon the neurologic pathways involved as being merely incidental. This theory is the "explosive" theory, and believes that a fit arises as the result of some wide-spread change in the brain tissue, not dependent upon spread of nerve impulses, but upon some metabolic change such as anoxemia, hypocalcemia, hypoglycemia, alkalosis, and so forth. This last theory has stimulated a constant, intensive, unremittent search for abnormalities of a chemical or physiological nature in the epileptic, and the findings of this search will be further detailed in this paper.
Pathological physiology of Idiopathic epilepsy

Lennox (41) postulates three main factors operative in the causation of convulsions. The first factor is an inherent constitutional tendency to seizures, present in all patients who develop seizures, irrespective of the cause. This constitutional factor has already been discussed, and it must be conceded that little is known about it, any more so than we know, for example, about the ulcer constitution, the lymphatic diathesis, or the gall-bladder predisposition. The second factor in convulsions includes abnormalities of the idiopathic epileptic, these abnormalities including functional or structural abnormalities in the brain, or abnormalities outside of the brain as endocrine, gastro-intestinal and so forth. The third factor, which determines the frequency and severity of the epileptic seizures is physico-chemical, and includes changes in the acid-base balance, fluid balance, circulation, oxygenation of the blood, and so forth.
Abnormalities within the Brain

Gross brain changes which may be the cause of symptomatic epilepsy, have been enumerated under clinical conditions which may produce epilepsy. The material reported below concerns brain changes in the idiopathic epileptic only.

On autopsy, the idiopathic epileptic shows gross brain changes in many cases, though it must be conceded that occasionally the brain is grossly and microscopically normal. Bateman (6) reports the necropsy findings on 178 institutional epileptics as follows:—In 34 cases the epilepsy was found to have been symptomatic, such changes as cerebral syphilis, brain tumor, and so forth being found. The other 146 showed the following:—bilateral frontal atrophy in 60, unilateral frontal atrophy in 4, unilateral cerebral agenesis in 4, temporal lobe atrophy in 2, generalized atrophy in 3, occipital atrophy in 3, cystic choroid plexus in 15, tumor of the choroid plexus in 3, atheromatous vessels in 5, dilatation of the ventricles in 7, cerebral edema in 8, chronic thickening of the meninges in 8. These findings must be evaluated as to the relation of cause and effect. Thus, merely because we find cloudy swelling of the liver in a case of coronary thrombosis, we do not say that the patient died of this cloudy swelling. Likewise, the above pathological
conditions may or may not have been important etiological factors.

Concerning the size of the brains of persons with seizures, Munson (44) compared the weights of the brains of 245 idiopathic institutional epileptics with normal brains, and found that up to the age of twenty five, the brains of epileptics were much lighter than normal, and after that age, the brains of epileptics were of the same weight as the normal group. Munson interprets this as meaning that the epileptics with light brains die early.

At operation, Dandy (14) reports pools of subarachnoid fluid in dilated sub-arachnoid spaces, especially over the frontal lobes. "At operation, these changes in the subarachnoid spaces are strikingly evident to the naked eye. At autopsy, they are very poorly or not at all in evidence. The reason is that when the fluid is lost, as at autopsy, the arachnoid membrane collapses on the brain, and very little is to be seen." Dandy believes the fluid present is compensatory for whatever atrophy there is present, and does not believe that the fluid is primary and the atrophy secondary.

As to the microscopic changes in the brains of convulsants, Spielmeyer (74) notes that while many cases of epilepsy, especially those of short duration, show no
gross or microscopic changes in the brain, still, in the large majority of cases, he is able to find sclerosis in Ammon's horn, and in the cerebellum. This sclerosis usually resembles a thick glial proliferation in locally circumscribed portions in Ammon's horn, and shows a loss of ganglion cells in definite areas. The changes in Ammon's horn and in the cerebellum, can be found not only in idiopathic epilepsy, but also in symptomatic epilepsy. Spielmeyer, however, believes these changes are the result and not the cause of the convulsions. He explains their selective predisposition for these brain areas by their relatively poor blood supply, so that in the case of spasm of the cerebral blood vessels (which he believes to be the essential cause of epilepsy), these areas would suffer first. The work of Gildea and Cobb (31) on the effect of anemia in the brain of the cat, tends to support Spielmeyer's work since they found that complete cerebral anemia of ten minutes or less would invariably result in permanent injury to the cat's brain, with focal areas of necrosis, followed by gliosis, producing essentially the same histologic picture reported by Spielmeyer.

If we accept Spielmeyer's conception of the convulsions as the cause of gliosis, rather than the effect we can explain the mental and physical deterioration which
in some cases, at least, accompanies chronic idiopathic epilepsy. Spratling, (76) in 1904, stated that at least fifty per cent of all epileptics sooner or later became feeble minded. More recent studies indicate that the older writers, who dealt with institutional cases, were too pessimistic in their prognoses. In 105 extra-mural patients with epilepsy of over five years duration, Fettermann and Barnes (22) found an average intelligence quotient of 74%. These patients were followed over several years, and according to the authors, no diminution of the intelligence quotient could be found on serial study, nor was there any relation between the intelligence quotient, the type of epilepsy, the frequency of the seizures, or the duration of the seizures. Lennox and Cobb's (45) study on 844 non-institutional cases does show that the degree of mental deterioration tends to parallel the duration and severity of the convulsive seizures. They found that 79% of their cases were mentally normal who had epilepsy less than one year, 74% normal who had epilepsy less than 5 years, 60% normal who had epilepsy less than 10 years, while only 52% of those patients who had epilepsy were mentally normal if the duration of the disease was 15 years or more.

As to the pathologic changes in the brains of ep-
ileptics as interpreted by neurological findings, Hodskins and Yakovlev (36) have found a Babinski toe sign present in 29% of 300 institutional epileptics. They found evidences of deterioration in chronic institutional epileptics in a somatic sense, as well as a progressive tendency toward mental deterioration. Progressively developing and eventually bilateral symptoms of the pyramidal series were found with spastic paralysis predominating in the lower extremities. A Parkinsonian-like syndrome eventually developed in some of the patients.
Effects of Physico-Chemical Changes in the Brain

1. Anoxemia of the brain. Anoxemia of the brain in experimental animals is regularly followed by convulsions. Sir Astley Cooper (12) first produced convulsions experimentally by tying off both carotids in rabbits, and then compressing the vertebrals digitally. Convulsions appeared, and by releasing the pressure on the vertebral arteries, the convulsions ceased.

Asphysia (18) regularly produces convulsions in the experimental animal. A parallel condition in man is seen in Stokes-Adam's syndrome. In this condition, loss of consciousness occurs if the heart-block lasts ten seconds, and convulsions if it lasts seventeen seconds.(32) The onset of paroxysmal tachycardia is occasionally accompanied by a seizure, and convulsions may appear in pernicious anemia, arteriosclerosis, and after extensive hemorrhage. During the fall of blood pressure produced by compressing both carotid sinuses, loss of consciousness occurs and sometimes a convolution as well. (72)(81) Anoxemia would seem to be the main cause of convulsions in the above clinical conditions, and in increased intracranial pressure, we could hypothesize that here, too, blood flow through the brain was decreased.

Critical analysis of the above data would show that while convulsions can be produced by the above mechanisms, there is no evidence that they are the operative
causes in idiopathic epilepsy. Soma Weiss (81) and Smith (72) state that none of the idiopathic epileptics they have studied have had hypersensitive carotid sinus reflexes. While fainting is caused by cerebral anemia, epileptics do not necessarily have a convolution every time they faint. Lennox (42) induced fainting in idiopathic epileptics with amyl nitrite, and of the twenty epileptics studied, in only one could convulsions be produced in this manner. If cerebral anemia were the underlying cause of epileptic convulsions, we should expect all of the epileptics to have had a convolution when they faint. Gibbs (30) could find no evidence that there was a decreased cerebral blood flow preceding or accompanying convulsions in man. Lennox and Gibbs (47) found the oxygen and carbon dioxide of blood leaving the brain thru the internal jugular vein, and of the arterial blood to be within normal limits in 88 epileptics, the analyses being made before and also during the convulsive seizures. Lennox (42) found the total oxygen consumption of epileptics to be slightly low, tho well within normal limits. Immediately before and during petit mal attacks, there was no significant change in oxygen consumption.

While it is true that no derangement of oxygenation of the brains of epileptics has been proven, still it must also be granted that the oxygen saturation of the epileptic's
blood has been repeatedly shown to have an influence on the seizures. Thus, Lennox and Gehnke (43) found that with patients living in a compression chamber, increased oxygen tensions would decrease the number of convulsions, while decreased oxygen tensions would increase both the number, and the severity of the seizures.
Vasoconstriction

Recurrent constriction of the cerebral arteries has long been one of the favorite mechanisms invoked by the epileptologist as a cause of fits. The theory is excellent, the experimental proof a failure.

That cerebral vasoconstrictor nerves do exist has been shown by Penfield. He is a firm believer in a cerebral vascular mechanism in epilepsy. He describes the changes that occur in the brain during operation when convulsions are induced by electrical stimulation. "The one constant visible phenomenon in the brain during an epileptic seizure is cessation of arterial pulsation.... pallor may be present during the seizure but more generally follows it.... the epileptic brain is subject to local vasomotor reflexes such as have never been observed in the normal brain." The cessation of arterial pulsation is found in localized "epileptogenic" areas of the brain, (Penfield), and according to the location of this area, the type of aura, or the absence of the aura, is determined. Nevertheless, Penfield (59) in his review of surgical therapy of epilepsy, states that sympathectomy in most cases is valueless. This is contrary to what we would expect if sympathetic overstimulation, or cerebral vasoconstriction, were the fundamental cause of epilepsy. Penfield believes that scars in the brain set off the
convulsion by a localized vasomotor reflex, and notes that often the convulsions cease when the scar and the surrounding nervous tissue are removed en bloc by sharp dissection. Dandy(14) notes blanching of the entire brain occurs during the onset of convulsions, and states that the brain as a whole shrinks away from the opening in the skull. During the clonic stage of the convulsion, the entire brain becomes congested and cyanotic.

There is much clinical evidence of cerebral vasoconstriction preceding the convulsion. Pallor of the face prior to the onset of the convulsion is a matter of common clinical observation. Jackson (37) noted constriction of the retinal arteries by means of the opthalmoscope, immediately prior to the onset of a fit.

Wilson (84) argues against cerebral vasoconstriction as a cause of convulsions. He states that the epileptic fit comes on suddenly, whereas convulsions due to asphyxia, both in man and in experimental animals, come on after a latent period. Moreover, many conditions with known cerebral anemia, as cerebral thrombosis, often occur without convulsion, and sometimes without loss of consciousness.
Role of Increased Intracranial Pressure

Fay (21) recently presented a paper entitled "the mechanical theory of epilepsy", in which he presents evidence for brain edema and increased intracranial pressure being the cause of the convulsions in all the convulsive states including idiopathic epilepsy. Prior to this paper, Dandy, the neurosurgeon, and Pendergrass, a radiologist, had noted that one of the most constant findings in the convulsive states was the excessive accumulation of fluid in the subarachnoid spaces, which accumulation was especially marked over the frontal lobes of the brain. Fay states that he had often noted the milky appearance of the arachnoid in the convulsive states, along with an increased amount of cerebro-spinal fluid, which accumulations of fluid were especially marked over the frontoparietal area. He believed this increased spinal fluid in the subarachnoid space was due to an external hydrocephalus, this external hydrocephalus being due to an impaired reabsorption of the spinal fluid by the Pachionian bodies into the dural venous sinuses. The excessive fluid was compensatory, he maintained, for a cerebral atrophy, this cerebral atrophy being due to an increased intracranial pressure. He admitted that the spinal fluid pressure was not greatly raised in idiopathic epilepsy, but he also maintained that a chronic slight increase in intracranial
pressure could be, and in fact, was the cause of the cerebral atrophy. He reported an average spinal fluid pressure of 11.2 mm Hg in idiopathic epileptics (normal—8 mm. Hg.) Winkleman (85) reported histologic changes in the Pachionian bodies of 300 epileptics, these changes consisting of aplasia, hypoplasia, and fibrosis, and he believed that these changes would be sufficient to cause an increased intracranial pressure in epileptics, because of a decreased reabsorption of spinal fluid. Swift (77) added data which supported Fay's theory, when he reported the presence of anomalous venous sinuses, and assymetrical development of the transverse and sigmoid sinuses, as being especially common in idiopathic epileptics. He also states that the average size of the posterior fossae were smaller than normal in epileptics. Further support to the theory was furnished by Elsberg and Pike (19) who found that the susceptibility of cats to convulsive seizures induced by absinthe, was increased. Smaller doses of convulsant drugs were needed to produce seizures in cats when the intracranial pressure was raised by the intravenous injection of distilled water, or the intraspinal injection of paraffin. Conversely, larger doses of convulsant drugs were needed to cause convulsions in cats in whom intracranial pressure was lowered by the intravenous
injection of hypertonic solutions. Fay reported excellent results for his fluid limitation treatment of generalized convulsive seizures, though he also states that petit mal attacks were not benefited by fluid limitation.

Rowntree (68) forced fluids into dogs by the use of the stomach tube (50 cc water per kilogram every thirty minutes) and found that invariably the following train of symptoms developed within four to eight hours. The symptoms were, nausea, vomiting, salivation, convulsions, stupor, and coma. The convulsions were typically those of status epilepticus, and ended in death if water administration was continued after the onset of convulsions.

On the other hand, Cobb (10) found the average cerebro-spinal fluid pressure of idiopathic epileptics to be within normal limits. Tumors of the posterior fossa, accompanied by early high increase of intracranial pressure are rarely accompanied by convulsions. Fremont-Smith (25) have shown that no rise in cerebrospinal fluid pressure occurs in epileptics in whom fluids are forced, (six liters a day), and conversely when fluids were restricted to 300 cc a day, there was no lowering of spinal fluid pressure. Reports in the literature on the effect of fluid limitation vary from great enthusiasm (Fay et al) to extremely uncomplimentary attitude (83).

Summarizing the above data, we may conclude that
increased intracranial pressure increases the susceptibility to convulsions. Symptomatic epilepsy in which increased intracranial pressure is often found, as in eclampsia, alcoholism, uremia, meningitis, after head trauma, and so forth, are benefited by dehydration therapy. We must, furthermore, conclude that no proven increase in intracranial pressure has been shown to exist in idiopathic epilepsy. Therefore, though not denying the utility of dehydration therapy in symptomatic convulsions which are accompanied by increased intracranial pressure, we must maintain that increased intracranial pressure is not the fundamental cause of idiopathic epilepsy. Permeability changes in the nerve cells causing them to take up abnormal amounts of water, thus producing a brain edema, cerebral anemia, and convulsions are asserted to be the cause of seizures of idiopathic epileptics. McQuarries (50) notes sodium and chlorine ions are stored in epileptics during periods of positive water balance, and potassium ions are at the same time excreted in excess. This would cause a disturbance of the electrolytic equilibrium on the two sides of the nerve cell membrane, so that the cell imbibes more water. McQuarrie asserts that these changes in mineral metabolism are not found in non-epileptics.
Electrical changes in the brain during seizures

Lennox, Davis, and Gibbs (47) in 1936 reported the changes in electrical activity of the brain during grand mal and petit mal seizures. They obtained records of the electrical potentials in the brains of twenty-one patients during hundreds of seizures.

In the case of Grand mal, for a variable period before the convulsions there is an increase in the electrical activity of the brain. During the convulsions, the waves in the graphic records (which represent changes in potential in the nerve cells) are slower and of very large potential. In the period of stupor following the convulsion, there is an almost complete absence of electrical activity.

More extensive studies were made on petit mal. These studies were felt to apply to grand mal as well, since impairment of consciousness is the essential feature of the fit, and the muscular movements in grand mal make the obtaining of graphic records difficult. Petit mal is invariably accompanied by a burst of action potentials much larger and less frequent than the patient's usual potentials. From a frequency of ten to twenty a second, the waves slow to one to three per second, and from a voltage of ten to fifty millivolts, they increase to one hundred to three hundred millivolts. These waves definitely represent potentials set up by discharging
cells in the brain, according to Lennox.

Lennox offers the following as an interpretation of the meaning of the large slow waves shown in the kymographic record during the convulsive attack. In normal activity, there are many clusters of neuronal cells discharging, not in unison, but in harmony. The usual rhythm of ten to twenty discharges a second, is a mosaic of the activity of many centers. During the seizures, the many waves become one. The large waves represent not a suppression, or an augmentation, but rather a synchronization of various discharging cell clusters. There is an integration of activity as regards timing, but disintegration as regards the delicate and complicated interplay of various discharging nuclei." The harmony of the symphony orchestra has become a single note. The representative constitutional government has become a totalitarian state." The origin of the sudden synchronization in which the individuality of the discharging nuclei is lost, cannot at present be answered. It cannot be primarily an organic disease of the brain because structural changes are constant, while convulsions are periodic. (42)
Abnormalities outside the Nervous system

Hypoglycemia, produced by such exogenous causes as over dose of insulin, or endogenous causes as adenoma of the isles of Langerhans, causes hunger, pallor, sweating, and sometimes convulsions. Ziskind (88)(89) reports that he fasted two hundred epileptics for periods of thirty-six hours. No increase in the number of attacks were noted. Blood sugar levels on these epileptics were within normal limits. Epileptics were no more sensitive to insulin injections, than the normal control subjects. Ziskind concludes that while hypoglycemia may cause convulsions, there is no evidence that hypoglycemia plays any part in idiopathic epilepsy.

Hypocalcemia, due to surgical removal of the parathyroids, or as a metabolic deficiency in infancy, is frequently accompanied by generalized convulsions, as well as laryngismus stridulus, and carpopedal spasm. The blood calcium and phosphorous are within normal limits in idiopathic epileptics, however. (33)(57)(70). No proven benefit has followed parathormone or calcium therapy in epilepsy.

McQuarrie (50) reports that the blood cholesterol and blood lecithin are lower than normal in idiopathic epileptics.

The hematology of the epileptic is normal.(66)
There is a slight leucocytosis following the convulsive seizure.

There is no constant abnormality of the blood or of the urine reported in epilepsy. Transient albuminuria is said to follow a seizure, but this is known to occur quite frequently after any severe muscular exercise.

According to Lennox (42), the cell count, spinal fluid pressure, and protein and chemistry are normal in the epileptic. Though convulsions are quite frequently a symptom of neurosyphilis, there is no evidence that syphilis is more common in the epileptic than in the general population.

Although changes in the endocrine glands have often been offered as a cause of epilepsy, there is no evidence that such changes exist. Talbot (88) refers to an autopsy series of 259 epileptics in which no morphological changes in the endocrine glands sufficient to account for the seizures were found. Wolf (86) recommends the use of the following endocrine products in epilepsy:—thyroid, pituitary, and gonadal hormones.

The allergist also claims epilepsy as within its field, and it is true that the convulsions of epilepsy do resemble those produced by anaphylaxis. Forman (34) reports the cure of ten epileptics by removing those antigens from the patient's environment and diet, to which they
were sensitive. Spangler (73) states that the percentage of positive skin test reactions is as high in epilepsy, as in allergy, and recommends routine skin testing of all epileptics.

Constipation is very common in epileptics. In 1916, a bacillus, B. epilepticus, was reported as the cause of epilepsy, but this work has never been confirmed. Removal of the colon, in whole or in part, has been tried in epilepsy, but with no improvement in the disease. Higgins (34) states that fits are more common in epilepsy when the patient is constipated.

The relation of the acid-base balance of the body to convulsions has caused much comment of late. Rosett (67) found that forced breathing often precipitated convulsive seizures in epileptics, and sometimes in normal persons as well. This effect is presumably due to the alkalosis produced by an excessive loss of carbon dioxide with hyperventilation of the lungs. Though epilepsy has been treated with some success by ketogenic diets, there is no evidence that there is a disturbance in the acid-base balance in epileptics. Geyelin (28) reports, "There is no evidence that there is a disturbance in the acid-base balance in epileptics, though it may be said that the blood of epileptics shows a distinctly wider range of pH from day to day, and from hour to hour, than does
the blood of normal persons."

Reflex irritation from such causes as teething and intestinal parasites, though still mentioned in some pediatric text books, are no longer considered to have any other relation to convulsions, than pure coincidence.
Summary and Conclusions

1. Certain alterations of the physiology of the body, though they do not cure epilepsy, and though they have no direct etiological relation to the disease, can modify epileptic seizures. The induction of alkalosis by means of hyperpnea, or by the ingestion of large amounts of alkali tends to precipitate seizures, while acidosis tends to inhibit seizures. Likewise, the retention of fluids by the body tends to precipitate convulsions, whereas a severe limitation of the fluid intake tends to inhibit them. Similarly, an increased oxygen content of the arterial blood tends to decrease seizures, while a decreased oxygen tension tends to precipitate them.

2. There is no evidence, however, pointing to any defect in the metabolism of the epileptic. While hypoglycemia, alkalosis, and lowered blood calcium can cause convulsions, it may be definitely said that these abnormalities are not found in the epileptic.

3. If on the one hand, we show that convulsions can be produced by cerebral anemia, by mechanical irritation of the brain, by ablation of certain portions of the brain, by various diseases, by convulsant drugs, by electrical stimulation of the brain, and so forth, STILL IT MUST BE CONCEDED that epilepsy can and does exist when no such pathologogical findings are present.
4. Epilepsy, then, is merely a symptom. Like every other symptom, it must be investigated to determine the cause.

5. Idiopathic epilepsy will some day cease to exist. It is inconceivable that convulsions can occur without cause, and that cause will some day be fathomed.
1. Anderson, C. L. "Epilepsy in the State of Michigan" Mental Hygiene vol 20 p 441--462 July 1936


3. Albutt, C. "Greek Medicine in Rome" McMillan and Company London 1922


5. Bagley, C. "Xanthochromia--the late symptoms of cerebral irritation following head trauma" in "Epilepsy and the Convulsive State" Williams and Wilkins Co. Baltimore 1931


9. Clark, L.P. "Psychobiologic Concept of Essential Epilepsy" in "Epilepsy and the Convulsive State" Williams and Wilkins Co. Baltimore 1931


12. Cooper, Sir A. "Principles and Practice of Surgery" Wells and Libby Boston 1835

13. Cushing, H. "Hyperactivation of the Neurohypophyses as the pathological basis of eclampsia and other hypertensive states" Am. Jour. Path. vol 8 p 145--173 March '34

15. Dandy, W.E. "Cerebral Pneumography" in Dean Lewis Surgery vol 12 p.89-136 W.F.Prior Co. Hagerstown, Maryland


17. Davidoff, L.M. & Kopeloff, N. "Repeated Experimental Convulsive Seizures in Animals" in "Epilepsy and the Convulsive State" Williams and Wilkins Co. Baltimore 1931


22. Fetterman, J. and Barnes, M.R. "Intelligence of Patients with Epilepsy" Arch. Neur. and Psych. vol 32 p 797--80 Oct. '34

23. Foerster, O. and Penfield, W. "The Structural Basis of Traumatic Epilepsy and the results of the radical operation" Brain vol 53 p 99--119 July '30

24. Forman, J. "Atopy as a Cause of Epilepsy" Arch.Neur and Psych vol 32 p 517--522 April '34

25. Fremont-Smith, F. and Houston, M.T. "Influence in Variations in Fluid Intake on Intracranial Pressure in Epileptics" Arch. Neur. and Psych. vol 39 p 453--466 April '33


27. Garrison, F.H. "An introduction to the History of Medicine" W.B.Saunders and Co. 1929


31. Gildea, E.F., and Cobb, S. "Effects of anemia on the Cerebral Cortex of the Cat" in "Epilepsy and the Convulsive State" Williams and Wilkins Co. Baltimore 1931

32. Gowers, W.R. "Epilepsy and other chronic convulsive disorders" Wm. Wood and Co. New York 1885


34. Higgins, H.H. "Intestinal Bacteria and their relation to the epileptic convulsion" in "Epilepsy and the convulsive state" Williams and Wilkins Co. Baltimore 1931


37. Jackson, H. "London Hospital Reports" Brit. M.J. vol 1 p 773--775 1875


41. Lennox, W.G. "Certain chemical and physiological conditions which may influence seizures" in "Epilepsy and the convulsive state". Williams and Wilkins Co. 1931

42. Lennox, W.G. "The physiological pathogenesis of epilepsy". Brain vol 59 p 113--122 April '36

43. Lennox, W.F. and Behnke, A.R. "Effect of increased oxygen pressure on the seizures in epilepsy". Arch. Neuropsychiat. vol 35 p 783--790 April '36

44. Lennox, W.G. and Cobb, S. "Epilepsy--from the standpoint of physiology and treatment". Medicine vol 7 p 105--265 May '38

45. Lennox, W.G. and Cobb, S. "The non-institutional epileptic" in "Epilepsy and the convulsive state". Williams and Wilkins Co. 1931


50. List, Carl.F. "Epileptiform attacks in cases of glioma of the cerebral hemispheres". Arch. Neuropsychiat. vol 35 p 322--347 Feb '36


52. Moon, R.O. "Hippocrates and his Successors". Longmans, Green and Co. New York 1923

53. Olkon, D.M. "Genuine epilepsy--studies of the microscopic changes in the capillary system as a probable etiologic factor" in "Epilepsy and the Convulsive State". Williams and Wilkins Co. 1931
54. Parker, H.L. "Epileptiform convulsions--the incidence of attack in intracranial tumors" Arch. Neur. and Psych. vol 23 p 1032--1041 May '30

55. Paskind, H.A. "Frequency of epilepsy in offspring of persons with epilepsy" Arch. Neur. and Psych. vol 36 p 1044--1048 Nov. '36

56. Paskind, H.A. "Relationship of Migraine, Epilepsy, and some other neuropsychiatric disorders" Arch. Neur. and Psych. vol 33 p 45--50 May '34

57. Patterson, H.A. "Some observations on the blood calcium content in epilepsy" in "Epilepsy and the Convulsive State" Williams and Wilkins Co. 1931

58. Pendergrass, E.P. "Interpretation of the encephalographic findings with comments on those found in the convulsive state" Arch. Neur. and Psych. vol 23 p 946--955 May '29


65. Radcliffe, C.B. "Epilepsy and other affections of the nervous system" John Churchill London 1854

66. Rosenthal, N.M. "Hematologic Findings in epilepsy" in "Epilepsy and the convulsive state" Williams and Wilkins Co. 1931


69. Seargeant, P. "Some observations on epilepsy" Brain vol 44 p 312--336 1921


73. Spangler, R.H. "Some allergic factors in essential epilepsy" Jour. of Allergy vol 3 p 45--63 May '31

74. Spielmeyer, W. "The anatomic substratum of the convulsive state" In "Epilepsy and the Convulsive State" Williams and Wilkins Co. Baltimore 1931


76. Spratling, W.P. "Epilepsy and its treatment" W.B. Saunders Co. Philadelphia 1904

77. Swift, G.W. "The posterior fossa in epilepsy" in "Epilepsy and the convulsive state" Williams and Wilkins Co. Baltimore 1931


80. Walsh, J.J. "Medieval Medicine" A.C.Block, Ltd. London 1930

82. Wiggers, C.J. "Physiology in Health and Disease" Lea and Febiger Philadelphia 1934


85. Winkleman, N.W. "Pathological Studies of the Pathogenin Bodies in various types of convulsive states" Arch.Neur. and Psych. vol 21 p 146--183 Jan '28

86. Wolf, W. "Endocrinology in Modern Practice" W.B. Saunders Co. Philadelphia 1937

