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The growing conception of epilepsy

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THE GROWING CONCEPTION

OF EPILEPSY

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Epilepsy, and its attendant ills, has troubled mankind since the beginning of time. Archeological excavations have disclosed that more than a quarter of a million years ago, Neolithic man was puzzled by the same symptom complex which exists today. In an effort to prevent the ravages of the condition, those Neolithic medicine men trephined the skulls of their savage brethren for epilepsy with a perforating outfit consisting of a flake of obsidian or a shark's tooth.

These post-glacial men were convinced that epilepsy and kindred convulsions were intracranial affairs, and in an effort to relieve the condition, resorted to what has been proven to be the earliest adventure of man in the line of major surgery.

Trepanation for convulsions, an operation not attempted by the civilized races until the middle ages, (46) (25), has continued to be the practice of savages throughout these thousands of years. Survivals of this practice still persist in Northern Africa, Polynesia and even in Montenegro, but no craniums exhumed on the sites of the earliest civilized potamic peoples show any signs of such operations.

The proceedure survived among the Gauls until after Gaul was under Roman domination, but the Roman surgeons following Caesar and his legions took no note of its existance.

Such appraently was the situation among those tribes and peoples which are now included among the earlier civilizations. In fact, among these peoples, the affliction was not classified with the organic diseases, due perhaps to the fact that traditional medicine, inherited from primaeval ages the belief that epilepsy implied demoniacal possession.

Clonic accidents were regarded among the very earliest Greeks as soul-racking visitations of divinities, especially Cybele, Poseidon, Hecate and Apollo.

In ascribing these conditions to divine enthusiasm, the Greeks recalled the behaviour of the Delphic pythoness when the priest-induced fit was upon her, or the frantic actions of the celebrants of the orgiastic rites of Dionysus. The Aesclapids in Ionia and in the west, first became aware that the condition might be organic due to the fact that convulsions, similar to these idiopathic attacks, accompanied

several physical diseases. Pythagoras, Acnon, Empodocles, Alcumaeon, Diocles, and Democritus, all of whom were beginning to construct a positive basis for medical science, - each in turn brought attention to bear upon this phenomenon which so touched, awed, and dismayed the bulk of mankind. Empodocles' interest in hysteria and epilepsy was very considerable and Democritus spent much energy in his curious quest of the source of the convulsions.

In the contemporary Hippocratic writings (44), are found many references to what, in agreement with ancient tradition, have been interpreted as epilepsy. The name Sacred Disease, or the disease of Hercules, occurs not only in the hippocratic writings, but is also mentioned in the works of Plato and Heradotus. Plato, In Timaeus, attributes the sacred disease to disturbances in the brain (30), caused by a mingling of white phlegm and gall. In his Laws, he discusses the claims to restitution of a man who had bought a slave and found him to be suffering from phthisis, stones, strangury and sacred disease. Hence, the term sacred disease, is one definite disease and not a

General term. There is little doubt that the name was coined by the people, certainly not by the physicians. Attempts were often made in antiquity to explain the name, but the great variety of such explanations indicates that late antiquity had already forgotten its real genesis.

As the writings of the time show, the people and the magicians believed that the sacred disease was caused by the Gods. The modes of convulsive siezures had been distributed in strange categories, in which the hand of the priest-magician may be seen. For instance, if during the onset of a siezuer, the patient both foamed at the mouth and struck the floor with his feet, Mars had entered the body of the sufferer. If he bleated like a goat, and ground his teeth, Cybele possessed him. If he had involuntaries, Hecate Enodie was the author. She too was responsible for the saltatory form.

It was precisely this type of fabulous belief, fostered by the despairing minds of the past, that the Coan school sought to destroy with one blow. Hippocrates, in his immortal critique and satire, derides the common belief and speaks of such ascript-

ion to the Gods as chittering folly (20). Hippocrates himself, (2) was of the belief that the Gods were not the cause of epilepsy, and that instead, it arose through heredity like many other diseases, though only in people of phlegmatic constitution. He confessed that the anatomical and physiological reasons for the appearance of the symptoms had not been defined definitely, yet the cause of the disease was surely in the brain.

After describing the circulation of "phlegm" in the human body, he proceeds to explain the probable etiological factors of epilepsy (20). When the phlegm is cut off from the heart and lungs, it runs down into the other vessels from the brain, and then the following symptoms occur: the patient becomes dumb, he suffocates, foam flows from his mouth, the teeth are clenched, the hands cramped, the eyes are twisted and the patient loses consciousness, and may lose excrements. These attacks affect sometimes the left, sometimes the right, sometimes both sides.

Each symptom is explained as follows: the patient is dumb when the phlegm suddenly enters the vessels, cuts off the air from both brain and vessels,

and furthermore, affects breathing. For when pneuma is taken in through the mouth and nose, it goes first to the brain and from here into the body, and is distributed along the vessels into the members, which it thus endows with understanding and movement. If therefore, the vessels are unable to receive the air, the person becomes dumb and unconscious. The hands become painless and numb and cramped since there is no circulation. The eyes are twisted, because the small vessels, cut off from the air, beat violently. The froth from the mouth comes from the lungs; for when no pneuma enters, it foams and effervesces as in a dying man. The excrement falls through the violence of the suffocation. When the pneuma does not as usual enter the body, the liver and upper entrails fall forward against the vessles; the gullet and stomach are held fast, and so suffocation arises. The patient kicks when the pneuma, shut in the legs, rushes up and down through the blood finding no outlet, and causing cramps and pain. When the cold phlegm flows back into the warm, it may cause sudden death if the cold overcomes the warm.

If the flux is less severe, the warm gains mastery, and after it has been well distributed and mixed, the vessels take air in again and the patient regains consciousness. The falling of the patient was presumably well known, but no mention is made of it in these particular writings. Neither does the author give detailed directions for the cure of the condition, except to say that since it is an unusually severe and trying disease, unusual means must be used to combat it. The method of treatment was detailed in only one case, where a patient was put on complete starvation diet, including total abstinence from beverages.

Following Hippocrates (29), the dogmatists, Praxagoras, and Diocles of Canystos, regarded epilepsy as due to derangement of the humors. The ancient schools of empirics, were tormented with resurgent questions concerning the nature of the epileptic clunus - what were the convulsions and by what precipitated.

The idea of epilepsy among the contemporary writers of the ancient Hindu civilizations (49),

coincided well with the humoral theory of the Greeks. These Hindu physicians believed that there were four kinds of epilepsy; one being produced by the derangement of each of the three humours, and the fourth by a combination of the three.

They believed that when wind, bile and phlegm were deranged by grief, sorrow and the like, they passed into vessels immediately communicating with the heart, and produced the disease, with the loss of sense and memory. It was also thought to be caused by the improper use and over-indulgence of the senses; as too much or too little listening, seeing, tasting smelling, etc.; improper mixtures, or putrefied articles of food; the neglect of the calls of nature; connection with women during the flow of the menses; by such passions as grief, sorrow and anger. By these causes, the mind was thought to be so affected as to cause epilepsy (49).

Alexandria contributed little to the line of inquiry in the pre-Christian Era except anatomies of the central nervous system. When Rome became the center of civilization, its medicine continued in the

hands of Greek physicians. Asclapiades (124 B. C.), who turned physician, was the leading medical figure in the Golden Age of Rome. He was an outstanding neurologist and many of his works on mental alienation still remain. The Latin poet Lucretius, in his "De Rerum Natura" (26), described with considerable color, epilepsy as it existed in his day.

Celsus (30 B. C. - 50 A. D.) as was the custom among the Roman writers, called epilepsy "morbus comitialis", because if it occured on the day of the comitia, it was thought to be an ominous sign, and it broke up the consultation. Celsus did not pay particular attention to, or place emphasis upon the causative factors of epilepsy, nor did he hesitate to use Hippocrates' description of it to his own ends. Therapy is what interested Celsus - "Purge the patient with alum or black veratrum, anoint his head with old oil and 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 of seizures by drinking the warm blood of

fallen gladiators. A miserable remedy", he adds, "serving merely to make more miserable those who suffer from an intolerable disease".

However, despite Celsus and due to the preponderating influence of Pliny, the hot blood of gladiators was held to be of prime efficacy. Perverse generation after generation advocated its use centuries after gladiatorial combats had ceased. "A young stag's blood will do", suggested Scribonius Vargus, "but the stag must be bled with the self same sword that has cut the throat of a gladiator". Finally, as the preposterous swords vanished, the formula was again altered: "Take the blood of a healthy young man of twenty five, quaff the liquor sanguinis and pray to Saint Hubert". This was the 17th century outgrowth of the old Roman belief (7).

Anctaeus, the Cappadocian, (2nd century A. D.), brought a precision and method to apply to the study of epilepsy which had hitherto been lacking. His chapters on epilepsy and hysteria are valuable contributions. He discribed all the natural phenomena of the disease with exquisite industry and accuracy,

and made a most searching analysis of the prodromal symptoms of epilepsy - motor, sensory and psychic. The grand mal attack is adequately pictured, and the physical and mental deterioration of chronic cases is dwealt upon in detail: "If the epilepsy passes into the chronic stage, the sufferer no longer is able to rehabilitate himself in the interval between crises. He is heavy, morose, bruised in spirit, cruel and intractable; nor will age or feebleness succeed in mollifying him. He sleeps little, has monstrous bad dreams; no appetite; digestion deranged; his complexion pale and leaden. Incapable of attention because of the dual abfuscation of mind and sensory faculties, he is hard of hearing, has ringing in the ears, and noises in the head. Speech is embarrased, halting; after the reason finally becomes so involved that the unhappy being sinks into a state of imbecility".

His method of treatment was quite modern, and included care of the patient during an attack, antisposmodic medication, and general hygienic measures. Aretaeus was an Asiatic Greek, and apparently never practiced medicine at Rome. He does not mention any writer but Hippocrates, but according to some writers,

he drew extensively from the Syrian, Archigenes of Apamea (54 - 117 A. D.) for much of his material (47). His advanced neurological conceptions would indicate that there was a rapid spread throughout the antique world, of the new information concerning mental and nervous diseases.

After Aretaeus came Galen (131 - 200 A. D.), who had achieved a very certain knowledge of the physiology of the brain, spinal cord and nerves by means of experiments and dissections on the lower animals. However, he clung to the traditional fictions of humoral pathology and ascribed epilepsy to an obstruction of the cavities of the brain by phlegm or black bile; convulsions, like paralyses, were due to a lack of phlegm in the nervous system.

Galen felt that after a lifetime of active research, he was not certain as to the etiological factors of epilepsy. "Whether convulsions arise from too much toil, too little sleep or food, or great anxiety or dry hot fevers such as are accompanied by frenzies, you should make no mistake in ascribing the cause to one of two things - either dryness or evacuation".

Galen traveled widely, and gained unparalleled drug-lore, but he did not use it to the best advantage in his treatment of epilepsy. He employed theriaca, supplemented by pedal venesection in the spring. Diet and regime were important considerations with him, and he wisely put much emphasis upon these matters.

Paseidonas, the Empirate (2nd half of 4th century) is an important representative of ancient psychiatry, of whose works scanty fragments have remained. Convulsions in epilepsy, he conceived as arising from the presence in the nerve centers of some materia peccans of which they strive to rid themselves. "Mania arises from excessive determination of blood to the brain or by the impletion of waste blood or bile. When mania arises from blood alone, the patient is siezed with inextinguishable laughter, seeing objects of mirth, he assumes a merry expression and sings constantly". Paseidonas regarded epilepsy in the aged and newly born as incurable.

From another portion of the Roman world, Sicca, south of Carthage, came Caelius Hunelianus (end of the 4th century) who is regarded by some as the arch-apostle of psychiatry in antiquity. He excelled in differ-

ential diagnosis, especially between epilepsy and hysteria. He considered most of the palliative measures of his time, but neglected with scorn the surgical suggestion of castrating the unfortunates.

Epilepsy was very prevalent in the era of Imperial Rome, and the government maintained medical hostileries for those fallen on public charge, where they were cared for with some show of humanity and science. Not infrequently institutional cases were taken in groups, under proper guardianship, to the baths and circuses.

Although the role of neuropathic manifestations in the religious life of the Greeks had been great, and greater yet in the practices of the Romans, such manifestations were insignificant compared with what was to come. "Possession by the Gods" became "possession by the devil" and the evils were multipled thereby.

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 he healed them"(Matth. 4:24).

Jesus gave his disciples "power against unclean spirits to cast them out". "In thy name shall they cast out devils" (Mark 16 : 17).

The Alexanderine and Byzantine compilers of the sixth and seventh centuries summarized in concrete form the scattered data regarding neuropsychic phenomena as observed in the eastern and western halves of the Empire. Alexander of Tralles, (6th century), is the outstanding figure of this group of writers (46). Aetius and Paul of Aegina, particularly Paul, exercised considerable influence upon midaeval medicine by their writings.

Alexander, in the twelve books of his "Therapeutica" taught that epilepsy was due to the obstruction of the brain by phlegm and black bile, and that it presented a three-fold aspect inasmuch as it may arise in the head, in the stomach, or other organs. His treatment aimed to remove the humoral obstruction by means of purgatives, venesection, rubbing and baths.

Arabian medicine was merely Greek medicine reclothed in Oriental dress, yet the clear and positive mind of the Arab had brought order and arrangement

into this reappropriated material. Rhazes (852-932 A . D.) physician in chief to the great Adudi hospital in Bagdad, and his teacher Rabban, had written much on nervous diseases and epilepsy, founded largely on their experience in the clinics at R ay and in the Moslem capital.

Impartial clinical research, as illustrated by the work of Rhazes, and Ali Babbas (writer of the Kingly book), fell under the ban of Avicenna, who wrote a lucid, comprehensive and self contained system which he called the "Canon", and bade his "brothers" to read no other. He considered that he had rendered the study of the ancients and the toilsome scrutiny of nature utterly superfluous. So powerful was his influence, that for four centuries, the art of impartial clinical observation lay as dead.

Meanwhile in the monkish hostels of Europe, Christian leaders had reared an array of martyrs and saints, available to those whose sad lot it was to be convulsion ridden. As a preserver from epilepsy, St. John the Baptist undoubtedly came first. The bonfires lighted on St. John's D ay were baptisms by fire, to

which the epileptics and hysterical of all lands - Greek, Mohemmedan, and Western Europe - resorted. Among the primitive Christian sects in Abyssinia and around Bosna, St. John is to this day worshipped as the protecting saint of those who are affected with epilepsy. Epilepsy has long been known as St. John's disease.

St. michael, the special adversary of Satan, was for a time the particular patron of epileptiform seizures, although from the tenth century forward, he shone more in his character of Plague Saint. Italy raised a special saint of her own to combat epilepsy. This was St. Vitus of Sicily, whose post-humous efficacy was far more wondrous than the powers ascribed to him during life. St. Cornelius, the centurion, St. Valentine and St. Giles were powerful intercessors to whom epileptics could appeal. St. Hubert, too was thought to have special power over epilepsy.

Among the English healing-saints, Guthloc of Croyland should be mentioned. He believed in taking active measures against Asmodeus and the other devils of epilepsy; he expressed them with his girdle by tying a half hitch about the middle of the patient.

An old method this, but one which persisted for long. For years the dancing maniacs carried girdles which bystanders cinched for them, to quiet the tumultuous demon.

These benighted practices continued to be popular until the time of the surgeons, Roger and Roland, who devoted much attention to epilepsy and associated disorders. In the "Glosses of Four Masters", a chapter deals with the surgical aspects of epilepsy, catalepsy and amnia. The Glosses are not very clear on this point but they seem to recommend the employment of a hot iron, rather than trephining, which was then more widely used.

During the middle ages, there were various theories propounded concerning epilepsy. Constantine, the African, believed, much as did Galen, that epilepsy came on at stated times, as for example, with the waxing moon; for all things moist increase with the moon's increase. Epilepsy, with the moon on the wane, must be very cold and little moist in its nature. He prescribed ass'es liver and the fourth stomach of ruminants.

Platearius urged the withdrawal of three drops of blood from the shoulder of the patient. Ganiopontus and some of the other masters followed Galen and Riascorides in prescribing paeonia, a remedy which remained in favor for centuries, down to the days of Heller and deHaen (19th century).

To Guy de Charliac (1363) epilepsy was simply a convulsion of the entire body arising from an excess of humidity. As a result of his indifference to these matters the topic was little discussed among surgeons for some years. However, some advancement had been made in the care of epileptic patients.

The traveller, Benjamin of Toledo, had seen hospitals for the insane in Bagdad as early as the twelfth century. In Western Europe (42), epileptic cases were cared for in such places as the "Kasten Hospital" at Frankfort, modelled on the Hamburg Hospital of 1375. Spain had several hospitals of this order: Valencia (1409), Saragosa (1425) Seville (1426) Toledo (1483).

The treatment afforded in such places had much in common with that of earlier centuries. John de Vigo (1514) recommended "Bathe the patient in a baine

made of goats milke, cowe milke or sheepe milke, or a baine of leaves of mallows and violets, the seeds of quinces, pullium and hollyhock. The roots of holly hock somewhat stamped, clean barley and twenty wardens or great peans boiled in the broth of a hen, with milk and with the broth of the head and feet of a calf" .

Ambrose Pare (1510-90) insisted that epilepsy and catalepsy were of uterine origin, as was hysteria. The mechanism was due to the ascent of the uterus and pressure of that organ upon the pylorus and heart. Pare admitted into his scheme, as a matter of course, demons, cacodemons, and the incomparable artifices of the Prince of Darkness.

With the increase of clinical facilities afforded by the hospitals springing up all over Europe, abundant psychiatric material was made accessible to those who were interested. Clinical teaching was revived at Padua by Mortanus. The great printing houses at Venice, Lyons, Basle, and Paris began pouring forth a full and flowing stream of classical and medical matter of inestimable worth to medicine.

From the Aldine Press there appeared in Venice in 1561 a quarto with the title "De Comitiali Morbo",

by Jerome Gabucinus of Fano. The preface is dated 1544. This is presumably the earliest monographic discussion of epilepsy in the newer literature. Medical literature dealing with epilepsy and other convulsive states entered a phase of marked expansion in the course of the sixteenth century. Several systemic dissertations attempting to classify the various known forms of the disease were written (Plater 1536-1614 and Leorellus Faventius), but the majority were widely scattered "Consilia" or letters of advice, which contained numerous discourses on epilepsy.

In spite of the advancement in medical literature, the universal inquietude regarding sorcery, black magic and demoniac possession continued unabated. In Brandenburg, Holland, Italy and particularly in the convents of Germany between 1550 and 1560, strange eruptions of epilepsy and hysteria, on a hugh scale, hardened and darkened the minds of judges, inquisitors and exorcists alike. In 1585, at Hamburg forty three "sorceresses" were tortured and went to the stake in one group. The story of the possession of Micole Obry (1565); of the possession of the Ursulines of Aix (1609-11); of Jeanne

des Anges and the Ursulines of Loudon (1632-39); of the outbreak at Louviens (1642) -- all linked together form the craze of nympholepsy and religious hysteria in France.

The pseudo-monarchs of demons ran into a veritable reign of terror. Finally Johan Weir (1515-88) laid a finger upon the sanguinary judges in behalf of the afflicted victims, -- "These convulsionaires, whom you call sorceresses, are not criminals", said he, "they are sick people, abused by false images. D o you think that these poor souls do not suffer enough, that you use your ingenuity to make them suffer more"? Pierre Channon and the cautious Montaigne tried in vain to persuade their countrymen that to broil human beings alive, was to put too high a value upon conjecture.

Among the common people, still survived the quaint custom of weighing an epileptic against his counterweight of grain or goods to be donated to the shrine of S t. Cornelius, St. Ghislain, or St. Giles. Huge balances were kept at many altars for this purpose. The patient was presented to the Saint, put in the balance against his gift of equal weight, and then

borne three times about the altar to the accompaniment of prayers and incantations. If a cure resulted from this ceremony the formularies of the Church required that it be announced as "extraordinary, supernatural and miraculous", which was well within the truth.

At the beginning of the seventeenth century, special monographs on epilepsy began to appear; their number indicated the highly increased efforts to actualize the disease and set it forth with its complications and sequelae. Vincentius Alsarius a Cruce brought out in Venice in 1603 his "De Epilepsia Libri tres" and in the same year Jean T axil published at Lyons a work with the same title which was immediately translated into French. The latter dealt largely with convulsions and epilepsy of childhood, and contained a noteworthy reference to the use of the trephine.

In 1609, J. Leo published at Leyden a quarto dealing with sensory and essential epilepsy; and in 1616, at Halle, Matthew Unzer issued his "Epilepsia .....descriptis".

It was not until well after the middle of the century that stable and sound ideas regarding the divers forms of epilepsy were obtained. Focal and reflex factors, the role of the blood, stomach, teeth, genitals, gravid uterus, nasal membrane, dura mater, etc., had hitherto failed to hold the attention of observers. Many of the old theories concerning the role of bile, phlegm, etc., were ruled out by the discovery of the mechanics of the circulatory system, by Harvey in 1646.

Weir and Lusitanus had unmasked feigned forms of the disease, and it remained for others to classify cases as hereditary, alcoholic, traumatic, syphilitic, sensory, etc. Masked, frustrated, and nocturnal epilepsies were noted. Shortly before the birth of Boerhaare in 1668, Leyden became the prime center of instruction of psychiatry in Europe. From the Leyden press came forth the following notable tracts on epilepsy, all in quarto, and all bearing the title "De Epilepsia": J. Cammerstein, 1645; B. Chiliani, 1664, J. Van Hogemade, 1666; J. Bel 1669; A. Bultynck, 1669.

At Tugolstadt, in 1675, appeard the "Tractatus de morbo sacro" of P. J. Shonefelder; the "de morbo comitali" of D. C. Volcker appeared at Enfurt in 1688.

While the symptomotology and natural description of epilepsy had been lifted out of the low plane of realith into a higher, the therapeutic handling remained unreal and degrading. The most popular anti-epileptic powders of the day consisted of the un buried cranium of a man who had met a violent death, pearls, coral, horn of licorne, musk, caribou foot, the dried and brazed secundines of a sanguine primipara, and other equally far fetched ingredients. So brisk was the trade in "after births" for use in "mal caduc" by the sage-femmes employed in the obstetrical wards of the Hotel Dieu of Paris, that a terrific scandal resulted there in 1672.

The better class of physicians treated their convulsed patients with paeonia, valerian, black hellibore, oak, mistletoe, oriental musk and opium. The use of mistletoe had come down from remotest Druidical ages. It is encountered in the anti-epileptic preseriptions of all times. Lauded by Bayle in Eng-

land, employed by Boerhaare and his pupils, Van Swieten and de Haen, by Tissot (1771) it doubtless continues in use to this day among certain classes of people. As for the use of powdered cranium, this was fostered by Paracelsus, who put a price upon the heads of executed criminals by ascribing special efficacy to the bone at the juncture of the sagittal and lambdoidal sutures.

Thomas Wills in 1667 reaffirmed, to the satisfaction of the learned of his day, the fact that the central nervous system is the seat and source of all convulsions, and Wills was supremely well qualified to question the beliefs of the ancients. His merits as a clinician had been well supported by researches on the structure and blood supply of the brain and its appendages, andupon the physiology and pathology of the nervous system. His clinical studies upon the behavior of "convulsionaires" were extraordinarily detailed and accufate. His portrayals of convulsions in childhood and adult epilepsy came nearer to the modern conceptions than any that had hitherto appeared. His reasoning on the line of neuropathology was

possibly not much less turbid and fallacious than much of that which exists today, and his influence was felt throughout the continent.

In Italy, Georgio Baglini, (1668-1707), one of the great apostles of experimental physiology, together with Bonelli and Stensons studies on the physiology of muscles, had a marked effect on the clinical investigation of clonus, and many able monographs on epilepsy came from the Italian writers.

During the seventeenth and eighteenth centuries, and until the latter part of the nineteenth, very little medical literature was p ublished; Europe was in the midst of a series of wars and the Americans were so occupied with conquering and governing their democracy that they had no time for research and publication. Information concerning the advance of medical science must be gained from widely varied sources, and references to epilepsy are rare.

Many of the unfortunate "witches" burned at the stake during the early years of the United States, were undoubtedly epileptics. But the condition went

unrecognized and they were afforded the same treatment that epileptics had been receiving from the hands of the ignorant populace for many centuries.

A history of George Washington and his family (22) reveals that his step-daughter, Patsy Curtis, was a victim of epilepsy, and she had been treated by many of the physicians of that day. A certain Joshua Evans is said to have "put an iron ring on Patsy for fits". Another, Mr. John Johnson, treated Patsy and was paid fourteen pounds for his frequent visits; they were unavailing however, and she died in one of her fits. Such was the usual end of epileptics at that time.

With the coming of the latter part of the nineteenth century, there was a revival of interest and the last 100 years has seen a great increase in experimentation and investigation. Much time, money and energy has been expended during this time in an effort to better understand and better treat these patients which are afflicted with epilepsy.

Only quite recently, in 1929, Lennox and Cobb published a scheme for classification of the epilep-

sies which is quite applicable to the problems at hand - that of briefly discussing the various factors in the etiology of epilepsy as they have been advanced during the last 100 years. Their classification is as follows:-

A. Factors within the brain tissue

1. Structural
   Gross changes
   Microscopic changes

2. Functional
   Physical and chemical factors
   Psychogenic factors

B. Factors other than within the brain tissue

1. Intracranial circulation

2. Sympathetic

3. Metabolism

4. Endocrine glands

5. Respiratory system

6. Gastro-Intestinal tract

Perhaps the first to be mintioned in the structural group should be the traumatic. Writers since the dawn of civilization have mentioned the possible connection between trauma of the head and subsequent epilepsy. It is thought at present by many of the foremost authorities, that trauma does play a very

definite part as an etiological factor of epilepsy.

The pathological nature of the lesion produced by the injury is thought to be a small softening or hemorrhage. The damage thus produced, results in the formation of a connective tissue and vascularized glial scar within the brain, which slowly contracts and produces a late effect. It may produce epilepsy of the Jacksonian type at first, but later it often becomes generalized. It is possible that many epilepsies may be due to some previous brain injury, even birth injury (15).

Additional pathological changes in the brain which may act as epileptogenous agents are listed by Foerster as follows (15):

Congenital brain processes, heredodegenerative processes, tumors, parasites, syphilis, tuberculosis, abscess, brain swelling, miningitis, encephalitis in childhood, epidemic encephalitis, multiple sclerosis, and presenile gliosis.

In some cases of intracranial tumor, epileptiform convulsions occur, and in other cases this symptom is entirely absent.

From the records of patients who had come to the Mayo Clinic from January 1, 1919 to Nov. 1, 1929, three hundred and thirteen cases were found wherein complete clinical studies had been made and necropsy data assembled. After a process of search, selection and exclusion, sixty-seven cases were assembled which presented symptoms of so called idiopathic epilepsy. This represented 21.6% of the total and is midway between S argents 30% for two hundred and seventy cases (36) and Dauman and Smith's 19% for one hundred cases (11).

In the series of cases from the Mayo clinic, all of the intracranial tumors associated with convulsions were situated above the tentorium. In most of the cases, the tumor was located in the frontal, parietal or temporal lobes of the brain, in descending order of frequency. The actual number of cases with convulsions reported as compared with the tatal number is too small to draw any conclusions as to the part intracranial tumors play in the production of epilipsy (17).

It is a well known fact that congenital syphilis manifests itself in much more subtle and varied ways

than acquired syphilis. The possibility of a class relationship between congenital syphilis and epilepsy has been suggested by many observations, the first probably that of Hoffman in 1712 (18), who described a case of epilepsy which he associated with the fact that the father was syphilitic.

Joseph Von Plenck in 1779 (6), and von Rosenstein in 1781, described cases of epileptics with gummata. Nearly a century later, Gros and Landereaux (16) noted the frequency of convulsions in congenital syphilis and regarded them as directly associated. Many other more recent writers have observed the association and many have noted the improvement caused by antisyphilitic treatment.

Many of the later writers, Saltmann (1880) and Nonne (1924) believe that epilepsy in its various forms is quite frequent in congential syphilis. On the other hand, Spratling (41) states that the connection may be only incidental. Abt (1) also believes that the statistics available are not of sufficient quantity to prove the point either way. There is a very vast amount of literature which gives considerable weight to the opinion that congenital

syphilis may be a direct or indirect cause of the epileptic syndrome. The whole situation is summed up very aptly by Shanahan who states, "an epileptic with syphilis is not necessarily a patient with syphilitic epilipsy, although syphilis is one of the many common causes which produce epilipsy. (37).

In consideration of the microscopic changes produced in the brain by the epiliptic state, or vice-versa, it must be understood that the field is as yet comparatively unexplored. The main difficulty as it presents itself today is whether or not epilepsy actually produces anatomical or histological changes, and can they be defined or determined? Up to the present, it has not been possible to decide definitely. However, many cases are found in which histological changes are recognizable, but the question remains as to whether or not this altered histology has any thing to do with the epileptic condition. And, likewise, there have been many cases in which, with the most up to date methods, nothing pathological could be demonstrated.

One of the most universal findings has been discovered in the study of "Ammon's horn" or the hippocampus, which is very often sclerosed. This sclerosis usually resembles a thick glial proliferation in locally circumscribed parts of the horn. In the Nissl picture, the change appears as a loss of ganglion cells in definite areas. These defects in the nerve cell picture correspond to the increase in the glia fibers in the previous picture. The histological analysis of such clerotic atrophy does not furnish any explanation of the process which produced it. The earliest states, - the first changes in this process - are thought to have been found.

According to S pielmeyer (40) the first change is a fresh loss of nerve cells on the border between the attacked focus and the normal contifuous tissue. Most of the cells disappear, those remaining are recognizable only as shadows. In place of the ganglion cells are seen proliferated glia cells of the rod form, which Nissl described years ago and which are now known as Hortega cells. These are surrounded

by the Stabchenzellen of Nissl. These mark the borders on the location of the disintegrating ganglion cells.

An important help in the analysis of the changes in the hippocampus is found in the changes in the cerebellum, which are similar in principle. These cerebellar changes are about as frequent as the changes in the hippocampus in the various epilepsies. Here also is found the sclerosis,- a proliferation of the fibroglia in the molecular zone. This replaces the disintegrated nerve-tissue substance, and the loss of the Purkinje cells, the shrinkage of the molecular zone, and the increase in the number of Bergman glia cells in a thick row. Here also it is possible to find the earliest changes often adjacent to old cellular losses in other places. These fresh losses are especially well marked by a branch-like network of proliferating glia cells. In the authors opinion, the changes are somehow related to the seizures.

The origin of the pathology is in question. It is thought by many that circulatory disturbances play a role here. In the opinion of Spielmeyer, the type

of the ischemic ganglion cells proves their genesis. He has found exactly the same changes in exactly the same places in the hippocampus in true organic obstruction in the circulation. It is seen therefore, that the organic occlusion of the circulation produces changes like those seen in epilepsy, and in similar locations. It might be concluded from this that in epilepsy, also, an impediment in circulation must be present, and since organic impediments are absent the circulatory function must at some time have been disturbed.

Taking into consideration Spielmeyer's findings that definite ischemic changes must have occurred, the cause for the ischemia might well be investigated. In order to prevent an ischemia from developing, it is essential that the capillaries leading to the area involved must be physiologically normal. Donaldson (10) says that altho the capillary may be so small as to be almost hidden, (the smallest are no larger than a red blood cell), it nevertheless is of fundamental importance for the activities of the tissues.

Capillary behavior and functional activity seem to be inseparable.

The actual mechanism or process whereby the normal capillary action is inhibited is not known.

There are many observers who believe that the ischemia is due to vascular spasm produced by vasomotor changes. Foerster (15) has seen over 100 cases at operation in which he produced epileptic attacks by faradic stimulation, and in all the attacks were preceeded by vasospasm. It is known that the cerebral blood vessels are innervated by vasomotor nerves and it is possible that some unexplained stimulation of these nerves is responsible for the seizures (32). Vaso-dilator drugs have been known in some instances to abort attacks. Vasomotor changes are most likely to come on at the menstrual periods, at the menopause and at puberty, after meals, and in the transition period to sleep,- illustrating the rationality of the vasomotor theory.

It is also considered that actual injury to the capillaries within the cerebrum takes place during birth. Considerable work has been done in an effort to prove this contention.

In an effort to obtain data on the earliest patterns of normal capillaries in the human being, Caesarian section babies have been studied. It has been found that even in spontaneous deliveries there is more trauma than is realized. L. Howard Smith (38), has done considerable work on the subject and has found that in 11% of the normal spontaneous deliveries there is bloody spinal fluid shortly after birth. He also found that in dystocia and forceps delivery, the percentage is very much higher, leading one to believe that there is very often some birth injury. The capillary patterns of these babies were compared with those delivered by Caesarian section, and the comparative studies showed that dystocia and forceps deliveries gave rise to distortions of the capillaries. It would appear that the results of the investigations prove the existence of a "physiologic intracranial damage incident to labor" (12). Therefore, it is not unlikely that epilepsy may have its etiologic substratum in the capillary damage occuring at birth, which in turn gives rise to the development of the metabolic imbalance, and when severe enough cause the convulsions.

Undoubtedly there are many physicochemical conditions in the body which may influence seizures and which react and interreact in a vast intricate manner. Of these the most important are changes in acid-base balance, in fluid balances, and in oxygenation.

The study of the whole field of physicochemical forces was begun in a large part by Geyelin in 1921 (14). He showed that fasting influenced seizures favorable in a certain proportion of patients with epilepsy, and suggested that the benefit was due to the acidosis induced.

There are four ways in which a reduction in the alkalinity of body fluids may be accomplished. The first and most natural method is through the production of lactic acid by means of physical exercise. In some of the patients who were having very frequent minor attacks it was found that the frequency of attacks was greatly reduced when the patients were actively exercising, and it was also significant that such a large proportion of attacks occured at night or at times when the patient was at rest. A second method of inducing acidosis is by the use of fasting or diet which is rich in fat and poor in carbohydrate.

The effectiveness of ketosis in certain cases has been demonstrated by Geyelin (14), Talbot (43), Peterman (33), and Lennox (24). As McQuarrie has shown, (28), the selection of foods with an acid residue is useful in supplementing a ketogenic diet.

A third method of inducing acidosis is through the ingestion of acids or acid forming salts. Some writers believe that the beneficial effects of a ketogenic diet lies in the production of the anesthetic aceto-acetic acids, rather than in the development of acidosis. Lennox (24) believes that inorganic acidosis does temporarily decrease seizures in the patients who are also helped by ketosis. His experiments suggested that the number of seizures paralleled the acid-base condition of the body and not the amount of ketone bodies.

A fourth method by which temporary acidosis may be induced is through the accumulation of carbon dioxide in the blood. It has been found that this may be effective in reducing the frequency of the seizures. The apnea which occurs in the tonic phase of a convulsion may be natures way of stopping the attack. (24).

A second physiological constant, the disturbing of whose balance may influence seizures, concerns the volume of body fluids. From what evidence is available, such as the convulsions which occur in water intoxication and in conditions associated with edema of the brain, it would be expected that the retention of water in the body and brain would tend to induce seizures, whereas dehydration would tend to inhibit them.

It is as yet a question whether or not epileptics do present an actual abnormality in the water balance either of the body as a whole, or of the brain. Winkleman (48), Pancoast and Fay (13), have demonstrated pathology of the Pacchyonian bodies with deficient drainage and abnormal accumulations of fluid in the brains of many epileptics which they have examined. Even Hippocrates observed that the brains were unusually moist (2) and Alexander (4) treated epiliptics showing increased collections of fluid by direct drainage of the cortex with some degree of success.

Using new methods of encephaolgraphy, the increased supracortical fluid collections have been

demonstrated to be quite common to the epileptic (8). Investigation has shown that these abnormalities are manifest even in early stages of the symptom complex.

Many recent physiological observations have indicated that excessive fluid predisposes experimental animals to convulsions. It has been shown (34) that large quantities of water, when given to a dog by a stomach tube, produce typical convulsive seizures and the animal might die in status within four or five hours. In the work of Ayer (5) on irrigation of the subarachnoid spaces of animals with various solutions, the protocols describe convulsive attacks rapidly induced by this method. Kubie (23) found that cerebral edema did not occur when the animal was given excessive fluid if free drainage of cerebro-spinal fluid was permitted.

These experiments, together with the findings of Fay and others would tend to substantiate the theory that hydration does cause convulsions, and that the primary cause for the edema is a failure of the pacchyonian bodies to function adequately. Treatment of epilepsy by dehydration method has been found very

effective, and it has often been of benefit where other measures of treatment have failed. Observations of the patients during the treatment has brought out many encouraging features. There was very often (13) a lessening of irritability and an improvement in memory and mental alertness. In instances where true cooperation was obtained, grand mal attacks were either favorably influenced or controlled altogether. The most common early improvement was lessening of the duration of the attacks, with freedom from the stuporous or sleeping phase immediately following the convulsion.

Considerable investigation has been made pertaining to the relation of decreased calcium content of the blood and nervous tissues, to the epileptic state. Calcium is of vital importance to the excitability of the nervous system, and it was conceived that a calcium deficiency might determine the hyperirritability and seizures found in epileptics. Sabbatani (35), was perhaps the first to undertake a careful study of the action of calcium salts on both normal and epileptic individuals.

When he experimentally reduced the calcium in animals, there occurred excitability, convulsive seizures, and an increased local irritability of the cerebral cortex. On the other hand, an increase in calcium gave rise to a depression. From these phenomena he concluded that ep ileptic seizures are induced by a reduction of calcium and that by increasing the calcium content of the body, the convulsive seizures would be reduced or stopped. Four years later Singuerri (31) repeated the experiments of Sabbatani and confirmed his results. More recent investigation has been less conclusive and there is at present much disagreement among experimenters as to the significance of these findings. Patterson (31) has done considerable work on the concentration of calcium in the body fluids of both normal and epileptic subjects, and he has found that the total blood calcium value in epileptics was normal within quite wide limits of individual variation, and he believes that the significance of the ionized calcium content of the blood in epileptics cannot be evaluated without further investigation.

Another factor which must be considered among the possible etiological factors of epilepsy is the individuals sensitivity to certain substances, especially proteins. It has been known for many years that certain individuals are unable to tolerate some specific protein substances, either in their diet, or in their environment. The possibility of such sensitivity having an influence or a relationship to epilepsy was not considered for years after the protein sensitivity or allergic reaction was discovered.

In 1904, Spratling (41) who was probably the first to conceive an allergic conception of epilepsy, suggested that individual suseeptibility to certain food stuffs must be taken into consideration as an etiological factor in the attacks of some epileptic patients.

Pagniez and Lieutaud in 1919 noted changes in the white cell count in an epileptic patient after the ingestion of chocolate and suggested that the hemoclastic crisis so produced, as well as the seizures which followed, were of an anaphylactic nature.

The sensitization factor in the etiology of epilepsy was again called to attention by Ward (31) in 1922 and Howell (19) in 1923, who presented reports

of cases in which skin tests had been performed, and in which the patients were found to be definitely relieved by abstinance from the offending food or by altering the environmental conditions.

At present with the mechanism of so called idiopathic epilepsy still indefinite, certain experimental hereditary, biochemical, clinical and therapeutic factors, which run more or less parallel in allergy and epilepsy, are considered in support of the hypothesis that periodic convulsive manifestations may be a response of the system to an allergic metabolic disturbance.

It is not known just what the mechanism of the disturbance may be. Nevertheless, the most recent studies tend to run parallel to present day conceptions, and are intimately concerned with the acid-base equilibrium and water balance factors of metabolism. (39) It is not now possible to do more than conjecture upon the relationship of allergy to these other factors which have been proven to be of significance in, or at least associated with, the etiology of epilepsy.

In spite of a vast quantity of research work which has been and is being done in an effort to ascertain certain fundamental facts which may be of

significance in the etiology of epilepsy. The question is almost as puzzling at present as it was a hundred thousand years ago.

The Ancients believed that epilepsy had a supernatural element and their treatment and concepts were in accord with that idea, and they sought, usually unsuccessfully, to appease the Gods and relieve their suffering brethern.

During the Greek and Roman civilizations considerable investigation was done upon the subject and these are written records of their poor success in trying to understand and treat epilepsy.

Later in the middle ages, and even during the early years of our own country, the epiliptic patients were subjected to considerable persecution as a result of their unfortunate condition.

In the last hundred years there has been a more scientific approach to the subject and considerable advance has been made along lines pathological, physicochemical and nervous investigation.

At present however, no definite conclusions have been reached, and epilepsy continues to be one of the

most puzzling of all the afflictions which beset mankind. Many mysterious diseases and conditions have been explained during the recent decades but epilepsy continues to be a puzzle to the modern physician, much the same as it was a hundred thousand years ago.

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