Periodicity and Hypsarrhythmia in the EEG

A Study of Infantile Spasms, Diffuse Encephalopathies, and Experimental Lesions of the Brain

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Introduction

In 1956 and 1958 Lesse, Hoefer, and Austin1,2 reported on clinical and electroencephalographic (EEG) findings in 11 patients suffering from a variety of diffuse encephalopathies of different etiologies and clinical outcome, but with a common EEG abnormality, namely, periodic synchronous bursts of irregular slow and spike-and-wave activity, mainly of high amplitude and with depression of activity in the interval. It was our impression that the EEG pattern was related to a profound cerebral, chiefly cortical, disturbance. The clinical features of this disturbance are: organic mental changes, myoclonic and generalized convulsions, rigidity, and a choreo-athetoid form of dyskinesia. Earlier authors3,4 had considered the EEG pattern to be specific for subacute sclerosing leukoencephalitis of the Dawson5 and van Bogaert6 varieties. Only one of our own original cases fell into this category, and we concluded that the clinical picture was indicative of a state of physiological impairment with release phenomena of subcortical structures and was not pathognomonic for any clinical entity. The symptoms in some of our cases were reversible.

The present investigation was started with the assumption that part or all of the features, but particularly the EEG pattern, might be found, if looked for, in other conditions and that it might also be produced experimentally in animals.

This report is based on clinical and EEG findings in 54 patients, who presented periodic bursts and in some instances the related EEG pattern of “hypsarrhythmia” described by Gibbs and Gibbs,7 and on EEG findings in five of nine primates subjected to several experimental procedures.8 The clinical data have been analyzed in some detail for possible correlation with the original concept of diffuse cerebral impairment developed in our earlier study and also for possible etiological factors as well as for physiological mechanisms that might emerge.

Clinical Data

Forty of our group of 54 patients were children suffering from infantile spasms. Six other infants suffered from various forms of neurological disorders with mental retardation. Three older children had intractable major seizures. Five other patients, ranging from 8 to 59 years, had various forms of diffuse profound encephalopathy. The four groups will be described separately.

A. Children With Infantile Spasms.—Complete clinical and EEG records were available in 40 children suffering from infantile spasms. Thirty-seven were studied at the Babies Hospital and three as outpatients. The onset of the illness occurred from a few days after birth to the age of 30 months. In 33 children the onset was at six months or earlier.
PERIODICITY, HYPSARRYTHMIA--EEG

The clinical description of the spasms was quite uniform in all cases. A spasm consisted of a brief flexion of all four limbs on the trunk with the head drooping in “salaam” fashion. A variant consisted of flexion of arms, extension of legs, and extension of the head backwards in opisthotonus. An individual spasm lasted for a few seconds. Spasms occurred in clusters of up to 10 or 12, and many clusters were noted with a total of hundreds of spasms every day. The child may cry out with the spasm and may sleep after a “cluster.” In several instances the spasms were unilateral, in the early stage of the illness.

Additional types of seizures were reported in 17 of the infants, and in several there were more than one additional type of seizures. In 11 patients grand mal attacks occurred either before or after the onset of the spasm. One child had a single known grand mal, another had two, the remaining nine had frequent major convulsions. Ten children had focal or unilateral clonic seizures. One child was seen in focal status. One child had akinetic seizures. Three were reported to have had myoclonic seizures, but it is possible that these were a variant of the spasms seen in the other infants.

The mental status was evaluated, wherever possible. Two children 11 and 17 months of age were considered normal. Two others were seen before the age of two months and no attempt was made to judge their mental development. The other 36 were seriously retarded or had severely regressed after apparently normal initial development.

Motor performance was impaired in nine infants as follows: diffuse bilateral spasticity, two; spastic diplegia, two; hemiplegia, three; monoplegia, one; generalized atonia, one. Blindness was suspected in 11 infants who did not respond to visual stimuli.

Deafness was similarly encountered in five. Two infants had optic atrophy, in one case associated with a retinal pigment disorder and coloboma. Five infants were blind or deaf or both and had in addition states of spasticity. One of the infants with optic atrophy had spasticity.

Skeletal abnormalities were found in 12 cases. Eight children had microcephaly by clinical and radiological criteria. One of these in addition had hypoplasia of both feet. Two children had megalcephaly, one with arrested hydrocephalus. One infant had premature closure of the sagittal suture, and one had rarefaction of long bones.

Significant abnormalities were recorded in the immediate family of 20 (or one half) of the children. Grand mal seizures had occurred in eight instances with two fatalities during status. Two siblings of our group had infantile spasms with retardation. Four other relatives were retarded, one with spasticity. Two had siblings with febrile fits. There were two instances of mongolism. Pregnancy preceding that of one infant in our group resulted in the birth of an anencephalic monster. The mother of another had adenoma sebaceum and was considered to have a forme fruste of tuberous sclerosis.

Past History: The past history of one child revealed repeated episodes of respiratory arrest. Another had chicken pox approximately at the time of onset of the spasms. Repeated fevers of unknown origin and repeated episodes of otitis media had occurred in one case each.

Prenatal Maternal Complications: These occurred in eight cases. In four repeated vaginal hemorrhages occurred during the first or early in the second trimester. One of these was treated with hormones. One mother was exposed to German measles, one had pyelonephritis, one underwent treatment with chloramphenicol for an infectious process, and one made repeated attempts at inducing abortion with mechanical means during the fourth, fifth and sixth months and in addition by deliberate exposure to x-ray radiation.

Perinatal Complications: Such complications occurred in 15 cases. There were four instances of precipitate labor of two hours in three and three hours in one case. One child sustained a fracture of the clavicle during delivery. Two other children were born prematurely at 6½ and 7 months, re-
spectively. In two instances cesarean section was elected, in another case it was performed with the mother in shock. Two infants had respiratory distress at birth.

Postnatal Complications: Eighteen infants had been immunized prior to the onset of the spasms. Fifteen had received DPT injections, five of these had additional vaccinations for poliomyelitis. In five infants the spasms reportedly started one day, two days, one week, ten days, and two weeks, respectively after the third injection of DPT vaccine. In the other cases the injections had been given three to six weeks before onset or at an unrecorded date. The relationship is possibly fortuitous but worthy of note.

EEG Findings: Hypsarrhythmia has been generally accepted as the EEG pattern associated with infantile spasms, and some authors use the two terms interchangeably. It is defined by Gibbs and Gibbs as follows: "It consists of random high voltage slow waves and spikes. These spikes vary from moment to moment, both in duration and location. At times they appear to be focal, and a few seconds later they seem to originate from multiple foci. Occasionally the spike discharge becomes generalized. . . .

Fig 2.—Infant girl, 14 months of age. Infantile spasms since age six months. The record shows continuous, irregular slow wave and spike-and-wave activity of hypsarrhythmic pattern. Calibration and time as in Fig 1.
The abnormality is almost continuous and in most cases it shows as clearly in the waking as in the sleep record. Periodicity is a far more regular pattern. Synchronized bursts of irregular slow wave, slow spike, and spike-and-wave activity recur typically every five to eight seconds and last for one to three seconds, but both duration and periodicity may vary. The bursts are strikingly similar in all areas of the head and are usually identical in homologous leads. The bursts are usually separated by stretches of more or less complete suppression of all activity. The difference between the two EEG patterns is shown in Fig 1 and 2. The records of 21 children showed both periodicity and hypsarrhythmia. In eight others periodicity changed to hypsarrhythmia with sleep or vice versa (Fig 3). In five children hypsarrhythmia was the main abnormality, but on some occasions periodic bursts occurred without suppression but with irregular "hypsarrhythmic" activity in between (Fig 4). Seven children had only periodicity and no hypsarrhythmia at any time. Six had only hypsarrhythmia and no periodicity. The remaining child had neither of the two patterns but represented continuous slow spike-and-wave activity in all leads. One of the children had a focal discharge of spike activity against a background of alternating hypsarrhythmia and periodicity. Clinically

Fig 3.—Infant girl, 16 months of age. Infantile spasms since age of 13 months. A, with the child awake, shows hypsarrhythmia. B, with the child asleep, shows transition to periodicity. Calibration and time as in Fig 1.
there was no difference between the various subgroups.

Laboratory Findings: The cerebrospinal fluid was examined in 20 cases. The total protein was found slightly elevated in two. Pneumoencephalograms or ventriculograms were performed in eight cases. In four there was some degree of unilateral or bilateral cerebral atrophy. An occipital porencephaly was present in one. Studies of phenylpyruvic acid in 22 cases and of urinary amino acid excretion in five cases were normal. Examinations of the urine for cyto-megalic inclusion disease were negative in eight cases. Tests for toxoplasmosis were negative in four, questionably positive in one case. Lactic dehydrogenase in the serum was elevated in one case. Sickle cell anemia and a microcytic form of anemia were found in one case each.

Follow-Up: Histories were available in fifteen cases. The seizures had stopped in 3 but had continued or became worse in 12. Four children had died, two were placed in institutions. No follow-up was available for the remaining 19, but some were reportedly improved on steroid therapy.

B. Children With Neurological Deficit (Without Infantile Spasms).—In six children severe neurological disorders were found to be associated with periodic bursts in the EEG. All but one had grand mal convulsions; in one no clear description of the seizures was available. Two children in addition had "decerebrate" seizures, others had focal or unilateral seizures as well. They were seen between the ages of 17 days and 8 months. In five the illness had started in the neonatal period, in one at one month. Five were retarded. One was only seen at 17 days and was not followed. One child with a tetralogy of Fallot had frequent anoxic episodes. Two children were born by breech delivery. In several children spasticity and blindness were found. Skeletal abnormalities occurred in several. One child in addition to periodic discharges had long-sustained runs of slow spike-and-wave activity in the EEG. Thus, except for the absence of infantile spasms, the two groups were quite similar.

C. Periodicity in Older Patients.—In the EEG records of eight patients, age 8 to 59, periodic bursts were found. One of these, a girl of 12, had a history of infantile spasms in early childhood but later developed grand mal and psychomotor seizures. This case might be considered a late follow-up on infantile spasms. She was severely retarded with an IQ of 59 and was blind. Another child seen at age nine had a history of intractable grand mal seizures, with up to 30 seizures per day, and was grossly retarded with a porencephalic cyst and a his-
Fig 5.—Boy, age nine years. Sickle cell anemia, several episodes of prolonged cardiac arrest.
The record shows irregular periodic bursts associated with myoclonic jerks indicated by X.
Calibration: 50μv. Time: one second.

Fig 6.—Boy, age 12 years. Chronic encephalopathy with severe mental deterioration and
myoclonic, as well as generalized, convulsions. The record shows irregular periodic bursts of
spike-and-wave activity. The two lower tracings are electromyographic recordings from the
left deltoid and biceps. They show myoclonic contractions synchronous with the periodic EEG
bursts. Time and calibration as in Fig 5.

The etiology of severe protracted cyanosis and
anoxia for several weeks in the neonatal pe-
riod. A third child, seen at 8 and again at
15, suffered from grand mal, petit mal, and
psychomotor seizures. She was of normal
intelligence and had no grossly demonstrable
neurological deficit.

The remaining five cases represent severe
encephalopathies of heterogeneous etiology
and resemble the group of cases reported
1958. One child aged nine had severe
sickle cell anemia with a hemoglobin con-
tent of 6.2 gm, anuria, and, after several
episodes of cardiac arrest, had a striking
EEG pattern of periodicity (Fig 5). An-
other child of eight had a full-blown clinical
picture of Dawson's inclusion body leuko-
encephalitis, which was verified by post-
mortem studies. Another child followed for
several years has a seven-year history of
mental deterioration of progressive severity,
dyskinesia, blindness, spasticity leading to
quadriplegia, and periodic recurrent myo-
clonic seizures at the rate of the periodic
bursts (Fig 6). This patient always had a
markedly elevated γ-globulin in the spinal
fluid with readings as high as 54%. Because
of this and the long duration of the illness,
the diagnosis of Schilder's disease was con-
sidered. But several verified cases of Daw-
son's inclusion body encephalitis have been
reported which lasted up to eight years,
and no final diagnosis was made in this case.

A young woman, age 23, with an ence-
phalopathy of unknown etiology, presented
with a severe organic mental syndrome with
confusion, delusions, grand mal, and psy-
chomotor seizures. Her records showed both
periodic bursts and hypsarrhythmia at vari-
ous times. At autopsy she was found to
have degenerative central nervous system
disease, possibly anoxic in origin, and central
necrosis of the liver.
The necropsy on a woman of 54, a chronic alcoholic with cirrhosis of the liver, showed widespread acute necrosis of neurons in the cerebral cortex and hippocampus. These lesions were thought to be due to anoxia. In addition there were multiple foci of necrosis and a loss of myelin in the central area of the pons (pontine myelinolysis). Her EEG showed striking periodicity with suppression bursts (Fig 7).

D. Animal Experiments.—It was felt that structural or functional impairment of the cortex and of subcortical white matter, experimentally produced, might lead to the appearance of periodic EEG bursts in animals. Thus EEG records were obtained on nine primates, three baboons and six rhesus monkeys. In five of these animals periodic discharges were recorded under a variety of conditions. The most striking examples of this pattern were found in two baboons, in which the caudate nucleus and the frontal white matter had been “scooped out” bilaterally, two years previously. One (Fig 8A) showed periodicity in barbiturate-induced sleep, the other showed the same activity during curarization (Fig 8B). The bursts in this case were abolished by arti-
Perioperative respiration. In another baboon, however, which was tested two years after bifrontal cortical extirpation and bilateral removal of the caudate nuclei, no periodic bursts were noted during barbiturate-induced sleep. In this case the lesion was more extensive, inasmuch as in the other two the frontal gray matter had been spared.

Three rhesus monkeys, one intact, the other two after minor surgical procedures, showed periodic bursts in barbiturate-induced sleep. Four others subjected to a variety of procedures showed no periodic bursts.

Comment

A distinctive EEG pattern has been found in a heterogeneous group of diseases of the central nervous system. In an earlier study, an attempt was made to determine whether there are any consistent clinical features in the cases with the EEG changes. The clinical picture is characterized by organic mental changes (usually severe), myoclonic or generalized seizures or both, and evidence of basal ganglia involvement. In the present investigation, periodic discharges of abnormal, mainly paroxysmal activity, are described in a group of young children with infantile spasms and other seizure disorders. In addition the EEG changes were found in a small group of older patients similar to those described in 1958. The same pattern was finally seen in experimental animals under certain conditions. Severe organic mental changes in the form of retardation or regression were found in the infants. They also show the two seizure types. Spasticity and other evidence of structural neurological deficit, as blindness and deafness, were found. Basal ganglia symptoms are not expected to appear clinically in infants.

The electroencephalographic patterns may vary in individual patients at different times. The classical picture of periodically recurring EEG discharges may be seen to coincide with equally periodic myoclonic movements. The EEG complexes persist in cases where the movements are abolished by anesthesia.

In simultaneous recordings of muscle action potentials with the EEG tracings, the onset of the movement may precede the EEG discharge by a fraction of a second. In cases where an EEG follow-up was obtained in the terminal stage it was noted that single spike discharges recur at the rate of the original slow wave complexes. The periodic bursts recorded in our animal experiments resemble closely those reported by the earlier authors and thought to be pathognomonic for subacute sclerosing leukoencephalitis.

In 28 of 40 children with infantile spasms periodic suppression bursts were recorded, alternating with hypsarrhythmic activity. In seven children periodic bursts and in the remaining five hypsarrhythmia was the only abnormality. In view of this relationship and because the clinical pictures were identical in all cases, it is concluded that the two EEG abnormalities are closely related.

No common etiology was found in our studies for the various clinical states in which the periodic EEG discharges occur. But in analyzing the cases of infantile spasms and other seizure types in this age group, it is striking to note that in one half of the cases family histories of central nervous system disease or seizures or both were obtained. Prenatal and perinatal complications were also noted frequently in the histories of the infants. Many of these conceivably might involve anoxic conditions, and indeed frank anoxic states were recorded in five of the children. Two in addition had been delivered by breech. Among the older cases there is one with a history of cardiac arrest. Autopsy findings in two others showed suggestive anoxic changes. Liver disease, while noted in three cases, does not seem highly significant in the development of the syndrome.

Infections (chickenpox) and DPT immunizations may conceivably have precipitated the onset of the spasms in six of our cases, where the disease reportedly started between one day and two weeks after the third injection.

Probably the first clinical report on infantile spasms is that by West in 1841, con-
cerning a child with "salaam" spasms and mental deterioration. Few sporadic cases were reported until 1924.14 Since then numerous studies on infantile spasms have appeared. Gibbs and Gibbs 7 in 1952 described hypsarrhythmia as the EEG pattern of infantile spasms. Most authors in the past decade have accepted this correlation, and some have used the two terms interchangeably. In most publications infantile spasms were considered a rare inflection with series of 20 to 30 cases collected over several years. Burnett, Gibbs, and Gibbs 15 on the other hand reported on 450 cases. Only 34 of these had normal EEG records. Follow-up studies were made on 27 of these, and 15 were found to be clinically normal at a later time. Thus, the EEG seems to be prognostically important. One third of the Gibbs' series had other forms of convulsive seizures as well. Eleven per cent died before the age of three. Eighty-seven per cent were or became mentally deficient. Birth trauma and encephalitis were presumed to be the commonest causes.

Bower and Jeavons 16 collected 22 cases of infantile spasms in three years. All but one had mental deterioration, 15 gross, 6 moderate. Spasticity and other forms of motor deficit, blindness, microcephaly, and hydrocephalus were noted in this series. The EEG pattern in their cases is mainly hypsarrhythmia, but they also saw "centrencephalic" patterns resembling closely what in the present report is called "periodicity." Prenatal or perinatal brain damage including anoxia and maldevelopment are considered etiologic factors. Immunization against diphtheria or pertussis is briefly discussed but rejected as etiologically significant because seven of their patients had not been immunized. In this respect Bower and Jeavons disagree with Baird and Borofsky.17 These latter authors analyzed presumptive etiologic factors in 51 cases which were subdivided into two groups. One group comprised 27 children who were retarded from birth. Three had hereditary stigmata (phenylpyruvic oligophrenia, tuberous sclerosis, and familial mental deficiency). One had congenital toxoplasmosis, seven others had histories of maternal illness, seven others had prolonged or difficult deliveries with prolonged anoxia in two. The other group of 24 children had apparently developed infantile myoclonic seizures after smallpox vaccination in two and after DPT immunization in nine cases. The others had suffered from various forms of encephalitis (six cases), tuberculous meningitis (two cases), and head trauma with subdural hematomas in two cases. Forty-three of this group of 51 had mental retardation and 29 had hypsarrhythmia.

Millichap and his associates 18 studied etiologic factors in 61 patients with infantile spasms, hypsarrhythmia, and mental retardation. Mental retardation was present in 84%. Cortical blindness or visual inattentiveness was found in 30%, spastic diplegia in 30%, and hypotonic diplegia in 28%. Many other defects were found, including cerebral atrophy in eight of 16 in whom pneumoencephalographic studies were performed. The etiology was undetermined in 43%. Birth injury or anoxia had occurred in 15% and prenatal injuries in 13%. Various other factors are listed, including inborn metabolic disorders. One child had an encephalopathy with hypoglycemia, one child developed spasms after DPT, and another developed spasms after influenza immunization.

Trojaborg and Plum 19 studied a series of 30 cases of infantile spasms. Asphyxia at birth had occurred in eight; in four others the deliveries had been complicated. The EEG showed hypsarrhythmia in 80% and other abnormalities in 20%. Autopsies were performed in four cases. All showed cortical atrophy and subcortical degenerative changes. In two cases porencephaly was found. There was marked glial proliferation.

Poser and Low 20 reported on autopsy findings in three cases of "hypsarrhythmia." The outstanding features were chronic edema and spongy degeneration with little glial reaction and little evidence of repair. In one case the gray matter was primarily involved. In the second case the changes
were mainly in the white matter. Distribution was mixed in the third case. The authors consider a metabolic disorder with an enzymatic defect as possibly responsible.

Harris and Pampiglione discuss EEG and histopathology in 11 children with infantile spasms. They point out that similar EEG changes have been found in neuronal lipiodosis and in other metabolic disorders including phenylketonuria. Cerebral biopsies in two cases suggested neuronal lipiodosis. The autopsies revealed gross cerebral malformations with agyria in one, a porencephalic cyst with suppurative meningitis in one, and signs of diffuse cerebral atrophy in six.

Sinton and Patterson report the case of an infant who was born apneic and apparently had infantile spasms a few hours after birth. The EEG showed hypsarrhythmia and in addition hypersynchrony correlated with massive myoclonic jerks. He later had generalized convulsions and died in status epilepticus at the age of one year. The autopsy showed slight atrophy in the occipital and parietal regions and considerable atrophy of the cerebellum and brain stem. Cystic cavities were seen in the region of the putamen. There was diffuse gliosis and loss of nerve cells throughout the cord, medulla oblongata, andpons. Profound changes in the vermis and the lateral cerebellar lobe consisted in total loss of Purkinje cells and reduction in number of granular cells. There were also marked degenerative changes in the basal ganglia and thalamus with astrocyte proliferation. There was marked patchy and random reduction of cortical nerve cells in the cerebral cortex, insula, and Ammon’s horn.

Thus, in a few cases studied, postmortem findings appear to be of a great variety and not highly specific in infantile spasms.

Several authors have, in recent publications, reviewed the clinical features and EEG findings in cases of subacute leukencephalitis and panencephalitis. They are in essential agreement with Radermecker’s original concept (1949) of the pathognomonic nature of the EEG bursts for the subacute encephalitides. We have stated our reasons for disagreement.

This seems to be further supported by findings of several authors. Pallis and Spillane saw three cases of subacute progressive encephalopathy in patients 45 to 51 years of age. The clinical features were mutism, hypokinesia, rigidity, and myoclonus. One patient had periodic EEG bursts in sleep. The histological findings were minimal neuronal loss in the gray matter of the cortex, basal ganglia, and dentate nuclei and status spongiosus.

Dodge and co-workers found periodic synchronous EEG discharges separated by electrical silence in the record of a child three years of age suffering from phenylketonuria and mental retardation, who developed severe hypoglycemia and convulsive seizures with coma.

Zappoli studied a case of severe acute head injury in a young adult male. Thirty-two hours after the accident, the EEG showed patterns “characteristic of subacute leukencephalitis.” At the time the patient was in deep coma. Three days later, when the patient was more alert, the periodic bursts had disappeared. The patient recovered fully after two weeks.

Pampiglione reported on EEG findings after cardiorespiratory arrest in 60 children. He developed criteria for the evaluation of cerebral damage after resuscitation. In the case of a child, 2½ years of age, high-voltage periodic bursts of irregular activity were recorded after several episodes of cardiac arrest. The child died the next day. This pattern is prognostically very serious after cardiac arrest. We have reported on a similar case (Fig 5).

Fisher saw periodic EEG complexes associated with myoclonic jerks and dementia in nine case of Jakob-Creutzfeldt disease. The patients ranged in age from 49 to 68 years. A similar case was reported by us in 1958.

Rayport studied two cases of Jakob-Creutzfeldt disease which were verified by biopsy and postmortem. In these patients routine EEG’s and electrocorticograms as
well as depth recordings were performed. EEG and cortical recordings from the pial surface showed periodic bursts closely resembling those reported by us and others. The bursts were attenuated in amplitude when the electrodes were placed on subcortical white matter. High-voltage bursts identical with those seen in surface recordings were again encountered with depth electrodes from the globus pallidus. This indicates to Rayport the presence of separate loci for the generation of the periodic bursts.

One final group of related findings should be mentioned in this discussion. The EEG in the early human premature infants shows discontinuous activity with more or less regular periodicity ranging from nine seconds to about one minute. These bursts were seen up to the eighth fetal month in several studies by Dreyfus-Brisac, Samson, and Fischgold. In a recent review of this subject Dreyfus-Brisac states that the "rhythmic potentials of the premature are very likely due to archaic structures, which arrive precociously at a functioning level (central gray nuclei)."

Thus, in reviewing our own findings and those of others, several possible clinical etiologies seem to emerge, some most clearly seen in the cases of infantile spasms, others common to all groups discussed. A strong hereditary factor of central nervous system disease and seizures is suggested in up to one half of the cases of infantile spasm and other infantile disorders. Infections and an untoward response to immunization may be responsible in some cases. Several authors have reported on cases with inborn metabolic errors. These cases are not prominent in our own material. Of the exogenous causes, anoxia and, to some extent, hypoglycemia seem to be most important. Coma after head injury and in diffuse diseases of the central nervous system seems to be a significant factor. Trauma in combination with anoxia appears to be operative in our primate studies, though the exact type or extent of trauma is not certain as yet. No trauma had been produced in one or two of our animal experiments. It is our impression that periodically recurring EEG bursts are varying aspects of an underlying abnormality regulated somewhere in subcortical or brain stem areas, not necessarily in a single region as the result of excitatory or release phenomena occurring is partly impaired structures.

The concept of periodicity as a response to this situation is supported by many biologic phenomena. Among these are the "dial" bursts recorded from the exposed cortex of carnivores and primates under barbiturate anesthesia as reported by Adrian and Moruzzi and by Hoefer and Pool. With additional impairment or in deeper anesthesia, these bursts may be transformed into the complexes seen in our present experimental observations. Bremer recorded periodic recurrent oscillation at frequency range from the visual area of the cat in the encéphale isolé preparation after section of corticothalamic fibers. These discharges were enhanced by local application of strychnine. Swank and Watson found periodically decreased spontaneous electrical activity followed by bursts in anesthetized dogs and monkeys. Henry and Scoville recorded suppression-burst activity from isolated frontal cerebral cortex in many cases during lobotomy operations. These bursts were still seen in some cases at reoperations many months later. Similar findings in humans and in experimental animals were reported by Echlin, Arnett, and Zoll. Thus there is much evidence that isolated brain, deafferented cortex, and the isolated brain stem in cases with cortical and subcortical impairment produce periodic discharges under certain conditions. It is conceivable that the effects of these periodic bursts vary according to site of origin and path of conduction of these impulses. Periodic myoclonic movements would thus occur in special situations, and it is even conceivable that the myoclonic jerks may occur a fraction of a second before the electrical bursts in the EEG if conduction from a pacemaker in the brain stem is relatively delayed in the direction of the cerebrum while conduction toward the spinal pathways is unimpeded.
The patterns of the EEG in premature infants do not necessarily represent cerebral damage, but may be understood in terms of physiological isolation of structures from each other because of incomplete myelination at this stage.

Reversible EEG abnormalities associated with clinical recovery as in cases of coma after head injury and in some of our earlier cases of encephalitis may be explained as resulting from reversible changes caused by relatively benign processes which nevertheless cause physiological deafferentation.

Summary and Conclusions

In an earlier study (1958) of patients suffering from diffuse encephalopathies of heterogeneous origin a distinctive EEG abnormality, periodic synchronous bursts, was found in conjunction with organic mental changes, myoclonic and generalized seizures, rigidity, and choreo-athetoid dyskinesia.

The present investigation was begun with the assumption that the same or a similar combination of clinical and EEG abnormalities might be found in other conditions and that the EEG abnormality might be produced experimentally in animals. Findings are reported on 54 patients and on nine primates subjected to various procedures.

Forty of the patients were children with infantile spasms. In 34 of these, periodic EEG bursts were found. Some had hypsarhythmia in addition; six had hypsarrhythmia only. Clinically there was no difference between the various subgroups, and it was concluded that the two EEG abnormalities are closely related. Thirty-six of the children were grossly retarded or had regressed after initial normal development. Fifteen had additional forms of seizures, mainly grand mal. Spasticity was found in 9, blindness in 11, and skeletal abnormalities in 12.

Six other infants had periodic EEG discharges, mental retardation, and various forms of neurological disorders. Five had generalized convulsions.

Three older children had intractable major seizures, two associated with mental retardation, spasticity, and blindness. All three had periodic EEG bursts.

Five patients, ranging from 8 to 59 years, had striking periodic EEG discharges, associated with various diffuse forms of encephalopathy. All had myoclonic and generalized convulsions and profound mental impairment. All but one had dyskinetic movements. In the first of these patients the findings developed after cardiac arrest. The second had a verified form of Dawson's encephalitis; the third probably had Schilder's disease; the fourth a degenerative encephalopathy, possibly due to anoxia; the fifth patient, a chronic alcoholic with Laennec's cirrhosis, had widespread necrosis of neurons of cortex and hippocampus and a central area of pontine myelinolysis.

In five of nine experimental animals periodic EEG discharges were recorded. The pattern was most striking in two baboons after bilateral removal of the caudate nucleus and removal of frontal white matter.

A number of etiological mechanisms are discussed. A strong genetic factor appears to be operative in infantile spasms; anoxia, inflammatory and degenerative diseases occur frequently in the histories. In some instances abnormal responses to immunization may have occurred.

Periodic discharges of electrical activity are found in many bioelectrical observations. They occur in isolated brain, deafferentated cortex, and in isolated brain stem in cases of cortical or subcortical impairment, possibly as release phenomena.

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